BMC Urology

RESEARCH

Open Access

Effectiveness of methenamine hippurate in preventing urinary tract infections: an updated systematic review, meta-analysis and trial sequential analysis of randomized controlled trials

Nathalie Cordeiro Hobaica[3], Giovanna Cardoso De Oliveira[1], Breno Cordeiro Porto[1], Carlo Camargo Passerotti[1], Rodrigo Afonso Da Silva Sardenberg[2], Jose Pinhata Otoch[1] and Jose Arnaldo Shiomi Da Cruz[1,2,3*]

Abstract

Introduction Urinary Tract Infections (UTIs) are a significant health problem worldwide, especially among women. methenamine hippurate has been proposed as a preventive measure against recurrent UTIs. This updated systematic review and meta-analysis aimed to evaluate the effectiveness of methenamine hippurate in preventing UTIs, incorporating the latest research findings and employing trial sequential analysis to assess the robustness of the evidence.

Materials and methods A systematic review was conducted across MEDLINE, Embase, Scopus, Cochrane, and Google Scholar up to March 2024 for randomized controlled trials comparing methenamine hippurate with placebo or antibiotic in adult women with a history of recurrent, confirmed UTIs. Key outcomes included symptomatic UTIs as primary outcome and positive urine culture, asymptomatic bacteriuria and adverse effects as secondary outcomes. It is important to state that asymptomatic UTIs with negative urine cultures were not adequately accounted for in the studies; therefore, this outcome was excluded from our meta-analysis. Additionally, adverse effects related to antibiotic resistance were not described in the studies, so only the adverse effects of the medications themselves were considered. The risk of bias was evaluated using the Cochrane Risk of Bias 2, and statistical analysis was conducted using RStudio software.

Results We retrieved 5 articles, encompassing 216 patients in the methenamine group and 205 patients in the control group (Antibiotic). Our analysis revealed non-inferiority in the rate of symptomatic UTI episodes between the two groups (RR 1.15; 95%CI 0.96,1.38; $p=0.41$; $I^2=0\%$). Similarly, there were no notable distinctions in the rate of positive urine cultures (RR 1.20; 95CI 0.91, 1.57; $p=0.25$; $I^2=28\%$), and the rate of adverse effects (RR 0.98; 95CI 0.86, 1.12; $p=0.35$; $I^2=9\%$)**.** However, we observed a decreased frequency of asymptomatic bacteriuria in the control group (RR 1.91; 95CI 1.29, 2.81; $p=0.0001$; $I^2=0\%$). In trial sequential analysis, existing studies were not able to achieve the futility boundaries.

*Correspondence:
Jose Arnaldo Shiomi Da Cruz
arnaldoshiomi@yahoo.com.br
Full list of author information is available at the end of the article

Conclusions Overall, our meta-analysis provides evidence supporting methenamine hippurate as an effective, non-inferior and safe prophylactic option for preventing recurrent UTIs in adult women, as demonstrated by the current evidence base. Nevertheless, more RCTs are necessary to achieve the futility boundaries in trial sequential analysis.

Keywords Methenamine hippurate, Urinary tract infections, Systematic review, Meta-analysis, Randomized controlled trials

Introduction

Urinary Tract Infections (UTIs) are a common global health issue, particularly affecting women, with approximately 7 million women seeking outpatient care annually for uncomplicated UTIs [1]. These infections, caused by bacterial invasion of the urinary tract, include conditions such as cystitis and pyelonephritis [2]. Due to anatomical factors, women are more susceptible to UTIs, and recurrence is a significant concern [2]. with up to 27% of women experiencing a repeat infection within six months. This recurrence contributes to both clinical and economic burdens [1].

Antibiotics, such as trimethoprim-sulfamethoxazole, nitrofurantoin, and fosfomycin, are commonly prescribed for acute UTI treatment but come with side effects, including gastrointestinal disturbances and allergic reactions. More critically, widespread antibiotic use is fueling the rise of antimicrobial resistance (AMR), which complicates treatment [3]. Long-term antibiotic use in treating UTIs leads to high overall resistance to commonly used antibiotics, such as ampicillin (39.6%), trimethoprim (23.8%), trimethoprim/sulfamethoxazole (22.4%) [4], Despite the current approach to managing UTIs predominantly involves antibiotics, there are ongoing concerns about overuse, antibiotic resistance, and potential aftereffects [5].

While current guidelines from the American Urological Association (AUA) and the European Association of Urology (EAU) [6] focus on optimizing UTI management, challenges remain in antibiotic selection, treatment duration, and the management of recurrent infections. Recent studies, including a meta-analysis by Bakhit et al. (2021) [7], suggest that methenamine hippurate may offer a promising alternative for preventing recurrent UTIs, though the results have been inconclusive, necessitating further investigation.

Given the concerns over antibiotic resistance and adverse effects, exploring non-antibiotic alternatives like methenamine hippurate is essential. This urinary antiseptic works by releasing formaldehyde in acidic urine, exerting bactericidal effects within the urinary tract [3]. Its unique mechanism and favorable safety profile make it an attractive candidate for UTI prevention [8].

