

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	EVALUATION OF THREE-DOSE FOSFOMYCIN TROMETHAMINE IN THE TREATMENT OF PATIENTS WITH URINARY TRACT INFECTIONS: AN UNCONTROLLED, OPEN-LABEL, MULTICENTER STUDY
<b>AUTHORS</b>	Chen, Shan; Qiao, Lu-Dong; Zheng, Bo; Yang, Yong; Zhang, Kai; Guo, Hong-Feng; Yang, Bo; Niu, Yuan-Jie; Wang, Yi; Shi, Ben-Kang; Yang, Wei-Min; Zhao, Xiao-Kun; Gao, Xiao-Feng; Chen, Ming

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Naber , Kert Technical University of Munich, Germany
<b>REVIEW RETURNED</b>	14-Oct-2013

<b>GENERAL COMMENTS</b>	<p>It is an interesting open-label, non-controlled, multicenter clinical trial using three doses of FT in the treatment of acute uncomplicated cystitis, recurrent UTI or complicated UTI. I have only a few questions/comments.</p> <p>1) From exclusion criteria we learn that acute pyelonephritis or acute episode (better than bout) of chronic pyelonephritis were not included. Therefore I suggest a more specific terminology in: Page 3, lines 19/21; page 4, line 6 and 37/39; page 7, lines 9/11; page 18, line 4; such as "...patients with acute uncomplicated cystitis, recurrent lower UTI or complicated lower UTI" (lower should be added because pyelonephritis was excluded). Page 3, line 9: "...to treat lower urinary tract infections..." (lower should be added as well)</p> <p>2) Microbiological efficacy: it is completely unusual to consider "partially cleared" as an "effective" result. By change, no patient felt into this category. Therefore, I suggest to skip the category "partially cleared" and include this category into "not cleared". To categorize "replacement" or "reinfection" also as effective therapy is sometimes done, but to my opinion not correct, because it is an "unwanted" outcome. Therefore I suggest to reorganize Table 3 as follows:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: left;">Diagnosis</td> <td style="text-align: center;">Total Eradication</td> <td style="text-align: center;">Persistence</td> <td style="text-align: center;">Replacement/reinfection</td> </tr> <tr> <td style="text-align: left;">N (100%)</td> <td style="text-align: center;">N (%)</td> <td style="text-align: center;">N (%)</td> <td style="text-align: center;">N (%)</td> </tr> <tr> <td style="text-align: left;">AUC</td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: left;">Recurrent UTI</td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: left;">Complicated UTI</td> <td></td> <td></td> <td></td> </tr> </table> <p>By the way: the usual terminology is for cleared-eradication and for not cleared persistence. Usually for other bacteria only the term reinfection is used, but I like the differentiation between replacement without symptoms and reinfection with symptoms. Therefore the two terms should be used, but could be summarized in the table ( or not, whatever the authors like better).</p>	Diagnosis	Total Eradication	Persistence	Replacement/reinfection	N (100%)	N (%)	N (%)	N (%)	AUC				Recurrent UTI				Complicated UTI			
Diagnosis	Total Eradication	Persistence	Replacement/reinfection																		
N (100%)	N (%)	N (%)	N (%)																		
AUC																					
Recurrent UTI																					
Complicated UTI																					

	As limitation of the study it should also be mentioned that the study is not controlled. All in all, the study is well performed and presented.
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<b>REVIEWER</b>	Tasbakan, Mehmet Ege University
<b>REVIEW RETURNED</b>	14-Oct-2013

<b>GENERAL COMMENTS</b>	<p>1. There is no data about strains on positive cultures and resistance profiles. Is it possible to give this info on table.</p> <p>2. In methods it is not clear that if patient has clean culture at day 8 but positive by same bacteria on day 15. How did they define this "not cleared, partially cleared or relaps. Could you state clearly this situation?</p> <p>3. You did not mention about fosfomycin resistance in discussion. I recommend you to check this article " Is there a rise in resistance rates to fosfomycin and other commonly used antibiotics in Escherichia coli-mediated urinary tract infections? A perspective for 2004 – 2011. PULLUKCU H, AYDEMİR S, TAŞBAKAN MI,, SIPAHI OR, HALL FC, TUNGER A. Turk J Med Sci 2013; 43(4): 537-541"</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Name Kurt G. Naber

Institution and Country Technical University of Munich, Germany

Please state any competing interests or state 'None declared': Consultant, Investigator, Speakers Bureau of Zambon and Pierre Fabre (manufacturer and Distributor of FosfomycinThromethamine)

It is an interesting open-label, non-controlled, multicenter clinical trial using three doses of FT in the treatment of acute uncomplicated cystitis, recurrent UTI or complicated UTI.

