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Methenamine hippurate for recurrent urinary tract infections

New trial increases confidence in this non antibiotic alternative

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Over half of women have at least one urinary tract infection in their lifetime.[1] Recurrence (that is, at least three repeated infections per year or two infections in the preceding six months) occurs in about a quarter of women who have one episode.[2] Daily low dose antibiotics is the prophylactic intervention recommended by current guidelines.[3 4] Women with recurrent urinary tract infection describe frustration about the condition, its management, fears about frequent antibiotic use and consequences such as adverse events and resistance, and a desire for non-antibiotic alternative research.[5 6] Given the increasing global burden of antibiotic resistance,[7] strategies that minimise unnecessary antibiotic use are paramount at both the individual and community level.

Methenamine hippurate is a urinary antiseptic and non-antibiotic alternative. Systematic reviews[8 9] synthesising existing trials concluded that while methenamine hippurate might be effective, the evidence is inconclusive and large, well conducted randomised trials are needed. In the linked article (doi:10.1136/bmj-2021-0068229), Harding and colleagues report a large trial (n=240) of adult women presenting with recurrent, uncomplicated urinary tract infection who were randomised to receive methenamine hippurate or low dose antibiotics for 12 months.[10] Women were recruited from UK secondary care centres, with three monthly assessments up to 18 months.

The primary outcome, ascertained over 12 months, was incidence of symptomatic urinary tract infection treated with antibiotics. Although self-reported, the diagnosis needed clinician confirmation, and clinicians recommended any antibiotic treatment. Despite no blinding, the authors reported that most treating clinicians had no involvement in the study. The primary analysis was a modified intention-to-treat analysis, consisting of all participants observed for at least six months and analysed according to their original allocation; this was important because crossover between groups was allowed and some participants chose to switch treatments.

Over 12 months, the incidence of antibiotic treated urinary tract infection was 0.89 and 1.38 episodes per person year in the antibiotic group and methenamine hippurate groups, respectively (absolute difference 0.49 episodes (90% confidence interval 0.15 to 0.84)). Because this study was a non-inferiority trial with a difference between treatments less than the prespecified non-inferiority margin of one episode per person year, the authors reported that methenamine hippurate was no worse than antibiotics at preventing urinary tract infection.

Patient partnership guided the non-inferiority margin chosen, along with the decision to use a clinical definition rather than a microbiological definition of urinary tract infection for the primary outcome.

Results were consistent across other secondary analyses, including sensitivity analyses that excluded days taking therapeutic antibiotics for urinary tract infection during the 12 month follow-up time; important because 43% of participants in the antibiotic group and 56% in the methenamine hippurate group received therapeutic antibiotics. Regardless of the prophylactic intervention taken, about halfthe women had a recurrent infection during the 12 months.

Balanced decisions require consideration of harms and treatment acceptability, as well as possible benefits. The number of adverse events and reactions was low and similar across the randomised groups, although the two serious adverse reactions were both in the antibiotic group and all four hospital admissions related to urinary tract infection and all six episodes of febrile infection occurred in the methenamine hippurate group. Long term safety data are lacking for methenamine hippurate. Treatment satisfaction was high and comparable between the groups, although women who took once daily antibiotic prophylaxis reported higher convenience scores than those taking twice daily methenamine hippurate.

One motivation to find effective non-antibiotic alternatives is to minimise antibiotic resistance, yet few methenamine hippurate trials have measured this outcome reliably. Harding and colleagues measured resistance in *Escherichia coli* isolated from perineal swabs as a secondary outcome. However, it was optional for participants to provide swabs every six months, with more missing data as the trial progressed. Only about half of participants provided an 18 month swab, introducing uncertainty. At six and 12 months, resistance rates to at least one antibiotic were higher in the antibiotic prophylaxis group than the methenamine hippurate group (72% *v* 56%, P=0.05), but at 18 months, the rate of multidrug resistance was higher in the methenamine hippurate group (20% *v* 5%, P=0.06).

Harding and colleagues conducted a non-blinded pragmatic trial, and appropriately acknowledge most caveats and limitations in their article. For example, because several antibiotics were used (trimethoprim, nitrofurantoin, or cefalexin) and subgroup analyses were uninformative, how methenamine hippurate compares with different antibiotics remains unknown. Although the results need cautious interpretation, they align with others,[11] and this new research increases the confidence with which

methenamine hippurate can be offered as an option to women needing prophylaxis against recurrent urinary tract infection.

Whether the non-inferiority margin (one episode of urinary tract infection) used in this trial was of the right magnitude to capture any clinically meaningful difference between treatments will likely inspire debate. However, we agree with the authors that decisions on preventive treatment for recurrent urinary tract infection are well suited to shared decision making,[12] where options are presented, the benefits and harms of each option are discussed, and each patient's values and preferences are considered before patients and clinicians decide together on the next steps. Harding and colleagues' trial will help to inform this important conversation.

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