This systematic review aims to assess the effectiveness of methenamine hippurate in preventing UTIs through an updated analysis of randomized controlled trials (RCTs). By incorporating trial sequential analysis, we aim to provide more reliable estimates of its efficacy compared to standard antibiotics and placebo. The findings of prior systematic reviews, such as those by Lee et al. [3] and Bakhit et al. [7] suggest some potential benefits of methenamine hippurate, but further robust data is needed to confirm its role in UTI prophylaxis.

Material and methods

Search strategy

This systematic review and meta-analysis were performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of interventions and the Preferred reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [9] Statement guidelines.

We conducted a comprehensive search of MEDLINE, Embase, Scopus, and Cochrane CENTRAL, along with Google Scholar for additional internet sources, from their inception until March 2024 for randomized controlled trials of methenamine hippurate vs antibiotic/placebo trials in women with recurrent urinary tract infection. Please refer to appendix our search strategy. A highly sensitive search strategy was also used in a way to better identify randomized trials in the databases.

The references from all included studies, previous systematic reviews and meta-analyses were also searched manually for any additional studies. The prospective meta-analysis protocol was registered on PROSPERO under protocol CRD42024512556.

Eligibility criteria for study selection

We included randomized controlled trials (RCTs) that assessed adult women (aged ≥ 18 years) with a history of recurrent or confirmed UTIs. Studies were eligible if they compared the efficacy of methenamine hippurate with placebo/no treatment or any antibiotic and reported at least one of the clinical outcomes of interest. We excluded non-randomized controlled trials (non-RCTs), studies without a methenamine arm or without a comparison to placebo/antibiotics, studies involving women with catheters, patients with anatomical abnormalities

(e.g., solitary kidney, ureteral or urethral stricture), or patients with active urinary tract infections.

The exclusion of women with active UTIs was critical for the integrity of this review since our purpose with this work is to evaluate methenamine hippurate as prophylaxis method for recurrent UTIs, not for the treatment of active infections. Including women with active UTIs could introduce significant confounding, as the focus of this review is on the prevention of future UTI episodes, rather than the treatment of an ongoing infection. By excluding women with active UTIs, we ensured that the results reflect the true prophylactic effect of methenamine hippurate. We also excluded studies that reported the use of acidifying agents in combination with methenamine hippurate, as these could interfere with the outcomes of interest. Case reports, systematic reviews, and bibliographic reviews were excluded to maintain a high standard of evidence.

Outcomes

The primary outcome was the recurrence of clinical UTIs, as defined by the presence of any of the following symptoms: dysuria, nocturia, urgency, fever, urinary frequency, burning, suprapubic pain, and loin pain. This outcome was chosen because recurrent UTIs are most commonly diagnosed based on clinical symptoms in women, with symptoms being the primary guide for treatment decisions. While microbiological confirmation (e.g., positive urine culture) would provide a more objective measure of UTI, clinical symptoms alone are frequently sufficient for diagnosing recurrent UTIs in clinical practice. The secondary outcomes included positive urine cultures associated with UTI symptoms, asymptomatic bacteriuria, and adverse effects (e.g., nausea, diarrhea, rash, and others).

Screening

After deduplication, in which we used Endnote online™ 20 (Clarivate, Philadelphia, PA) [10], two independent researchers (NH and GO) screened the studies by title and abstract, and disagreements were solved by a third (JC). Following this process, full text screening was performed. No automation tools were used during the screening process.

Data extraction and quality assessment

Two authors (BP and NH) independently extracted the data based on a predefined protocol and disagreements were solved by a third (JC). The data primarily assessed were the type o study, the language of each paper, number of patients enrolled, mean age of patients, methenamine dosage, which antibiotic was used and each dose, the duration of follow-up, and all the outcomes previously mentioned. Risk of bias was assessed in randomized studies using version 2 of the Cochrane Risk of Bias assessment tool (RoB 2) [11]. Two independent authors completed the risk of bias assessment (NH and GO). Disagreements were resolved through a consensus after discussing reasons for discrepancy. Regarding the UTI definition of each study included, it was not possible to obtain since it was lacking in the majority of them.

Statistical analysis

Dichotomous data are presented as relative risk (RR) with 95% CI. Pooled estimates were calculated with the random-effects model, considering that the patients came from different populations. We considered a study to exhibit considerable heterogeneity if, following the statistical analysis, the I^2 statistic is equal to or greater than 30%.

We performed a Trial Sequential Analysis (TSA) (alpha = 5%, beta = 90% for a relative risk reduction of 5%) focusing on type 2 errors for the main outcome. It may be useful to explain that Trial Sequential Analysis (TSA) is a valuable tool in meta-analyses as it helps control random errors, particularly when data is sparse or when repeated significance testing occurs. By applying monitoring boundaries, TSA assesses whether a meta-analysis has sufficient information to draw reliable conclusions or if additional studies are necessary. It also helps avoid type I (false positive) and type II (false negative) errors. In the context of my meta-analysis, TSA is valuable because it allows us to determine whether the available evidence is robust or if further trials are needed, ensuring the reliability of our conclusions RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL, was the software used for statistical analysis [12].