I have only a few questions/comments.

1. From exclusion criteria we learn that acute pyelonephritis or acute episode (better than bout) of chronic pyelonephritis were not included. Therefore I suggest a more specific terminology in: Page 3, lines 19/21; page 4, line 6 and 37/39; page 7, lines 9/11; page 18, line 4; such as "...patients with acute uncomplicated cystitis, recurrent lower UTI or complicated lower UTI" (lower should be added because pyelonephritis was excluded).

Page 3, line 9: "...to treat lower urinary tract infections..." (lower should be added as well)

Response: to define more specifically the UTIs described in this study, the term "lower" was added where applicable. Also, "bout" was changed to "episode" as suggested.

2. Microbiological efficacy: it is completely unusual to consider "partially cleared" as an "effective" result. By change, no patient fell into this category. Therefore, I suggest to skip the category "partially cleared" and include this category into "not cleared".

Response: the "partially cleared" category was removed.

3. To categorize "replacement" or "reinfection" also as effective therapy is sometimes done, but to my opinion not correct, because it is an "unwanted" outcome. Therefore I suggest to reorganize Table 3 as follows:

Diagnosis Total Eradication Persistence Replacement/reinfection

N (100%) N (%) N (%) N (%)

AUC

Recurrent UTI

Complicated UTI

Response: Table 3 was reorganized as suggested.

4. By the way: the usual terminology is for cleared-eradication and for not cleared persistence.

Usually for other bacteria only the term reinfection is used, but I like the differentiation between replacement without symptoms and reinfection with symptoms. Therefore the two terms should be used, but could be summarized in the table ( or not, whatever the authors like better).

Response: The term “cleared” was replaced with “eradication” and “not cleared” with “ persistence”, as suggested.

5. As limitation of the study it should also be mentioned that the study is not controlled.

All in all, the study is well performed and presented.

Response: The fact that the study was uncontrolled is now mentioned in the Discussion section, as a limitation of the study:

“Another shortcoming of the study is the lack of a control group. This is due to the fact that our primary objective was to evaluate clinical, microbiological and overall efficacy of fosfomycin tromethamine, an antibiotic which is widely used abroad, but less in China, for the treatment of urinary tract infection.”

Reviewer Name Meltemİsıkgöz Tasbakan

Institution and Country Ege University Medical Faculty Infectious Disease and Clinical Microbiology Department

Please state any competing interests or state 'None declared': None declared

1. There is no data about strains on positive cultures and resistance profiles. Is it possible to give this info on table.

Response: Bacteriology results will be presented in another manuscript. This is now mentioned in the Microbiological efficacy subsection:

“Causative pathogens and their resistance profiles will be presented elsewhere.”

2. In methods it is not clear that if patient has clean culture at day 8 but positive by same bacteria on day 15. How did they define this "not cleared, patially cleared or relaps. Could you state clearly this situation?

Response: This situation was defined as “not cleared”, now renamed as “persistence”:

“persistence (pathogenic bacteria were still present on days 8 and 15 or the patient had a negative culture at day 8, but positive for the same bacteria on day 15)”

3. You did not mention about fosfomycin resistance in discussion. I recommend you to check this article " Is there a rise in resistance rates to fosfomycin and other commonly used antibiotics in Escherichia coli-mediated urinary tract infections? A perspective for 2004 – 2011.PULLUKCU H, AYDEMİR S, TAŞBAKAN MI,, SİPAHI OR, HALL FC, TUNGER A.Turk J Med Sci 2013; 43(4): 537-541'

Response: we would like to thank the reviewer for the suggestion. The reference was included, along with a sentence on fosfomycin resistance changes in UTI pathogens:

“Fortunately, unlike resistance against cephalosporins and fluoroquinolones of common UTI pathogens, the resistance rate to fosfomycin has not increased in the recent years.[16]”