NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of urinary tract infection (recurrent): antimicrobial prescribing (NICE guideline NG112)

Surveillance report

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Surveillance decision

We will update the NICE guideline on urinary tract infection (recurrent): antimicrobial prescribing.

The update will focus on methenamine hippurate as prophylaxis against recurrent urinary tract infections (rUTIs).

Background

Guideline development

Low-dose antibiotic prophylaxis is the current standard treatment for recurrent urinary tract infections (UTIs), as recommended by the NICE guideline, see the sections on antibiotic prophylaxis and choice of antibiotic prophylaxis. The guideline, which was developed in 2018, does not make any recommendations about methenamine hippurate for prevention of rUTIs.

Evidence on methenamine hippurate for the prevention of rUTI was considered as part of the guideline development. The evidence was limited to 2 randomised controlled trials (RCTs) from an existing systematic review (Muller et al. 2017), which considered the effectiveness of nitrofurantoin compared with methenamine hippurate. The evidence, assessed as low quality, indicated that using nitrofurantoin as prophylaxis against rUTI significantly reduced the incidence of UTI in adults and children compared with methenamine hippurate (2 RCTs, n=196: 35.8% versus 51.2%; risk ratio [RR] 0.60, 95% confidence interval [CI] 0.43 to 0.85; number needed to treat [NNT] 7, 95% CI 4 to 102). When specific antibiotics were compared, there were significantly more mild adverse effects with nitrofurantoin compared with methenamine hippurate (2 RCTs, n=196: 35.8% versus 7%; RR 4.22, 95% CI 2.06 to 8.67; number needed to harm [NNH] 3, 95% CI 2 to 6; moderate quality evidence). Overall, the committee concluded that the evidence was insufficient to recommend the use of methenamine hippurate as a non-antibiotic prophylactic treatment alternative at that time.

Reasons for the decision

New published evidence

The purpose of this exceptional review was to examine any impact on the NICE guideline following completion of the ALTAR trial (ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women), a National Institute for Health Research (NIHR) funded study (NIHR HTA 13/88/21). The full Health Technology Assessment (HTA) report and economic analysis is available along with published findings in the BMJ: Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial (2022).

ALTAR study methods

The ALTAR NIHR-funded study was a pragmatic, non-inferiority trial. Women with rUTIs were recruited from across the UK and randomly assigned to methenamine hippurate (1 g twice daily) or low-dose antibiotics (once-daily 50/100 mg of nitrofurantoin, 100 mg of trimethoprim or 250 mg of cefalexin) over a 12-month treatment period and a 6-month follow-up period. Primary analysis was by modified intention-to-treat. The main outcome for this study was absolute difference in symptomatic, antibiotic treated UTIs, with a predefined non-inferiority margin of 1 episode of UTI per person year. A patient group helped define the margin, with a reduction 1 UTI agreed as worthwhile, and therefore set as the non-inferiority margin between the 2 arms. Secondary outcomes included post-treatment UTIs, total antibiotic use, microbiologically proven UTIs, antimicrobial resistance, adverse reactions and treatment satisfaction. Cost-effectiveness was assessed by incremental cost per quality-adjusted life-year gained in within-trial analysis over 18 months post randomisation, as well as in model-based analysis where findings from the within-trial analysis were extrapolated over the estimated lifetime of a woman experiencing rUTIs, using a Markov model.

Key ALTAR results

The ALTAR study recruited 240 adult women (120 in each arm, aged 18 years or over) across 8 secondary care NHS settings. There was a median of 6 UTIs in the 12 months in both groups before the trial; average age was 50 years.

The modified intention-to-treat analysis comprised 205 participants (antibiotics, n=102; methenamine hippurate, n=103). Key findings reported in the NIHR report include:

The trial confirmed non-inferiority:

- UTI infections per person per year: 0.89 (95% CI, 0.65 to 1.12) in the antibiotics group and 1.38 (1.05 to 1.72) in the methenamine hippurate group;
- there was an absolute difference of 0.49 episode per year (90% CI, 0.15 to 0.84) in favour of antibiotic prophylaxis, but not exceeding the non-inferiority limit of 1 episode of UTI.
- This finding was consistent across the modified intention-to-treat, strict intention-to-treat and per protocol analysis.

The UTI incidence rate in the 6 months following treatment completion:

- 1.19 episodes per year in the antibiotic arm versus 1.72 episodes per year in the methenamine hippurate arm; with an absolute difference of 0.53 episode per year (95% CI, -0.03 to 1.09).

Results for antimicrobial resistance and multidrug resistance were as follows:

- During treatment, a higher proportion of participants in the antibiotic arm (46/64, 72%), when compared with the methenamine hippurate arm (39/70, 56%), demonstrated antibiotic resistance in E. coli cultured from perineal swabs (p=0.05).
- Post-treatment, a higher proportion of participants in the methenamine hippurate arm (9/45, 20%), when compared with the antibiotic arm (2/39, 5%), demonstrated multidrug resistance in bacteria isolated from perineal swabs (p=0.06).

The adverse event rate was low for antibiotic prophylaxis and methenamine hippurate with a mean (standard deviation) of 1.9 adverse events (2.8) and 1.8 adverse events (2.4), respectively (adverse events included lower respiratory tract infection, nausea, diarrhoea and abdominal pain).