Results

Study selection and characteristics

After performing our screening, we identified 999 articles. Following the deduplication and screening process, 5 articles [13–17] were deemed relevant and included in our analysis (Fig. 1/PRISMA flow chart). For a comprehensive overview of the data of included studies, please refer to Table 1. Combining the data from these articles, we analyzed a total of 231 patients who received oral methenamine hippurate 1 g twice daily and 220 patients that were placebo or undertook antibiotics. The mean age of all patients was 56.9 years old. One study used placebo as their control arm [17], four studies used oral antibiotics as control group treatment, among these, 2 used trimethoprim 100mg [13, 14], one ciprofloxacin 500 mg [15] and the other included 3 lines of treatment with 50/100 mg of nitrofurantoin, or 100 mg of trimethoprim or 250 mg of cephalexin [16]. We must note that all

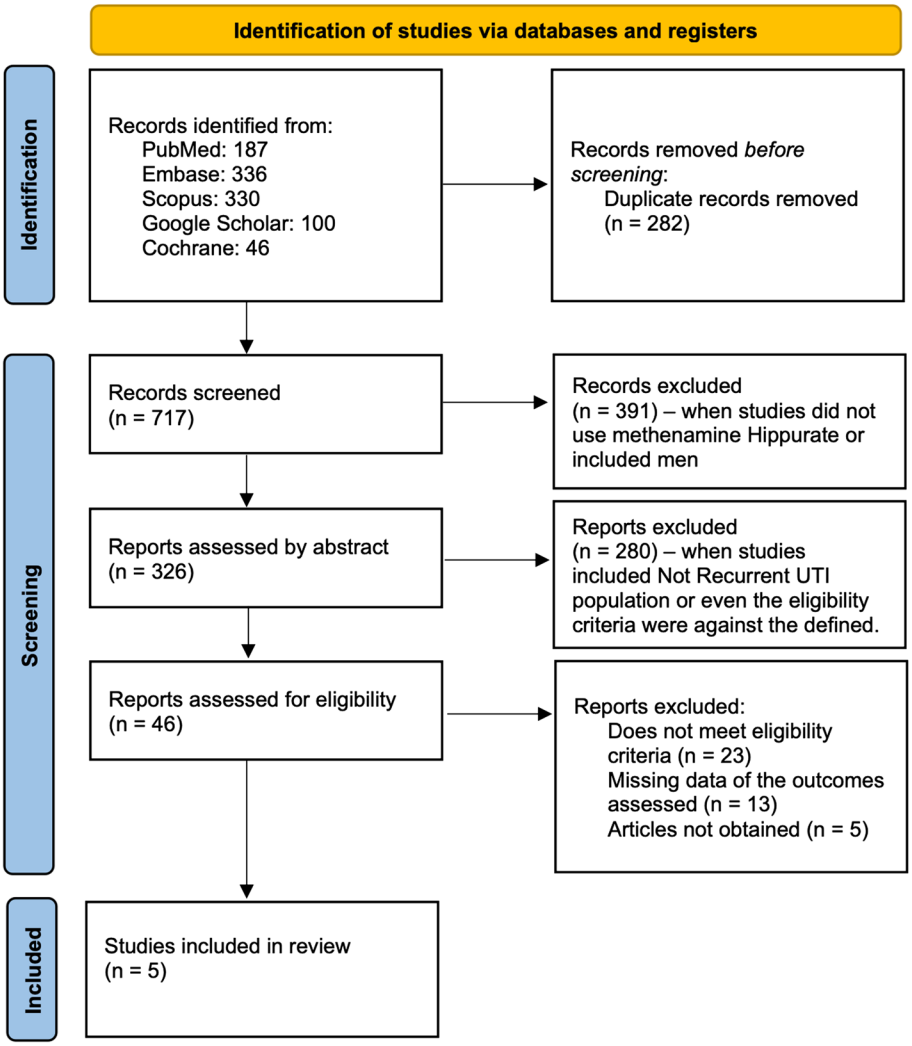

Fig. 1 PRISMA flowchart

the antibiotics were used with the intend of prophylaxis. Most of the studies lacked information about the duration of antibiotics usage. Also, more information about the outcome definition of each study included regarding symptomatic UTI and urine culture can be found in Table 2.

Meta-analysis

When comparing the symptomatic clinical UTI episodes after both clinical interventions, Methenamine or Antibiotics, no differences were seen between groups (RR 1.15; 95%CI 0.96,1.38; $p=0.41$; $I^2=0\%$) (Fig. 2). The TSA was only performed for the primary outcome, since the other outcomes had insufficient sample (Fig. 3). We must note that for this outcome 4 studies had data included, counting with 421 patients.

Regarding the secondary outcomes, no notable distinctions were observed in the positive urine culture rate (RR 1.20; 95CI 0.91, 1.57; p=0.25; $I^2=28\%$) (Fig. 4); nor were significant the rate of adverse effects between both approaches (RR 1.91; 95CI 1.29, 2.81; $p=0.0001$; I2=0%) (Fig. 5). For these both, unfortunately only 3 studies could be assessed, and the positive urine culture we counted 335, while in the rate of adverse effects there were 318.

