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TOP TRIALS REVIEW

Fosfomycin trometamol in the treatment of urinary tract infections (UTIs)

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Fosfomycin trometamol in the treatment of urinary tract infections (UTIs)

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Note. In the "Clinical Significance" boxes and in the section titles, we have used the complete denomination "fosfomycin trometamol" to emphasise that we are referring to the oral formulation only.

Section I. Antimicrobial activity and pharmacological properties of fosfomycin trometamol in the treatment of urinary tract infections (UTIs)

Adapted from:
Zhanel GG, Walkty AJ, Karlowsky JA. Fosfomycin: A First-Line Oral Therapy for Acute Uncomplicated Cystitis. Can J Infect Dis Med Microbiol. 2016;2016:2082693.

Background

Current European and American guidelines recommend, among others, fosfomycin as first-line therapy to treat acute uncomplicated urinary tract infections (UTIs) in adult females.

UTIs belong to the most common infections in humans. Approximately 50% of women incur in a UTI at least once in a lifetime, whilst 25% suffer recurrently. Causative pathogens include *Escherichia coli* (*E. coli*; 75–90%), *Staphylococcus saprophyticus* (5–15%), or rarely, *Klebsiella* spp., *Enterococcus* spp., *Streptococcus agalactiae*, and *Proteus mirabilis*.

Aims

The review attempted to summarise English-language peer-reviewed data published from 1975 to 2015 on fosfomycin's characteristics and its role in the therapy of acute cystitis. For the purpose of this publication, data on the mechanism of action of fosfomycin and its bactericidal, pharmacokinetic and pharmacodynamic properties have been extracted.

Mechanism of action

Fosfomycin irreversibly inhibits MurA, an enzyme catalysing the first step of the peptidoglycan biosynthesis necessary for bacterial cell wall synthesis. This mechanism of action is unique and differs from that of other bacterial cell wall inhibitors (*e.g.*, β-lactams or glycopeptides).

In vitro microbiology

Fosfomycin is active *in vitro* against both Gram-negative and Gram-positive bacteria as indicated by the values of minimum inhibitory concentrations (MICs) shown in ***Table 1***.

Table 1 Fosfomycin's MICs for the most common cystitis-causing pathogens. Table adapted from Tables 1 and 3 of the original review.

Bacteria	Number tested	Fosfomycin		
		MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range (µg/mL)
Gram-negative bacteria:				
Escherichia coli	9338	0.5–4	2–16	0.03–512
Klebsiella spp.	995	8–16	32–128	≤2–512
Proteus mirabilis	1472	≤2–4	32–>128	≤1–>512
Gram-positive bacteria:				
Enterococcus spp.	137	16–32	64	0.25–>256
Staphylococcus saprophyticus	227	64–128	256–>512	≤2–>512
Streptococcus agalactiae	50	32	64	2–64

MIC_{50}, minimum concentration (µg/mL) required to inhibit the growth of 50% of isolates; MIC90, minimum concentration (µg/mL) required to inhibit the growth of 90% of isolates.

MIC is the lowest concentration of an antibiotic that inhibits the growth of a microorganism upon overnight incubation. MIC_{50} and MIC_{90} values describe the lowest antibiotic concentration at which 50 and 90% of bacteria are inhibited, respectively. The breakpoint concentration of an antibiotic indicates the species susceptibility or resistance to it: a bacterium is considered susceptible when MIC is less than or equal to the susceptibility breakpoint concentration.

For *E. coli*, the most frequent cause of cystitis, fosfomycin's MIC value of ≤64 µg/mL of an isolate is considered susceptibility, whereas a MIC of ≥256 µg/mL denotes resistance, which in *E. coli* is rare (<1%). Fosfomycin displays higher MIC values for *Klebsiella* spp., *Enterococcus* spp. and *Staphylococcus saprophyticus*, than for *E. coli* and *Proteus mirabilis*.

Table 2 includes data from a Canadian surveillance study of *E. coli* isolates from patients with UTIs. Rates of susceptibility to fosfomycin were close to 100% for all isolates, including multidrug-resistant (MDR) bacteria. Importantly, fosfomycin susceptibility rates were superior to other frequently prescribed agents.

Table 2 *In vitro* activity of oral antibiotics against *E. coli* isolated from urine samples. The multidrug-resistant category comprises isolates resistant to ≥3 agents from antimicrobial classes included in the table. Table adapted from Table 2 of the original review.

E. coli isolate (number tested)	Antimicrobial agent	MIC interpretation	
		% susceptible	% resistant
All *E. coli* (868)	Fosfomycin	99.4	0.1
	Amoxicillin-clavulanate	81.3	5.7
	Ciprofloxacin	77.4	22.5
	Nitrofurantoin	96.1	1.5
	Trimethoprim-sulfamethoxazole	74.7	25.3
Multidrug-resistant (15)	Fosfomycin	100	0
	Amoxicillin-clavulanate	13.3	66.7
	Ciprofloxacin	0	100
	Nitrofurantoin	60.0	40.0
	Trimethoprim-sulfamethoxazole	6.7	93.3

Pharmacokinetics, pharmacodynamics and drug interactions

Fosfomycin is water-soluble and distributes widely into tissues. A 3-gram oral dose of fosfomycin results in serum C_{max} of 22–32 µg/mL after 2–2.5 hours of ingestion. Its serum half-life is 5.7 hours and oral bioavailability 34–41%. Fosfomycin is not metabolised by the organism, but 54-65% of it is excreted unchanged by glomerular filtration into the urine. Peak urinary concentrations reach ~4000 µg/mL and remain at levels >100 µg/mL for 48 hours. The urinary concentration above MIC_{90} for *E. coli*, *i.e.*, 4 µg/mL, persists for circa 80 hours (***Table 3***).

