Editorial

Support for nitrofurantoin in uncomplicated urinary tract infections

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Comment on: 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 in Women: A Randomized Clinical Trial. JAMA 2018;319:1781-9.

Received: 01 August 2018; Accepted: 20 August 2018; Published: 23 August 2018.

doi: 10.21037/gpm.2018.08.01

View this article at: http://dx.doi.org/10.21037/gpm.2018.08.01

Urinary tract infections (UTI) are among the most common bacterial infections with a high burden of disease; nearly every other woman is affected once in her lifetime (1).

Antibiotic therapy is recommended as a first line therapy, consequently UTI are responsible for a relevant share of all antibiotic prescriptions worldwide. Due to emerging resistance rates and a lack of new drugs in the market pipeline our therapeutic options should be used according to the principles of antibiotic stewardship.

Inappropriate prescriptions of broad spectrum antibiotics—when a more targeted therapy is sufficient—contribute to the increase in resistance rates.

Fluoroquinolones for example have an excellent effectivity in UTI, but should be reserved for complicated infections. The uncritical use of quinolones (not only in uncomplicated UTI) has contributed to increasing resistance rates worldwide. As a result, many guidelines on UTI as well as the US Food and Drug Administration give an explicit advice against using fluoroquinolones in uncomplicated UTI (2-4).

Which therapy can be recommended?

Promoting symptomatic (non-antibiotic) therapy for UTI is a reasonable alternative approach, taking into account, that the majority of women experienced in UTI prefer a non-antibiotic therapy (1). Some recent trials proved the effectiveness of a symptomatic therapy with ibuprofen or diclofenac in women UTI (5-7). Refraining from prescribing of antibiotics would certainly have a positive impact on the development of antibiotic resistance. Unfortunately, some caveats must be considered, when offering a symptomatic therapy. Compared with immediate use of antibiotics, a symptomatic treatment is less effective in symptom resolution and is associated with a higher rate of patients developing pyelonephritis. Predicting, which patient would profit from a symptomatic therapy and which would not, remains a task to be completed. Till then, antibiotic therapy will remain the most effective therapeutic option, leaving the question which antibiotic to choose.

The choice of antibiotics is influenced by individual and regional factors. Individual patient factors like allergies, comedication, comorbidities and patients' preferences have to be taken into account during the clinical encounter. Regional factors include local resistance rates and guidelines.

Differences in local resistance rates are a reasonable explanation for different recommendations, but most guidelines on antibiotic prescription do not routinely consider this aspect in their recommendations (8).

Despite of slight differences between countries, nitrofurantoin, pivmecillinam, fosfomycin, trimethoprim or trimethoprim/sulfamethoxazole are the most recommended first-line antibiotics. These drugs have been introduced in the market for more than three decades and are still well established.

Direct comparisons of guideline recommendations (and clinical trials) are hampered by different drug regimes. Dosing schemes for nitrofurantoin for example vary between 3 and 7 days and different doses (9).

Despite its common use for UTI, resistance rates for nitrofurantoin are still very low with rates of less than 5%, reported in a recent meta-analysis (10).

In contrast, fosfomycin-trometamol is a single dose drug

only, thus improving adherence and patient acceptance. Since its recommendation in different guidelines, prescription rates increased. Fosfomycin although plays a role in multi-drug resistant infections (i.e., intensive care units) where it is used as intravenous (IV) therapy for longer periods. Nevertheless, resistance rates are still low in most countries and a recent guideline update concluded, that the microbiological collateral damage of using fosfomycin is quite low (2).

In summary, current evidence supports the use of both drugs for treating women with uncomplicated UTI, but a direct comparison with a 5day course of nitrofurantoin is missing. This missing link has now been closed with the study by Huttner *et al.* published in *Journal of the American Medical Association* (*JAMA*) (9). The aim was to assess the comparative efficacy of 5-day macrocrystalline nitrofurantoin (100 mg 3 times/d) and single-dose fosfomycin trometamol (3 g) for clinical resolution of women with uncomplicated UTI.

Adult women with typical symptoms of a UTI and positive dipstick results were included (irrespective of the microbiological results) in this open label trial. The intended sample size of 300 patients per group could not be reached, but 513 patients were enrolled in three study sites. Most patients were outpatients, but at one study site 20% of hospitalized patients were included.

The primary outcome was clinical response within 28 days.

Baseline cultures were positive (defined as $>10^2$ colony-forming units/mL) in 80/75% (nitrofurantoin/fosfomycin group) of the patients included, reflecting a diagnostic accuracy comparable to similar studies in the field. The same holds true for the inclusion/exclusion criteria thus allowing a high generalizability of the results.

As expected, E.coli was the dominant causative agent (57% in the nitrofurantoin/65% in the fosfomycin group), but their share on all bacteria was lower than in similar studies in the ambulatory setting (5-7). Mixed flora was detected in 26% of the cultures—indicating a urine contamination.

The follow up consisted of two visits at 14 and 28 days after inclusion. No information is given if patient symptoms were assessed only retrospectively during the follow up visits (carrying a high risk of recall bias) or via patient diaries or direct contacts.

After 28 days, 70% of the women in the nitrofurantoin group and 58% in the fosfomycin group reported a complete resolution of symptoms (P<0.004). The difference between both groups at day 14 was even higher (75% nitrofurantoin versus 66% fosfomycin, P<0.03). Correspondingly, the rate of microbiological failure was lower in those who were treated with nitrofurantoin (success rate 82% versus 73% after 14 d).

Apart from a higher rate of pyelonephritis in the fosfomycin group (5/247 versus 1/246), data showed no relevant difference in the occurrence of side effects.

The open-labelled study design is a possible limitation, as patients may have perceived the treatment with nitrofurantoin as more intensive.

Fosfomycin has a peak urine concentration for 48 hours only, so that a single-dose could be a disadvantage compared with five-day course of nitrofurantoin. However, a single dose is the recommended therapy scheme by the manufacturer, and most trials (5,11) used this scheme. Alternative prescribing practices such as two doses in 72 hours have only been studied in postmenopausal women yet (12).

Overall Huttner *et al.* have conducted a well-designed trial, used the most relevant outcomes and analyzed their data including intention-to-treat analyses and accounted for missing data. Their results provide a strong endorsement for the role of nitrofurantoin compared to fosfomycin in UTI.

This study may increase clinicians' critical awareness towards clinical effectivity of fosfomycin. Using published and unpublished data, the US Food and Drug Administration concluded that the effect of fosfomycin is inferior to nitrofurantoin, ciprofloxacin and trimethoprim/sulfamethoxazole (13). Higher recurrence rates (within 28 days) in patients receiving fosfomycin were also found in another recent trial by Gagyor *et al.* (2015). It remains unclear if this observation may be dose depend. Perhaps lower doses (2×100 mg) of nitrofurantoin—as recommended in many countries—are equally effective.

In summary, the study by Huttner *et al.* demonstrated a superiority of nitrofurantoin in uncomplicated UTI compared with fosfomycin.

To strengthen a prudent use of antibiotics in the clinical practice, future trials on dosing of antibiotics are still needed, even if the drugs have been on the market for decades.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gynecology and Pelvic Medicine*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm.2018.08.01/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Schmiemann G. Support for nitrofurantoin in uncomplicated urinary tract infections. Gynecol Pelvic Med 2018;1:4.