At the same time, a higher rate of asymptomatic bacteriuria was associated with methenamine hippurate in comparison as the antibiotic group (RR 0.98; 95CI 0.86, 1.12; $p=0.35$; I2=9%) (Fig. 6). Here 4 studies were included, with an amount of 366 patients' data assessed.

Since none of the outcomes assessed presented a I^2 higher or equal as 30%, any kind of sensitivity analysis was performed. However, visual inspection suggests the presence of clinical or methodological heterogeneity,

Table 1 Baseline characteristics of included studies

Study	RCT type	Language	Patients enrolled (N), Methenamine/ Control	Groups, Methenamine/ Control	Mean age—years, Methenamine/ Control	Symptomatic UTI episodes (N)—Methenamine/ Control	Positive urine culture (N)—Methenamine/ Control	Asymptomatic bacteriuria after 6 or 12 months (N)—Methenamine/ Control	Adverse effects, Methenamine/ Control	Methenamine hippurate dosage	Antibiotic used and dose	Duration of follow-up
Botros, 2022 [13]	Two arm, parallel	English	43/43	Methenamine/ Antibiotic	73.2 ± 10.5 / 70.6 ± 15.0	28/28	NS/NS	NS/NS	4/6	1 g twice daily	Oral Trimethropim, 100 mg once nightly	12 months
Brumfitt, 1983 [14]	Three arm, parallel	English	25/20	Methenamine/ Antibiotic	38.2 ± 18/39.9 ± 20.5	18/11	10/8	NS/NS	7 (gastrointestinal intolerance and rash of vagina)/1 (rash of vulva or vagina)	2000 mg, daily	Oral Trimethropim, 100 mg	12 months
Chu, 2016 [15]	Two arm, parallel	English	45/40	Methenamine/ Antibiotic	62.2 ± 10.04 /61.5 ± 12.1	0/2	1/4	1/2	NS/NS	1 g, two doses (daily)	500 mg ciprofloxacino	3 weeks
Gundersen, 1986 [17]	Two arm, parallel	English	15/15	Methenamine/ Placebo	74.5 ± NS / 74 ± NS	NS/NS	NS/NS	8/4	1/1	1 tablet (dose NS), twice daily	NS	6 months
Harding, 2022 [16]	Two arm, pragmatic	English	103/102	Methenamine/ Antibiotic	49.9 (19.1) / 50.3 (18.1)	59/47	54/42	44/22	82/83	1 g twice daily	50/100 mg of nitrofurantoin, 100 mg of trimethoprim or 250 mg of cefalexin	12 months

The continuous variables were represented by mean ± SD

Abbreviations: *BMI* body mass index, *UTI* urinary tract infection, *PSA* prostate specific antigen, *NS* non specified

Table 2 Outcome definition in each included study

Study	Outcome definition	Category
Botros, 2022 [13]	Recurrent UTI defined as two culture-proven UTIs within 6 months, or three within 1 year with associated symptoms.	Symptomatic UTI + Positive Culture
Brumfitt, 1983 [14]	At least one episode documented bacteriologically, symptomatic recurrence monitored over 12 months.	Symptomatic UTI + Positive Culture
Chu, 2016 [15]	Symptomatic UTI post-procedure defined by clinical symptoms and urinary analysis, no consistent culture data.	Symptomatic UTI + Unknown Culture
Gundersen, 1986 [17]	Frequent cystitis defined as two or more symptomatic episodes in the previous 6 months, evaluated in elderly women.	Symptomatic UTI + Positive Culture
Harding, 2022 [16]	Incidence of symptomatic antibiotic-treated UTIs, clinical diagnosis preferred over microbiological confirmation.	Symptomatic UTI (Clinical)

Symptomatic UTI + Positive Culture At least one episode documented bacteriologically, symptomatic *recurrence monitored over 12 months*

Symptomatic UTI + Unknown Culture Symptomatic UTI post-procedure defined by clinical symptoms and urinary analysis, no consistent culture data

Symptomatic UTI (Clinical) Incidence of symptomatic antibiotic-treated UTIs, clinical diagnosis preferred over microbiological confirmation

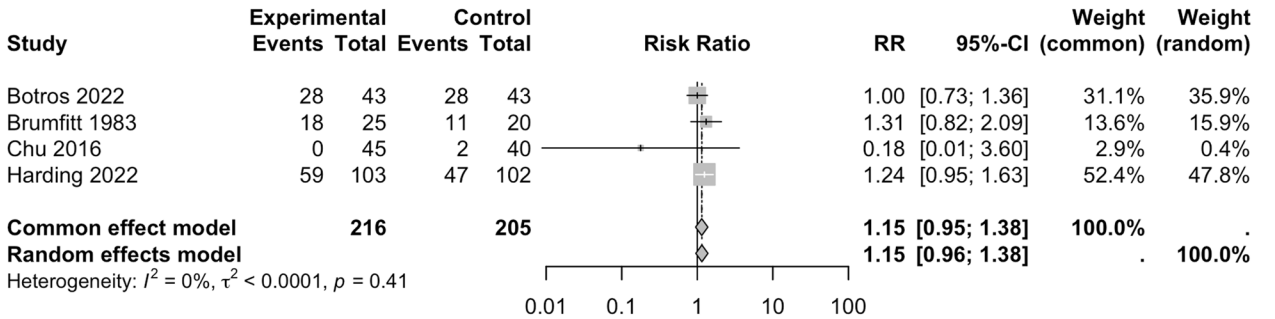

Fig. 2 Rate of symptomatic UTI comparing Methenamine and Antibiotics

particularly in outcomes that include data from Chu et al., which warrants further discussion.