Table 3 Pharmacokinetics of fosfomycin following a single 3-gram oral dose. Table adapted from Table 4 of the original review.

Parameter	Mean value or range
Serum/plasma	
Bioavailability (F)	34–41%
Maximum plasma concentration (C_{max})	22–32 µg/mL
Time to maximum concentration in the blood (T_{max})	2–2.5 h
Half-life ($t_{1/2}$)	5.7 h
Clearance (CL)	16.9 L/h
Urine	
Maximum urinary concentration (U_{max})	1053–4415 µg/mL
Time to maximum concentration in the urine (urinary t_{max})	4 h
Urinary concentration at 48 h	~100 µg/mL
Dosage adjustments	
Dose adjustment in elderly, pregnancy, renal impairment or hepatic adjustment	None required

Fosfomycin demonstrates concentration-dependent killing: assessing bacterial growth upon fosfomycin addition from time 0 to 24 hours, growth inhibition was directly proportional to its concentration. For *E. coli*, complete eradication occurred at 6–8 hours at fosfomycin concentrations of ≥4x MIC. Instead, its pharmacodynamic activ-

ity is time-independent, as the same rate and extent of bactericidal activity was observed using different schedules of administration.
Except for metoclopramide, no drug interactions have been reported for fosfomycin.

Conclusions

Current international guidelines (issued by the Infectious Disease Society of America, the European Society for Microbiology and Infectious Diseases, the European Association of Urology, and the Canadian Anti-Infective Guidelines for Community Acquired Infections) recommend fosfomycin as a first-line antimicrobial for the treatment of acute, uncomplicated cystitis. *In vitro* activity of fosfomycin against common uropathogens, including MDR strains, and its pharmacokinetic and pharmacodynamic properties support this therapeutic option.

Key points

- Fosfomycin, an inhibitor of bacterial cell wall synthesis, is considered a first-line treatment for acute uncomplicated UTIs in adult females.
- Fosfomycin inhibits the *in vitro* growth of both Gram-negative and Gram-positive bacterial pathogens.
- Susceptibility rates to fosfomycin are close to 100% for all *E. coli* strains, including MDR species, and are superior to other frequently used agents.
- Fosfomycin is excreted unchanged into the urine, which is paramount for the eradication of bacteria present in the bladder of patients suffering from cystitis.
- Dose adjustment in the elderly, pregnant women, patients with renal or liver impairment is not required and drug interactions are confirmed only for metoclopramide.

Clinical significance

Fosfomycin trometamol is an antibiotic-of-choice to treat uncomplicated UTIs based on its antimicrobial and pharmacological properties. International guidelines recommend fosfomycin as first-line treatment for UTIs.

Section II. The comparison of susceptibility and resistance of uropathogens to fosfomycin trometamol versus other antimicrobial agents

Adapted from:
Johansen TEB, Livermore DM, Cai T, Tutone M. SURF (SUsceptibility and Resistance of uropathogens to Fosfomycin in comparison with other antimicrobial agents): an international microbiological surveillance study. Poster presented at, 40th Congress of the Société Internationale d'Urologie, 2020 Oct 10-11, virtual.
and
Cai T, Johansen TEB, Livermore DM, Tutone M. Clinical implications of SURF-data (SUsceptibility and Resistance of uropathogens to Fosfomycin in comparison with other antimicrobial agents) on empirical treatment of uncomplicated urinary tract infections in women. Poster presented at, 40th Congress of the Société Internationale d'Urologie, 2020 Oct 10-11, virtual.

Background

An efficient UTI treatment constitutes a major health need as frequent recurrences occur and antimicrobial resistance rises.
One way of bacteria to inactivate antibiotics is through their degradation. The β-lactamases, such as chromosomal AmpC β-lactamase (AmpC) or extended-spectrum β-lactamase (ESBL), are a large group of hydrolysing enzymes that inactivate β-lactam drugs (e.g., penicillins). *E. coli* is the most common causative agent of cystitis and AmpC- and ESML-producing strains exist and are resistant to many agents.
Given the paucity of new therapies, it is crucial to determine whether bacteria continue to be susceptible to old antibiotics.
The European Association of Urology Research Foundation and the European Section of Infection in Urology endorsed the project.

Aims

An international microbiological surveillance study denominated SURF (that stands for SUsceptibility and Resistance of uropathogens to Fosfomycin in comparison with other antimicrobial agents) was carried out to assess the susceptibility of isolates from women with UTIs to fosfomycin and other antimicrobials. Clinical implications of SURF data on empirical treatment of uncomplicated urinary tract infections in women were also determined.

Materials and methods

Twenty centres from five countries (Belgium, Italy, Russia, Spain, United Kingdom) collected bacterial isolates from urine samples from female patients affected by community-acquired lower urinary tract infections between April and November 2019. Bacterial identification and susceptibility testing were performed for all isolates.

Results

A total of 2848 isolates were identified in urine samples and tested for antimicrobial susceptibility; 473 (16.6%) were originated from labs in Belgium, 581 (20.4%) in Italy, 565 (19.8%) in Spain, 393 (13.8%) in the United Kingdom, and 836 (29.3%) in Russia.
E. coli was the most common urological pathogen isolated from 2064 (72.5%) of the eligible urine samples from all countries involved in the study. The second most common bacterium was *K. pneumoniae* (237; 8.3%); it took second place in all countries but the United Kingdom, in which the second most frequent uropathogen was *Enterococcus* spp (***Figure 1***).

