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Nitrofurantoin vs Fosfomycin:

Rendering a Verdict in a Trial of Acute Uncomplicated Cystitis

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Urinary tract infections (UTIs) are common and contribute a significant burden to population health. In the United States, UTIs account for approximately 10 million ambulatory visits and an estimated \$2 billion in total costs each year.^{1,2} Compared with men, women incur a greater burden of disease, with more than half of women experiencing at least 1 UTI during their lifetime.³ Among women aged 18 to 70 years, acute uncomplicated UTI results in nearly 4 days of genitourinary symptoms and 3 days of restricted activity per episode.⁴

Acute uncomplicated UTI or cystitis refers to symptomatic bladder infection in women without structural abnormalities, urinary instrumentation, or systemic diseases such as immunodeficiency.⁵ Worldwide, acute uncomplicated cystitis is one of the most common indications for antimicrobial prescriptions. In the past decade, more antibiotic prescriptions with varying lengths of treatment for cystitis^{6,7} have contributed to the emergence of multidrug-resistant uropathogens (eg, vancomycin-resistant *Enterococci*, extended-spectrum betalactamase-producing *Enterobacteriaceae*, and carbapenem-resistant *Enterobacteriaceae*).

Accordingly, clinical practice guidelines for acute uncomplicated cystitis were updated by the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases in 2010.⁸ Nitrofurantoin monohydrate/ macrocrystals, 100mg twice daily for 5 days, and fosfomycin tremetamol, 3 g in a single dose, were both recommended regimens for acute uncomplicated cystitis; however, fosfomycin was recognized to have inferior efficacy compared with other recommended regimens.⁸ Additionally, data supporting fosfomycin for treatment of multidrug-resistant uropathogens are limited and lack generalizability.^{9,10} In the United States, the Food and Drug Administration has not approved fosfomycin for the treatment of *Klebsiella* infections, and the interpretation of fosfomycin susceptibility varies worldwide, with different sensitivity thresholds proposed by laboratory regulatory bodies.¹¹

In this issue of *JAMA*, Huttner and colleagues¹² report the results of a multinational, open-label, randomized clinical trial involving 513 nonpregnant women with acute uncomplicated

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cystitis from Switzerland, Poland, and Israel to compare the clinical efficacy of nitrofurantoin, 100 mg 3 times a day for 5 days ($n = 255$), vs a single 3-g dose of oral fosfomycin ($n = 258$). The primary outcome was clinical cure 28 days after completion of therapy, defined as complete resolution of signs or symptoms of infection. In the intention-to-treat analysis at 28 days, 70% ($n = 17\frac{1}{2}/44$) of patients receiving nitrofurantoin achieved clinical cure in contrast to 58% ($n = 139/241$) of patients receiving fosfomycin (difference, 12% [95% CI, 4%–21%]; $P = .004$). These findings were affirmed during an earlier observation point 14 days after completion of therapy. The effect of nitrofurantoin was even more pronounced in subgroup analysis of patients with *Escherichia coli* infection, in which 78% ($n = 80/103$) vs 50% ($n = 55/111$) of patients in the nitrofurantoin vs fosfomycin groups, respectively, experienced clinical cure (difference, 28% [95% CI, 15%–40%]; $P < .001$). Despite the clinical efficacy of nitrofurantoin, there was no significant difference in the duration of symptoms (4 days vs 3 days) or development of pyelonephritis (0.4% vs 2%) between patients receiving nitrofurantoin or fosfomycin, respectively.

Importantly, microbiologic responses were not integrated into the primary outcome and were evaluated as secondary outcomes. Huttner and colleagues¹² posit that a purely clinical outcome is most meaningful for patients, and that a composite clinical and microbiologic outcome would exclude patients without baseline positive urine cultures, which notably represented 27% of randomized patients in their study. Nevertheless, microbiologic responses included cure, defined as eradication of the infection strain without recurrence of bacteriuria ($<10^3$ colony-forming units/mL), and emergence of antimicrobial resistance at 28 days after completion of therapy. Similar to clinical response, patients receiving nitrofurantoin (129/175 [74%]) compared with fosfomycin (103/163 [63%]) had more frequent microbiologic cure at 28 days when evaluating those with positive baseline cultures (difference, 11% [95% CI, 1%–20%]; $P = .04$). This finding was also true at 14 days. Although the microbiologic response was not as robust as the clinical response, clinical response in acute uncomplicated cystitis is most important in clinical practice, and microbiologic test of cure is not standard of care. With respect to antimicrobial resistance, 2 patients receiving nitrofurantoin developed resistant strains during treatment whereas emergence of fosfomycin resistance was not observed.