We should point out that our primary endpoint, symptomatic UTI episodes, included data from all the included studies except for Gundersen et. al. As for the secondary endpoints, the positive urine culture was again not assessed in Gundersen and Botros trials; adverse effects included all, apart from the Chu cohort; and finally, the asymptomatic bacteriuria was assessed only in Chu, Gundersen and Harding cohorts.

Quality assessment

Since all the trials here included were RCTs, all of them were assessed by Rob-2 tool. The cohort from Gundersen [17] presented a low overall score of bias, while the Botros [13] trial showed a high risk of bias, mainly due to bias in the measurement of the outcomes. At the same time, the other studies included, Brumfitt, Chu and Harding et al [14–16], presented a risk of bias that regarded some concerns (Fig. 7).

Discussion

This systematic review, meta-analysis, and trial sequential analysis evaluated the effectiveness of methenamine hippurate in preventing recurrent urinary tract infections (UTIs) compared to antibiotics. Our findings indicate no significant differences in the incidence of symptomatic UTI episodes between the methenamine hippurate and antibiotic groups.

Similarly, both interventions demonstrated equivalent efficacy in reducing positive urine cultures. However, asymptomatic bacteriuria (ABU) was notably higher in the methenamine hippurate group (RR 1.91; 95% CI 1.29, 2.81; $p = 0.0001$; $I^2 = 0\%$).

The increased ABU in the methenamine hippurate group may be attributed to its mechanism of action, which relies on the urinary environment to release formaldehyde for bacteriostatic or bactericidal effects. While this mechanism effectively reduces symptomatic episodes, it may not eliminate bacteria as systemically or thoroughly as antibiotics. Antibiotics, with their broader and more systemic antimicrobial activity, likely contribute to the lower rates of ABU observed in this analysis. This finding emphasizes the need for further studies