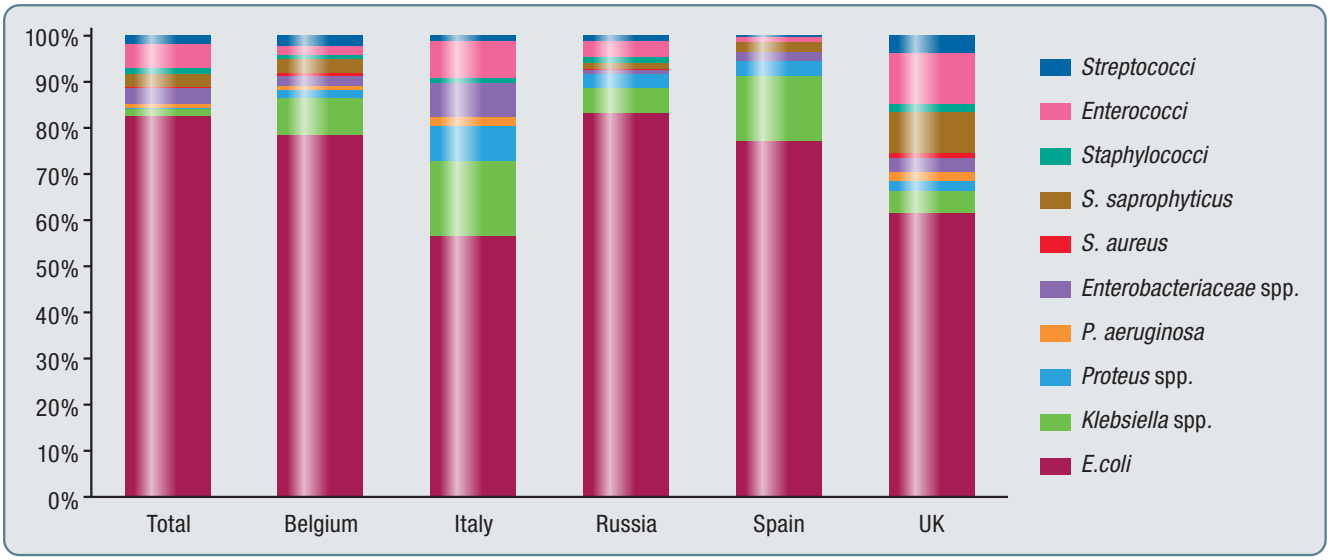

Figure 1. Distribution of species present in isolates stratified by the country of origin included in the study (adapted from Figure 3 of Johansen et al.)

Three agents were active against >90% of *E. coli* isolates: nitrofurantoin (98.5%), fosfomycin (96.4%) and mecillinam (91.8%). By contrast, ciprofloxacin was active against 77.4%, cefpodoxime against 83.1%, and co-trimoxazole against 69.2% of isolates, whilst only 48.8% of *E. coli* isolates were susceptible to ampicillin (***Figure 2***).

A susceptibility rate of >90% was obtained for fosfomycin (92%) and nitrofurantoin (95.7%) when testing ESBL-producing uropathogens. Other agents performed poorly (***Figure 3***). ESBL production was estimated by analysing all isolates identified as *E. coli* or *Klebsiella* spp. and found to be resistant to cefpodoxime. It is possible that this value may be overestimated as isolates may also owe cefpodoxime resistance to other mechanisms, *e.g.*, AmpC β-lactamase.

Multidrug-resistant (MDR) *E. coli* strains were defined as isolates resistant to more than three agents from unrelated antibiotic classes, with amoxicillin-clavulanate and ampicillin, and cefpodoxime and cephalexin being related. Italy had the highest rate of MDR (33.3%), followed by Russia (30.0%), Belgium (15.6%), UK (11.1%) and Spain (10%).

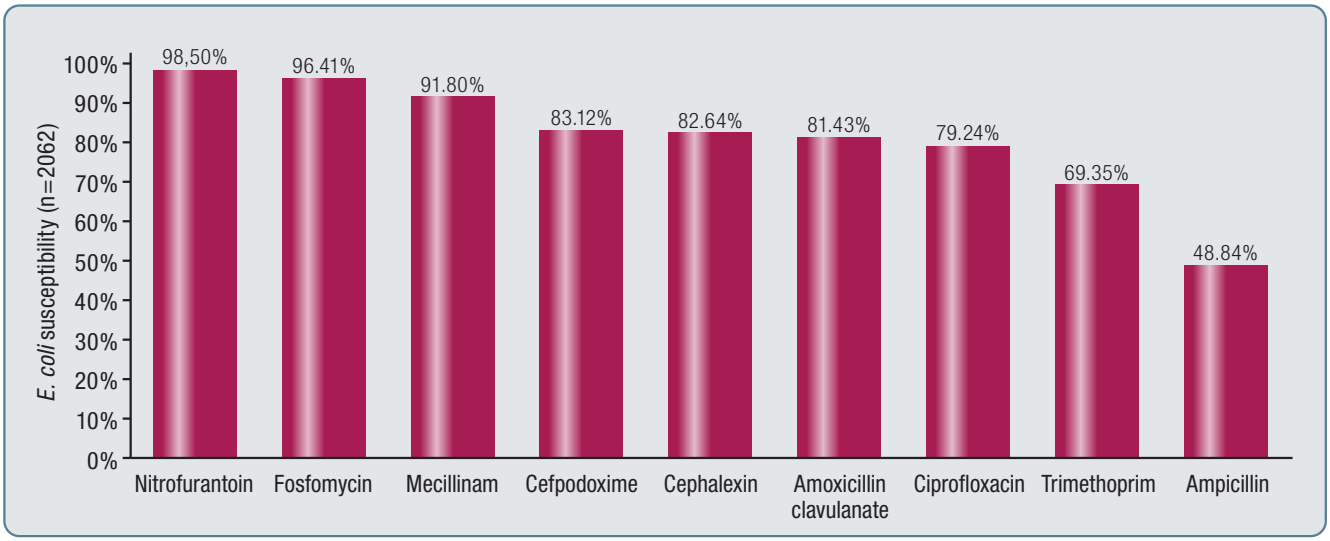

Figure 2. Frequency of the susceptibility of *E. coli* present in 2062 isolates to common antibiotics included in the study (adapted from Figure 2 of Johansen et al.)