Overall, Huttner and colleagues¹² provide a rigorous affirmation of the effect of nitrofurantoin vs fosfomycin. These findings differ from prior randomized clinical trials comparing the 2 drugs. In 1999, Stein¹³ published the results of a double-blind, placebo-controlled trial comparing a single 3-g dose of fosfomycin vs 7 days of nitrofurantoin, 100 mg twice daily. In contrast to the study by Huttner and colleagues,¹² patients were required to have microbiologic confirmation of UTI on enrollment, and follow-up occurred from 5 to 42 days. In per-protocol analyses, the only difference was early microbiologic response, in which nitrofurantoin demonstrated higher bacteriologic cure rates than fosfomycin (86% vs 78%). Clinical response remained high for both drugs across all time points. Another double-blind, placebo-controlled trial comparing a single 3-g dose of fosfomycin vs 7 days of nitrofurantoin, 50 mg 4 times daily, in women with clinically confirmed cystitis also found no difference in clinical response at any time point 4 to 42 days after starting treatment in per-protocol analyses.¹⁴ In contrast to the study by Huttner and colleagues,¹²

both trials defined clinical response as cure or improvement, and time points earlier than 14 days were evaluated.

These earlier trials suggest that the open-label design used by Huttner and colleagues¹² may have influenced patient reporting of genitourinary symptoms. In particular, patients randomly assigned to the nitrofurantoin group may have reported greater clinical improvement by virtue of taking a medication 3 times daily for 5 days. This perception of greater treatment intensity may have differentially reduced the frequency of clinical failure in the nitrofurantoin vs fosfomycin group, which was defined, in part, as the need for additional treatment for UTI. In contrast, patients who were still symptomatic after single-dose fosfomycin may have sought additional treatment sooner, thereby declaring earlier clinical failure. Nevertheless, these concerns appear to be mitigated by the consistency of effects when confining the analysis to microbiologic response and similar time to early clinical failure between groups (6.3 days vs 6.5 days).

Another limitation is the dosing regimen. Although current guidelines recommend nitrofurantoin, 100 mg twice daily, for uncomplicated cystitis, nitrofurantoin, 100 mg 3 times daily, was selected because it was the regimen most frequently approved in Europe. It is unclear whether reported results are dose dependent. In addition, only 76% (n = 194/255) and 71% (n = 183/258) of patients in the nitrofurantoin and fosfomycin groups, respectively, had positive baseline urine cultures. This suggests many patients may have had noninfectious urethral symptoms on enrollment.

Despite these limitations, this study differs from prior trials because the authors used intention-to-treat analyses, evaluated missing data through multiple imputation and sensitivity analyses, and included microbiologic outcomes. Thus, the preponderance of evidence described by Huttner and colleagues¹² suggests that nitrofurantoin may have better clinical effectiveness than fosfomycin for the treatment of acute uncomplicated cystitis among middle-aged women. In regions of the world where nitrofurantoin susceptibility is preserved, particularly for *E coli*, nitrofurantoin can be the agent of choice.

Outstanding issues remain the optimal nitrofurantoin dosing regimen and whether current recommendations of 100 mg twice daily are equally effective as 100 mg 3 times daily. The role of fosfomycin also requires examination. Clinical and microbiologic responses with alternative fosfomycin prescribing practices, such as fosfomycin 3 g followed by 3 g every 3 days for a total of 3 days, 6 days, or 9 days, for multidrug-resistant uropathogens should be tested.¹⁵ Nevertheless, despite the open-label design, which may have introduced bias, in this trial of acute uncomplicated cystitis with drug-susceptible uropathogens, the jury has deliberated. The verdict is in. Future trials for treatment of multidrug-resistant uropathogens are needed.

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