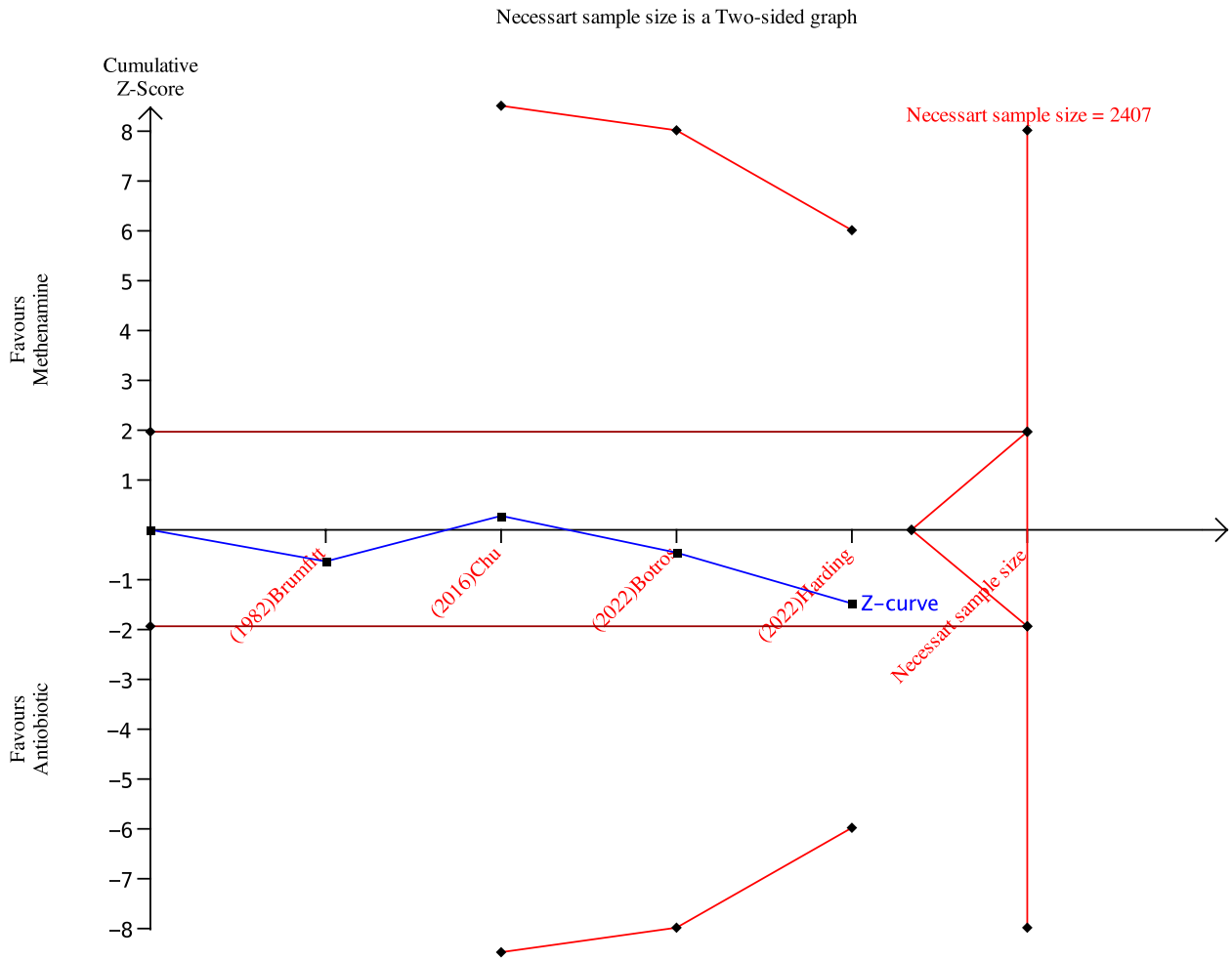

Fig. 3 TSA of the primary outcome of interest

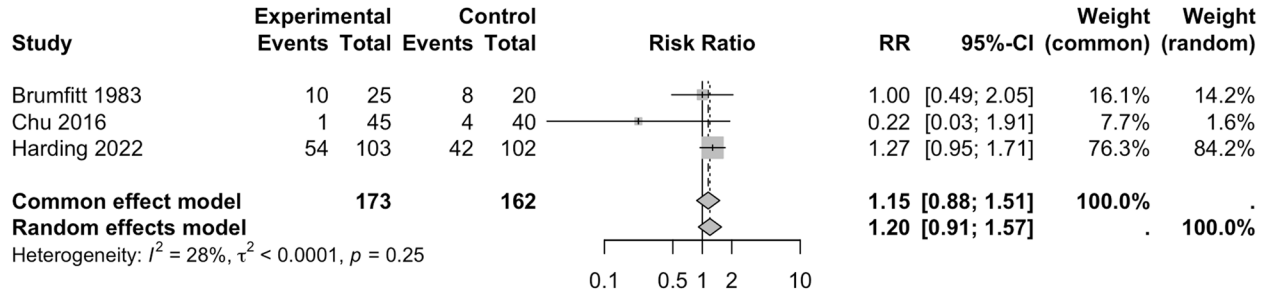

Fig. 4 Rate of positive urine culture comparing Methenamine and Antibiotic groups

investigating the relationship between ABU and long-term outcomes in patients using methenamine hippurate.

Regarding adverse effects, the analysis revealed fewer adverse events in the antibiotic group, contrary to expectations given the well-documented side effects of antibiotics, including gastrointestinal disturbances and allergic reactions. This unexpected result may stem from the limited reporting of adverse effects in the included studies, as only three articles provided data on this outcome. The underreporting of adverse events highlights the need for future research with comprehensive safety evaluations to