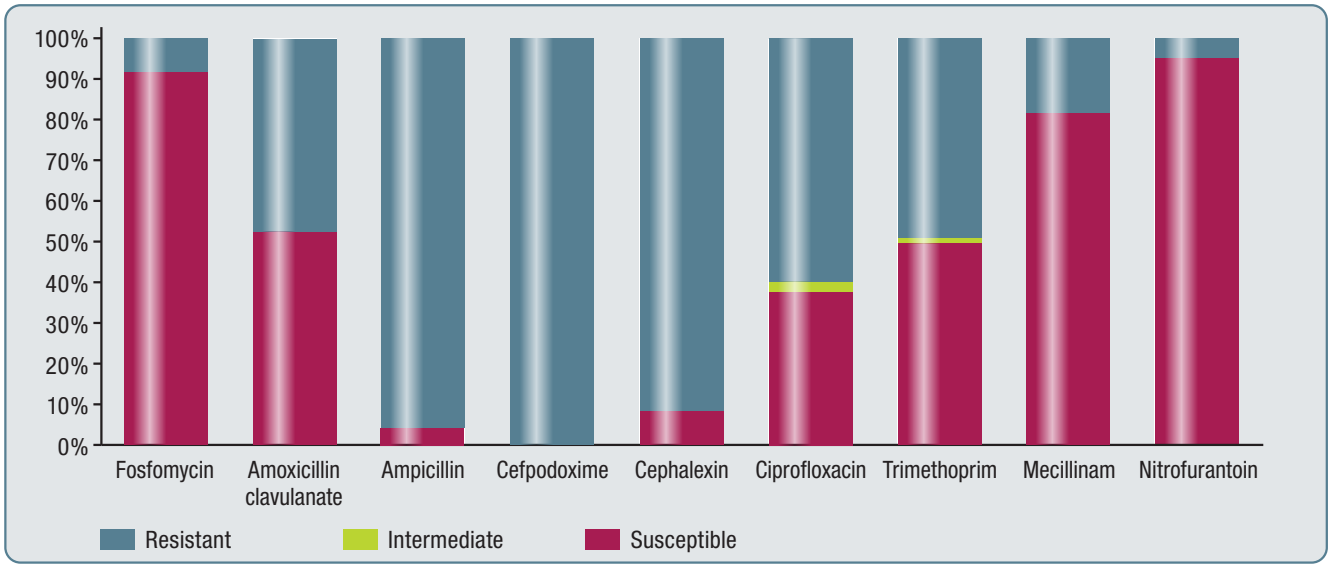

Figure 3. Susceptibility patterns of ESBL-producing *E. coli* isolates included in the study (adapted from Figure 2 of Cai et al.)

Conclusions

Fosfomycin possesses a good overall activity against *E. coli* isolated from community-acquired UTIs in women, together with nitrofurantoin and mecillinam, whilst the efficiency of other standard treatments is heavily compromised by resistance. Indeed, despite more than 30 years of extensive clinical use, the most common uropathogens display an optimal susceptibility rate (>90%) to fosfomycin, confirming that it is a valid first-line treatment option for women suffering from cystitis.

Moreover, the SURF data confirm that fosfomycin is not inferior to nitrofurantoin in terms of the incidence of antimicrobial resistance, further supporting the guidelines for empirical treatment of UTIs.

Key points

- *E. coli* was the most common uropathogen isolated from 2064 (72.5%), with *K. pneumoniae* being the second (237; 8.3%). MDR strains constitute circa 10% of uropathogens isolated in the countries included in the study.
- Fosfomycin was active against >90% of *E. coli* isolates. Moreover, the susceptibility to fosfomycin was >90% for ESBL-producing isolates.
- SURF data show that fosfomycin is not inferior to nitrofurantoin in terms of overall activity against *E. coli* and low incidence of resistance.

Clinical significance

Notwithstanding the long history of the use of fosfomycin trometamol, most uropathogens continue to be susceptible to this agent and bacterial resistance to fosfomycin is rare. In view of a dearth of novel agents to treat UTIs, these results endorse the clinical utility of fosfomycin.

Section III. The comparison of clinical outcomes obtained using fosfomycin trometamol versus other antimicrobial agents in uncomplicated UTIs in nonpregnant women

Adapted from:
Cai T, Tamanini I, Tascini C, Köves B, et al. Fosfomycin Trometamol versus Comparator Antibiotics for the Treatment of Acute Uncomplicated Urinary Tract Infections in Women: A Systematic Review and Meta-Analysis. J Urol. 2020 Mar;203(3):570-578.

Background

Over recent years, the therapy for acute uncomplicated UTI has changed as antimicrobial resistance increased and the principles of antimicrobial stewardship have been introduced.
Surveillance reports show an alarming increase in uropathogens resistant to fluoroquinolones and other antibiotics commonly used to treat UTIs, not seen for fosfomycin. International guidelines list fosfomycin as a first-line treatment for uncomplicated cystitis, but how does it compare to other treatments?

Aims

The objective was to compare the clinical and microbiological effectiveness, and safety profile of fosfomycin versus comparator antibiotics in women with acute uncomplicated cystitis in a meta-analysis of relevant randomised controlled trials (RCT).

Materials and methods

Literature Search Strategy
PubMed®, Cochrane CENTRAL (Central Register of Controlled Trials) and Scopus® databases were interrogated for search terms "(fosfomycin) AND (urinary tract infection OR cystitis)" and filtered for clinical trial, humans, female, English language and adults.