The other objective of this trial was to evaluate relative cost-effectiveness of both treatments. The economic evaluation comprised both within-trial (over 18 months post randomisation) and model-based analyses. The aim of the model-based analysis (a Markov model) was to extrapolate the results of the trial beyond the 18-month period. The model was designed to simulate the pathway of women who experience rUTIs from initial treatment to end of life. Probabilistic sensitivity analysis (PSA) was used to quantify any uncertainty in the results due to uncertainty in the parameters of the model.

Findings from the within-trial analysis showed that over 18 months of follow-up methenamine hippurate dominated antibiotic prophylaxis as it was, on average, less costly and more effective than antibiotic prophylaxis in terms of quality-adjusted life-years (QALY) gained. At the £20,000 willingness to pay threshold for a QALY gained, methenamine hippurate has a 65% probability of being considered cost-effective. However, Markov model analysis that extrapolates the findings of the trial over the estimated lifetime of a woman experiencing UTIs showed antibiotic prophylaxis dominated methenamine hippurate (methenamine hippurate was on average more costly and less effective than antibiotic prophylaxis). At the £20,000 willingness to pay threshold for a QALY gained, methenamine hippurate only has a 40% probability of being considered cost-effective, which is lower than the findings from the within-trial analysis. Sensitivity analyses showed there was considerable uncertainty in the economic evaluation findings due to imprecision.

Unlike the within-trial model where analysis is based on utility values that were collected when participants reported a rUTI during the study period (18-month), the Markov model has incorporated 4 health states (mild, moderate, asymptomatic, death) that simulate the pathway of women who experience rUTIs from initial treatment to end of life. Data from the trial as well as other UK-relevant data were used to define the transition probabilities and utility values of each health state. The differences in model structure, time horizon and utility values contribute to the different conclusions between the within-trial and lifetime models.

For further information on the study methods and results see the NIHR ALTAR trial report and the BMJ publication.

Other relevant information

Prescribing methenamine hippurate

The BNF confirms that methenamine hippurate is indicated in patients with recurrent uncomplicated lower UTIs. However, the BNF also highlights that methenamine hippurate requires acidic urine for its mode of action, and as such is often considered less suitable for prescribing in primary care (BNF, checked July 2022).

Antimicrobial stewardship

Widespread use of antimicrobials has been linked to microbes such as bacteria and viruses changing and becoming resistant to treatment. It is therefore important to reduce the use antimicrobials, particularly antibiotics, to protect our health and the health of future generations. Methenamine hippurate is a urinary antiseptic drug used for the prevention of recurrent UTIs. If widely used it would act as an alternative to low-dose prophylactic antibiotics for rUTIs, as recommended by the NICE guideline, and may contribute to the aims of antimicrobial stewardship.

Topic expert feedback

In this exceptional review we engaged with topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received feedback from 3 topic experts (1 consultant in infection control and 2 GPs) with all indicating that the guideline should be revisited to take account of the ALTAR trial, thereby providing an opportunity to consider methenamine hippurate as an alternative to antibiotic prophylaxis for patients with rUTI. The experts also emphasised the potential of this non-antibiotic prophylactic treatment to reduce overall use of antibiotics and factored this consideration into to their assessments of the ALTAR trial evidence.

Equalities

The scope of the NICE guideline includes adults and children (excluding neonates, those in the first 4 weeks of life) who develop rUTIs. Topic experts highlighted that the new evidence from the ALTAR trial, which applies to women (18 years or over), would therefore not directly relate to the populations excluded in the trial, including children, pregnant woman and men. There was some doubt whether the treatment would be appropriate in older patients or where there might be interactions with other medications. These considerations would inform any potential update.

Impact

The NICE guideline does not make recommendations on the use methenamine hippurate for treating rUTIs as there was insufficient good quality evidence at the time of guideline development. Evidence that was available at the time included 2 RCTs in a broad population of adults and children. The ATLAR randomised, non-inferiority trial provides

evidence that methenamine hippurate may provide effective prophylactic treatment for women with a history of rUTIs.

Importantly, non-antibiotic prophylactic treatment with methenamine hippurate could contribute to ambitions outlined in global antibiotic stewardship initiatives to reduce antibiotic use in people. The ALTAR results did however produce 1 anomaly: post-treatment, when compared with the antibiotic arm, a higher proportion of participants in the methenamine hippurate arm demonstrated multidrug resistance in bacteria isolated from perineal swabs. The study authors conjecture that this may be an outcome in participants from the methenamine hippurate arm of prolonged treatment of daily antibiotics or subsequent antibiotic treatment after stopping treatment with methenamine hippurate.

However, there remains some uncertainty about wider implementation of the treatment. The BNF highlights a potential barrier to methenamine hippurate use in primary care, as it requires an acidic urine for the treatment to work. Furthermore, the evidence gathered by the ALTAR trial was derived from secondary care settings and does not directly apply to primary care.

Following consideration of the results from the ALTAR study, as well as topic expert feedback and consideration of the aims of antimicrobial stewardship, the new evidence may have an impact on the guideline, particularly in relation to women with rUTIs and receiving treatment in secondary care.

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