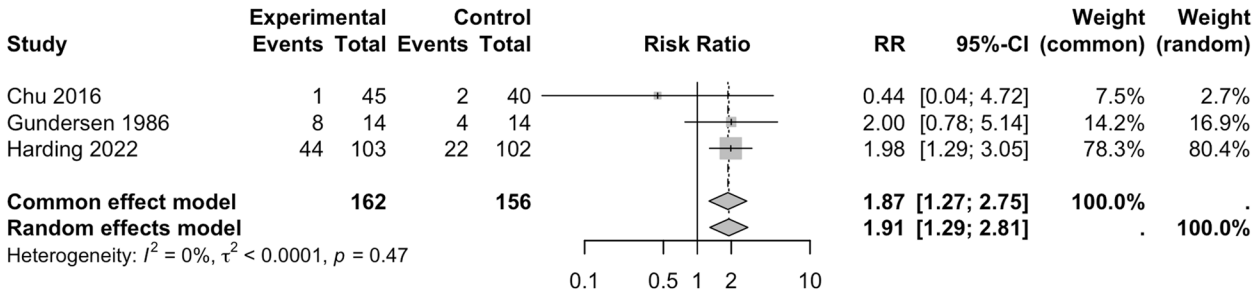

Fig. 5 Rate of adverse effects regarding Methenamine and Antibiotic groups

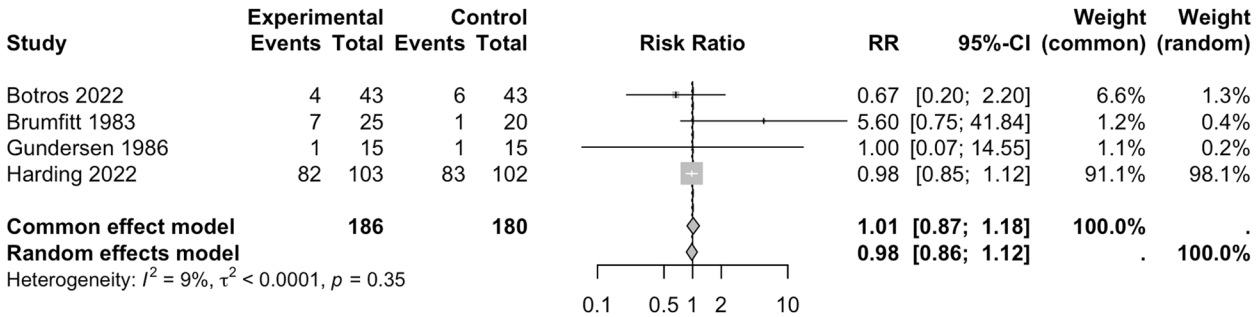

Fig. 6 Rate of asymptomatic bacteriuria comparing Methenamine and Antibiotic groups

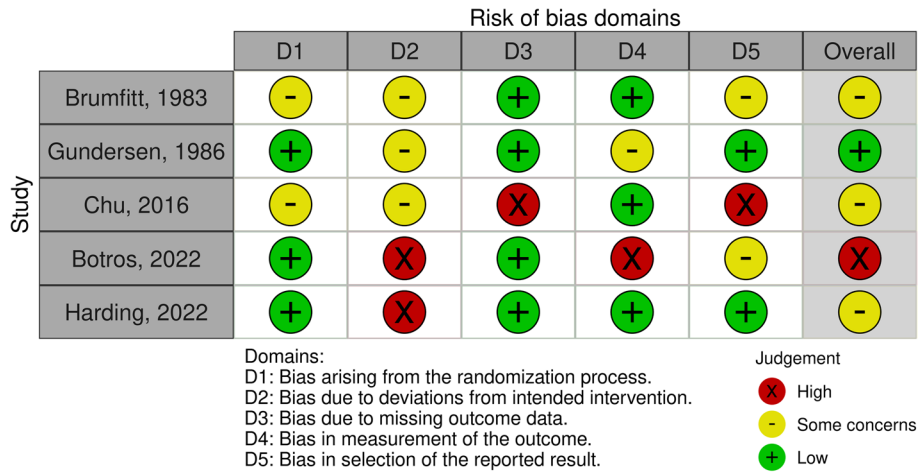

Fig. 7 Risk of Bias of included studies through RoB 2 toll

better understand the comparative safety profiles of these interventions.

The strengths of this meta-analysis lie in its focus on recent studies and its rigorous methodological approach, including trial sequential analysis, which enhances the reliability of the findings. However, several limitations must be acknowledged. First, the relatively small sample size and the scarcity of high-quality trials addressing methenamine hippurate's efficacy constrained the data available for analysis. Second, heterogeneity in study designs, particularly regarding definitions of UTIs and variations in control antibiotics, complicamethted the comparison of outcomes. Notably, only three studies assessed ABU and adverse effects, limiting the generalizability of these findings. Lastly, the lack of data on microbial resistance, a critical factor in long-term prophylactic use, further restricts the study's conclusions.

Our findings suggest that methenamine hippurate offers comparable efficacy to antibiotics in preventing symptomatic UTIs and reducing positive urine cultures, with a potentially favorable safety profile. However, the higher ABU rates in the methenamine group warrant further investigation to elucidate their clinical significance. The evidence supports methenamine hippurate as a viable non-antibiotic prophylactic option, particularly for patients aiming to minimize antibiotic exposure.

Future research should address the methodological shortcomings identified in this review, including the need for standardized UTI definitions, comprehensive reporting of adverse events, and evaluations of microbial resistance. Such studies are essential to refining clinical guidelines and optimizing the role of methenamine hippurate in UTI prevention. By expanding the evidence base, clinicians can better tailor prophylactic strategies to individual patient needs, balancing efficacy, safety, and the growing imperative to mitigate antibiotic resistance.

Conclusion

This comprehensive meta-analysis explored the comparative effectiveness of methenamine hippurate versus antibiotics or placebo for managing UTI in females. Encouragingly, our results revealed a favorable non-inferiority parameter for methenamine when compared with the established antibiotic treatment outlined in existing medical literature. This suggests that methenamine could present itself as an economically viable alternative for treating patients diagnosed with uncomplicated cystitis.

Given the limited number of evaluated patients and RCTs included in this meta-analysis, further research are warranted to validate and expand upon our findings, as well as confirmed through our TSA results. This will contribute to the development of more robust guidelines for the optimal choice of treatment in cases of UTI in women.

Appendix

Our search strategy was: (("methenamine hippurate") OR (methenamine) OR (hippurate*) OR ("hexamine hippurate") OR (Urex) OR (Hiprex) OR (Hip-Rex) OR (Urotractan)) AND (("urinary tract infection*") ("recurrent urinary tract infections") OR (UTI) OR (UTIs) OR (cystitis)).