Selection Criteria for Meta-Analysis
All RCTs were included that were carried out in nonpregnant females older than 18 years old with microbiologically confirmed and/or clinically suspected acute uncomplicated cystitis randomised to fosfomycin or to a comparator antibiotic.

Outcomes
The study primary endpoint was clinical or microbiological success, defined as the complete (cure) and/or incomplete resolution of symptoms (improvement) at the end of the treatment or microbiological eradication. Microbiological success was defined as eradication of the infecting strain with no recurrent bacteriuria after treatment.

Results

RCT Inclusion
There were 539 potentially relevant articles, of which 15 eligible RCTs, totalling 2,295 patients, were included in the meta-analysis. Studies were published between 1990 and 2018; 13/15 before the year 2000. A total of 14 studies were used for microbiological eradication analysis, whereas 11/15 were used to assess clinical resolution and adverse effects.

Comparators and treatment schedules
All patients randomised to the fosfomycin treatment arm received a 3-gram single dose treatment with fosfomycin. Fosfomycin was compared to fluoroquinolones (norfloxacin or ciprofloxacin) in five, to trimethoprim or co-trimoxazole in three, to

nitrofurantoin in three, and to β-lactams (cefalexin and amoxicillin) in two trials. Moreover, in two studies fosfomycin was compared to >1 antibiotic (ciprofloxacin, nitrofurantoin or co-trimoxazole). Single dose fosfomycin was compared to a single dose treatment of amoxicillin, norfloxacin, ofloxacin/co-trimoxazole or trimethoprim in five studies. The remaining 10 trials compared a single dose fosfomycin to longer treatment schedules.

Clinical Cure

Eleven of 15 RCTs were used for the evaluation of clinical cure. No significant difference in terms of clinical resolution was found when all comparators were combined in a total of 1,976 patients from 11 RCTs (OR 1.16, 95% CI 0.91-1.49, p=0.13). Clinical success (cure or improvement) in women with cystitis who were treated with fosfomycin compared with other antibiotic agents is shown in ***Figure 1***.

Microbiological eradication

Fourteen of the 15 RCTs were analysed for the evaluation of microbiological eradication. No significant difference in terms of microbiological eradication was found in in a total of 2,052 patients (OR 1.03, 95% CI 0.83-1.30, p=0.09). The forest plot in ***Figure 2*** shows microbiological success of fosfomycin compared with other antibiotic agents in women with cystitis.

Safety Outcomes

Eleven RCTs provided data for safety outcome evaluation. There were no differences in adverse effects in a total of 1,816 patients (OR 1.17, 95% CI 0.86-1.58, p=0.33; ***Figure 3***). Most adverse effects reported for fosfomycin were transient and short-lived, and were of the gastrointestinal type. There were no study withdrawals due to adverse events in any compared treatment groups in the three trials showing relevant data.

Conclusions

A single dose of oral fosfomycin is not inferior to comparator antibiotic regimens in terms of clinical and microbiological effectiveness, and safe-

	FT		Other ABTs			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Boerema JB. et al, 1990	6	61	2	50	1.0%	2.46 (0.52, 11.66)	
Ceran N. et al, 2010	13	77	12	65	4.3%	0.91 (0.45, 1.86)	
Crocchlolo P. et al, 1990	2	19	4	17	1.0%	0.45 (0.09, 2.14)	
Elhanan G. et al, 1994	5	58	5	54	1.7%	0.93 (0.29, 3.04)	
Gupta K. et al, 2005	18	20	38	42	26.5%	0.99 (0.83, 1.19)	
Harvard Davis R. et al, 1990	4	26	9	25	2.1%	0.43 (0.15, 1.21)	
Huttner A. et al., 2018	102	241	73	244	20.4%	1.41 (1.11, 1.80)	
Naber K. et al, 1990	8	150	9	158	2.6%	0.94 (0.37, 2.36)	
ReynaertJ. et al, 1990	1	116	5	16	0.6%	0.20 (0.03, 1.53)	
Stein GE. et al, 1999	22	229	24	217	6.7%	0.87 (0.50, 1.50)	
Van Pienbroek E. et al, 1993	81	92	84	99	33.2%	1.04 (0.93, 1.16)	
Total (95% CI)		**989**		**987**	**100.0%**	**1.04 (0.89, 1.21)**	
Total events	262		265				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.98$, df = 10 (P = 0.13); $I^2 = 33\%$

Test for overall effect: Z = 0.49 (P = 0.62)

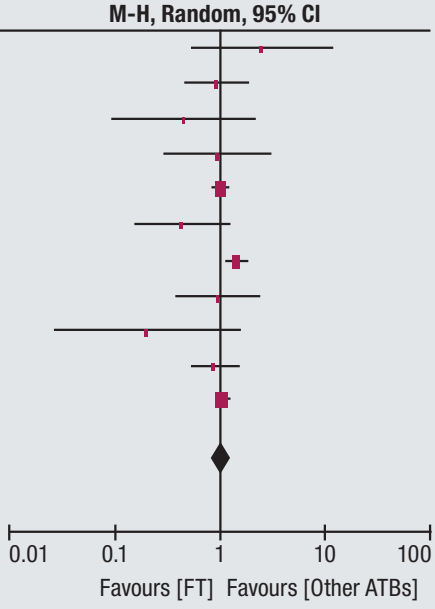

Figure 1. Forest plot of clinical resolution *ABTs*, antibiotics. *Event*, recurrent UTI. Adapted from the original Figure 2.

Study or Subgroup	FT Events	FT Total	Other ABTs Events	Other ABTs Total	Weight	Risk Ratio M-H, Random, 95% CI
Boerema JB. et al, 1990	1	61	2	50	0.6%	0.41 (0.04, 4.39)
Ceran N. et al, 2010	31	77	14	65	8.8%	1.87 (1.09, 3.20)
Crocchiolo P. et al, 1990	2	17	4	19	1.4%	0.56 (0.12, 2.68)
de Jong Z. et al, 1991	2	33	4	30	1.3%	0.45 (0.09, 2.31)
Elhanan G. et al, 1994	5	58	9	54	3.1%	0.52 (0.18, 1.45)
Gupta K. et al, 2005	19	20	41	42	25.4%	0.97 (0.87, 1.09)
Harvard Davis R. et al, 1990	9	26	13	25	6.7%	0.67 (0.35, 1.27)
Huttner A. et al, 2018	60	163	46	175	15.8%	1.40 (1.02, 1.93)
Minassian MA. et al, 1998	30	177	14	84	8.0%	1.02 (0.57, 1.81)
Naber K. et al, 1990	19	150	17	158	7.3%	1.18 (0.64, 2.18)
Neu HC. et al, 1990	15	80	22	78	8.0%	0.66 (0.37, 1.18)
Reynaert J. et al, 1990	2	16	2	16	1.1%	1.00 (0.16, 6.25)
Selvaggi FP. et al, 1990	7	28	4	25	2.8%	1.56 (0.52, 4.71)
Stein GE. et al, 1999	22	168	30	157	9.6%	0.69 (0.41, 1.14)
Total (95% CI)		**1074**		**978**	**100.0%**	**0.99 (0.81, 1.20)**
Total events	224		222			

Heterogeneity: Tau² = 0.04; Chi² = 20.06, df = 13 (P = 0.09); I² = 35%

Test for overall effect: Z = 0.15 (P = 0.88)

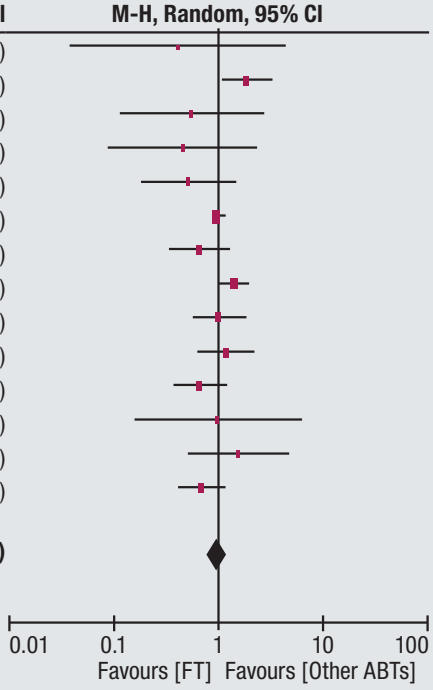

Figure 2. Forest plot of microbiological resolution. *ABTs*, antibiotics. *Event*, recurrent UTI. Adapted from the original Figure 3.

Study or Subgroup	FT Events	FT Total	Other ABTs Events	Other ABTs Total	Weight	Risk Ratio M-H, Random, 95% CI
Boerema JB. et al, 1990	10	61	2	50	4.2%	4.10 (0.94, 17.85)
Ceran N. et al, 2010	3	77	2	65	2.9%	1.27 (0.22, 7.35)
Crocchiolo P. et al, 1990	3	17	2	19	3.3%	1.68 (0.32, 8.86)
de Jong Z. et al, 1991	9	33	8	30	12.9%	1.02 (0.45, 2.31)
Elhanan G. et al, 1994	0	58	3	54	1.1%	0.13 (0.01, 2.52)
Gupta K. et al, 2005	0	0	0	0		Not estimable
Harvard Davis R. et al, 1990	0	26	0	25		Not estimable
Huttner A. et al, 2018	15	241	20	244	19.6%	0.76 (0.40, 1.45)
Minassian MA. et al, 1998	0	0	0	0		Not estimable
Naber K. et al, 1990	17	250	17	246	19.5%	0.98 (0.51, 1.88)
Neu HC. et al, 1990	7	80	9	78	9.9%	0.76 (0.30, 1.94)
Reynaert J. et al, 1990	1	16	1	16	1.3%	1.00 (0.07, 14.64)
Selvaggi FP. et al, 1990	0	28	0	25		Not estimable
Stein GE. et al, 1999	20	168	21	157	24.2%	0.89 (0.50, 1.58)
Van Pienbroek E. et al, 1993	7	116	0	115	1.1%	14.87 (0.86, 257.40)
Total (95% CI)		**1171**		**1124**	**100.0%**	**0.98 (0.72, 1.33)**
Total events	92		85			

Heterogeneity: Tau² = 0.01; Chi² = 10.56, df = 10 (P = 0.39); I² = 5%

Test for overall effect: Z = 0.12 (P = 0.91)

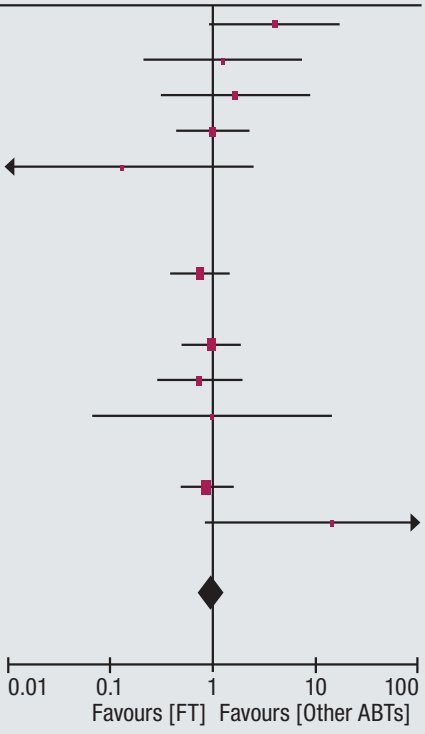

Figure 3. Forest plot of adverse events in women with cystitis treated with fosfomycin versus other antibiotic agents. Adapted from the original Figure 4.

ty profile in females with microbiologically confirmed and/or clinically suspected acute uncomplicated cystitis. Being a single dose, its prescription is associated with high compliance of patients. Given its favourable pharmacological characteristics, oral fosfomycin is to be considered a first-choice agent in the treatment of uncomplicated UTI.