Abbreviations

UTIs	Urinary Tract Infections
RCTs	Randomized Controlled Trials
AUA	American Urological Association
EAU	European Association of Urology
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
TSA	Trial Sequential Analysis
RR	Relative Risk
CI	Confidence Interval
I^2	I-squared (a statistical measure of heterogeneity)
RoB 2	Risk of Bias 2

Acknowledgements

Nothing to declare.

Authors' contributions

Substantive scientific and intellectual contributions to the study: Conception and design: Nathalie. C. Hobaica, Giovanna C. Oliveira and Breno C. Porto; Acquisition of data: Nathalie. C. Hobaica and Breno C. Porto; Analysis and interpretation of data: Nathalie C. Hobaica, Breno C. Porto and Carlo C. Passerotti; Technical procedures: Giovanna C. Oliveira and Breno C. Porto; Statistics analysis Giovanna C. Oliveira, Rodrigo A. S. Sardenberg and José A. S. da Cruz; Manuscript preparation: Giovanna C. Oliveira, Nathalie C. Hobaica and José A. S. da Cruz; Manuscript writing: Breno C. Porto and José A. S. da Cruz; Critical revision: José P. Otoch, Rodrigo A. S. Sardenberg and José A. S. da Cruz.

Funding

Not applicable.

Data availability

Data is provided within the Table 1 file.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Competing interests

The authors declare no competing interests.

Author details

[1]Surgical Technique and Experimental Surgery Department, University of São Paulo School of Medicine, Cincinato Braga St. 37 - Cj 32, São Paulo, SP 01333-011, Brazil. [2]International Teaching and Research Institute - Hapvida NotreDame Intermédica, Fortaleza, CE, Brazil. [3]Pontifical Catholic University of São Paulo, São Paulo, SP, Brazil.

Received: 30 July 2024 Accepted: 4 February 2025
Published online: 15 February 2025

References

1. Öztürk R, Murt A. Epidemiology of urological infections: a global burden. World J Urol. 2020;38(11):2669–79. https://doi.org/10.1007/s00345-019-03071-4.
2. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269–84. https://doi.org/10.1038/nrmicro3432.
3. Lee BB, Simpson JM, Craig JC, Bhuta T. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2007;4:Cd003265. https://doi.org/10.1002/14651858.CD003265.pub2.
4. Ny S, Edquist P, Dumpis U, et al. Antimicrobial resistance of Escherichia coli isolates from outpatient urinary tract infections in women in six European countries including Russia. J Glob Antimicrob Resist. 2019;17:25–34. https://doi.org/10.1016/j.jgar.2018.11.004.
5. Wang C, Liu K, Sun X, Yin Y, Tang T. Effectiveness of motivational interviewing among patients with COPD: a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Patient Educ Couns. 2022;105(11):3174–85. https://doi.org/10.1016/j.pec.2022.07.019.

6. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam tN, 978–94–92671–16–5. I, EAU Guidelines Office A, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/.
7. Bakhit M, Krzyzaniak N, Hilder J, Clark J, Scott AM, Mar CD. Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. Br J Gen Pract. 2021;71(708):e528–37. https://doi.org/10.3399/BJGP.2020.0833.
8. Hollyer I, Varias F, Ho B, Ison M. Assessment of methenamine hippurate for the prevention of recurrent urinary tract infections in adult renal transplant recipients: a single center, retrospective study. Conference Abstract Am J Transpl. 2018;18:943–4. https://doi.org/10.1111/ajt.14918.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med. 2021;18(3):e1003583. https://doi.org/10.1371/journal.pmed.1003583.
10. Team TE. EndNote. Philadelphia: Clarivate; 2013.
11. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
12. (2020). RT. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.
13. Botros C, Lozo S, Iyer S, Warren A, Goldberg R. Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial. International …. // 2022. https://doi.org/10.1007/s00192-021-04849-0.
14. Brumfitt W, Hamilton Miller JMT, Gargan RA. Long-term prophylaxis of urinary infections in women: comparative trial of trimethoprim, methenamine hippurate and topical povidone-iodine. Article J Urology. 1983;130(6):1110–4. https://doi.org/10.1016/S0022-5347(17)51709-7.
15 Chu CM, Smith AL, Arya LA, et al. Methenamine hippurate versus ciprofloxacin to prevent postoperative urinary tract infection: results of a randomized controlled trial. Conference Abstract. Female Pelvic Med Reconstr Surg. 2016;22(5):S2–3. https://doi.org/10.1097/SPV.0000000000000331.
16. Harding C, Chadwick T, Homer T, Lecouturier J, Mossop H, Carnell S, King W, Abouhajar A, Vale L, Watson G, Forbes R, Currer S, Pickard R, Eardley I, Pearce I, Thiruchelvam N, Guerrero K, Walton K, Hussain Z, Lazarowicz H, Ali A. Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. Health Technol Assess. 2022;26(23):1-172. https://doi.org/10.3310/QOIZ6538.
17. Gundersen R, Hoivik HO, Osmundsen K. Frequent cystitis in elderly women. A double-blind comparison of Hiprex and placebo in general practice. Tidsskr Nor Laegeforen. 1986;106(25):2048–9.

Publisher's Note