Key points

- Fosfomycin was not inferior to comparator agents in terms of clinical efficacy in women with microbiologically confirmed and/or clinically suspected acute uncomplicated cystitis.
- A single dose of fosfomycin achieved the same clinical efficacy as comparator antibiotics with longer treatment schedules (several days).
- Fosfomycin treatment was associated with only limited and transient adverse events confirming a favourable safety profile.
- The administration of a single dose of fosfomycin was associated with a low risk of bacterial resistance development.
- The single-dose treatment regimen ensures high compliance due to convenience for the patients.

Clinical significance

Proven clinical efficacy, infrequent side effects and low risk of resistance of fosfomycin trometamol are characteristics of great importance in the management of uncomplicated cystitis. These characteristics together with the convenience of a single-dose treatment scheme support fosfomycin trometamol as a first-line antibiotic to treat uncomplicated UTIs.

Section IV. The safety of fosfomycin trometamol to treat UTIs during pregnancy

1. German Embryotox Pharmacovigilance Institute data

Adapted from:
Philipps W, Fietz AK, Meixner K, Bluhmki T, Meister R, Schaefer C, Padberg S. Pregnancy outcome after first-trimester exposure to fosfomycin for the treatment of urinary tract infection: an observational cohort study. Infection. 2020 Feb;48(1):57-64.

Background

UTIs and asymptomatic bacteriuria (ASB) are the commonest bacterial disorders in pregnancy. Untreated UTIs increase risks for adverse pregnancy outcomes such as preterm birth, low birth weight and preeclampsia, and have to be treated. Fosfomycin is recommended to treat lower UTIs in non-pregnant and pregnant women, although no studies evaluated specifically fosfomycin's safety in pregnancy.

Aims

The study was performed to evaluate the teratogenic risk and pregnancy outcomes in women exposed to fosfomycin in the first trimester of pregnancy.

Materials and Methods

Data enrolment
Data were acquired prospectively by the German Embryotox Pharmacovigilance Institute in Berlin. Women received a questionnaire assessing drug exposure and medical history at first contact, and a follow-up form concerning gestational pathologies and neonatal assessment 8 weeks after the due date.

Study cohorts
The exposed cohort included pregnant women with fosfomycin use during the first trimester. The comparison cohort constituted randomly selected patients not exposed to fosfomycin, known teratogens or treated for cancer.

Outcome variables
The primary endpoint of this study was the risk of major birth defects and spontaneous abortion (SAB). Secondary endpoints were preterm delivery, birth weight, and the rate of electively terminated pregnancies (ETOP).

Results

Patient inclusion
One hundred fifty-two pregnancies exposed to fosfomycin were compared to 456 randomly selected not exposed pregnancies (ratio 1:3). The cohorts were similar in terms of maternal characteristics. First-trimester exposure to fosfomycin occurred to treat UTIs at a single 3-gram oral dose.

Pregnancy outcomes
Ninety-five (144/152) percent of pregnancies in exposed women resulted in live births, 5 pregnancies in SAB and 3 in ETOP; there were no stillbirths. In the 456 control cases, SABs were encountered in 53, ETOPs in 14 and stillbirths in 2. The cumulative SAB incidence was lower in the exposed cohort (6.2% vs. 23.1%, ***Table 1***

Table 1. Pregnancy outcomes in the two cohorts (Adapted from Table 2 of the original paper)

	Fosfomycin cohort	Comparison cohort	Measure of association	
Pregnancy outcomes	*n*	*n*	HR (95% CI)	HR adj. (95% CI)
Pregnancies	152	456[a]		
Live birth	144	388		
Spontaneous abortion	5	53	0.32 (0.13-0.80)	0.35 (0.14-0.90)
ETOP	3	14	0.61 (0.17-2.12)	0.84 (0.23-3.10)
Stillbirth	0	2		
Live-born infant	146	397		
Birth defects	*n*, % (95% CI)	*n*, % (95% CI)		
Major birth defects	1/146 0.7 (0.04-4.33)	15/399[b] 3.8 (2.20-6.26)		
All birth defects	15/147[c] 10.2 (6.02-16.55)	83/402[d] 20.6 (16.86-25.00)		
Preterm birth	*n* (%) 11/146 (7.5)	*n* (%) 49/397 (12.3)	OR (95% CI) 0.58 (0.29-1.15)	OR adj. (95% CI) 0.83 (0.37-1.87)
Neonatal weight, g	Median (IQR) 3350 (3145-3660)	Median (IQR) 3310 (3000-3700)	SDS diff. (95% CI) 0.02 (-0.17 to 0.21)	SDS diff. adj. (95% CI) 0.05 (-0.14 to 0.24)

HR, hazard ratio; *adj.*, adjusted; *CI*, confidence interval; *ETOP*, elective termination of pregnancy; *OR*, odds ratio; *IQR*, interquartile range; *SDS diff.*, standard deviation score difference.
[a] Including 1 pregnancy of twins resulting in 1 live-born infant and 1 spontaneous abortion
[b] Including 2 ETOP
[c] Including 1 ETOP
[d] Including 1 spontaneous abortion and 4 ETOP

and ***Figure 1***), with a statistically significant difference (HR adjusted 0.35; 95% CI 0.14–0.90).

Major birth defects

Birth defects were seen in 1/146 fosfomycin-exposed neonates (0.7%; 95% CI 0.04–4.33%) and in 15/399 control neonates/fetuses (3.8%; 95% CI 2.2–6.26%). Considering a baseline risk of 3–5% for major birth defects, no increased rates were detected in either cohort.

Neonatal characteristics

There were no notable differences in neonatal parameters between the two cohorts.

Conclusions

There is no increased risk of adverse pregnancy outcome after fosfomycin exposure during early pregnancy. These data should be confirmed in larger studies.

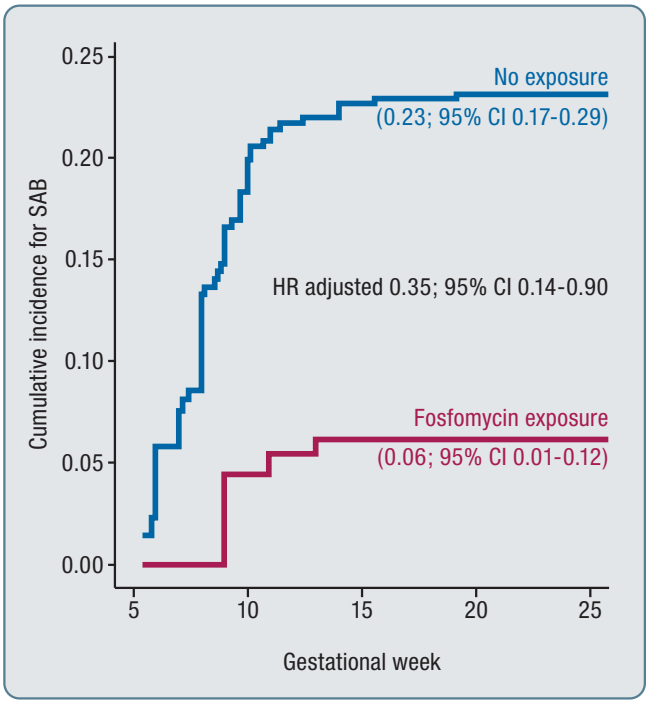

Figure 1. Aalen–Johansen estimator for the cumulative incidence of spontaneous abortion in exposed versus non-exposed women at gestational week 5. (Adapted from Figure 2 of the original paper)

Key points

- This is the first study specifically examining the teratogenic risk and pregnancy outcome after fosfomycin exposure in the first trimester of pregnancy.
- No differences in rates of major birth defects, SAB, ETOP, stillbirth and in neonatal characteristics were observed between exposed/non-exposed pregnant women.

Clinical significance

These findings support the recommendation to use fosfomycin trometamol in early pregnancy, in cases with resistance or allergies to other recommended antibiotics.

2. French EFEMERIS data

Adapted from:
Araujo M, Sicard D, Hurault-Delarue C, Montastruc JL, et al. Exposure to fosfomycin trometamol during pregnancy: a descriptive study using the EFEMERIS database. Abstract P107 2019. Fundamental and Clinical Pharmacology 2019, 33 (Suppl. S1), 23–47.
and
Araujo M, Benevent J, Sicard D, Damase-Michel C. Teratogenic risk of fosfomycin during the first trimester of pregnancy: A study with two complementary approaches within the EFEMERIS database. Abstract #14. Reproductive Toxicology 88 (2019) 133–150.

Background

Since 2015, fosfomycin has been recommended as first-line bactericidal antibiotic for UTIs in pregnant women. In December 2018, the European Medicines Agency asked for a re-evaluation of fosfomycin's safety in pregnancy.

Aims

Two studies aimed to demonstrate fosfomycin's safety during pregnancy by analysing pregnancy outcomes and teratogenic risk.

Materials and methods

Data collection

The studies mined EFEMERIS data, the French database containing records on drugs prescribed and dispensed during pregnancy and its outcomes, from July 2004 to December 2017.

Cohort selection

The outcome study included pregnant women with at least one prescription/dispensation of fosfomycin. The teratogenic risk study adopted a

conventional approach comparing: (1) pregnancies exposed to fosfomycin (n = 2,610), (2) pregnancies exposed to nitrofurantoin (n = 830) and (3) pregnancies not exposed to antibiotics (n = 109,479), and a sibling-based approach, pairing exposed and unexposed siblings (1,143 discordant pairs).

Results

A total of 5,336 women were included in the outcome analysis, of whom 44.2% took fosfomycin during the first, 38.5% during the second, and 26.1% during the third trimester.

Pregnancy loss occurred in 6.6% of exposed women versus 5.8% of pregnancy loss in the EFEMERIS database (P = 0.01). The incidence of preterm birth, neonatal characteristics and the congenital anomaly rate were similar in both cohorts.

Using the conventional approach, exposure to fosfomycin was not associated with a statistically significant teratogenic risk compared to the nitrofurantoin group (aOR 0.79 [0.46-1.35], P = 0.39), or the unexposed group (aOR 1.02 [0.76-1.37], P = 0.88). The sibling-based approach confirmed the findings.

Conclusions

The studies showed reassuring results on pregnancy outcomes after prenatal exposure to fosfomycin, although these data should be confirmed in larger studies.

Key points

- The EFEMERIS database is a valid resource to study drug influence on pregnancy outcomes.
- The rate of congenital anomalies in women exposed or not exposed to fosfomycin was similar.
- Exposure to fosfomycin in the first trimester of pregnancy carried no teratogenic risk compared to exposure to nitrofurantoin or no exposure to antibiotics.

Clinical significance

Based on the results of these two studies, the use of fosfomycin trometamol in pregnancy is not associated with an increased risk of birth defects compared to pregnancies not exposed to either systemic antibiotics or to fosfomycin or to nitrofurantoin during the first trimester.