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REVIEW ARTICLE

Use of Methenamine for Urinary Tract Infection Prophylaxis: Systematic Review of Recent Evidence

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Abstract

Introduction and Hypothesis Antibiotic resistance is an unavoidable consequence of antibiotic use and growing rates of resistance are an urgent issue. Methenamine is a non-antibiotic alternative used for urinary tract infection (UTI) prophylaxis. The objective of this review is to evaluate recently published literature regarding the efficacy and safety of methenamine for UTI prophylaxis.

Methods PubMed, Embase, and CENTRAL databases were queried in March 2023 using the following search terms: urinary tract infection, cystitis, bacteriuria, or dysuria, and methenamine. Studies prior to 2012 were excluded from this review to focus on appraisal of the most recent evidence. Prospective and controlled retrospective trials were included for review.

Results A total of seven studies (three prospective and four retrospective) met the inclusion criteria for review. Two of the 3 prospective studies demonstrated no or non-inferior differences in clinical efficacy to prevent recurrent UTIs between methenamine and antibiotic prophylaxis and the third showed decreased rates of UTI with methenamine use in patients with short-term indwelling catheters compared with cranberry alone. The retrospective studies consistently supported the efficacy and safety of methenamine for UTI prophylaxis in a variety of populations and clinical settings. Adverse effects reported with methenamine were similar to comparators and included nausea, abdominal pain, and headache.

Conclusions The use of methenamine for UTI prophylaxis was shown to be effective in a variety of settings without an increased risk of adverse effects compared with prophylactic antibiotics. Larger blinded clinical trials are needed to further define the role of methenamine in UTI prophylaxis.

Keywords Antibiotic resistance · Antibiotic-sparing agent · Antimicrobial stewardship · Prophylactic antibiotic · Recurrent urinary tract infection · Women's health

Introduction

Drug-resistant pathogens lead to over 1.25 million deaths globally each year, a number that is projected to increase to over 10 million annually by 2050 if action is not taken to address growing resistance rates [1, 2]. Antibiotic resistance is an unavoidable consequence of antibiotic use; preventing infections or utilizing non-antibiotic alternatives when possible is an important part of countering growing rates of resistance [3].

Urinary tract infections (UTIs) are one of the most common infections, accounting for over 400 million estimated cases worldwide in 2019 [4, 5]. Persons assigned female at birth, individuals with genitourinary tract abnormalities, and those with a need for urinary catheters are at an increased risk of developing UTIs. Symptoms of UTIs include urinary urgency, frequency, and dysuria and lead to a negative

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impact on quality of life [4–6]. UTI treatment is a setting of high antibiotic utilization with potential for antibiotic overuse. Some estimates indicate that nearly one third of antibiotics prescribed for UTI treatment are for conditions in which antibiotics are typically not warranted (e.g., asymptomatic bacteriuria, colonization) [7, 8].

Recurrent UTIs are commonly defined as two UTIs within 6 months or three UTIs within 1 year [9, 10]. Non-pharmacological management of recurrent UTIs is preferred and includes increased fluid intake, use of condom catheters rather than indwelling catheters, and catheter exchanges when warranted. If refractory to these changes, prophylactic antibiotics may be used when the expected benefit outweighs possible harms from antibiotic use for the individual patient. Antibiotic-sparing agents would be highly desired, to avoid the risks of antibiotic use, although current evidence for many of these treatments (e.g., cranberry, vitamin C, *Lactobacillus*) have limited data based on published guidelines [9–12]. However, methenamine has garnered particular interest recently as an antibiotic-sparing alternative [10, 13].

Methenamine is a urinary anti-infective approved by the Food and Drug Administration for the prevention of recurrent UTIs. In an acidic environment, methenamine gets hydrolyzed into formaldehyde and has a high renal elimination (95%) [14]. Formaldehyde has localized antiseptic effects and no known mechanism for the development of antimicrobial resistance, which is an ideal property for an antibiotic-alternative for UTI prevention. Methenamine is a low-cost agent and is generally well tolerated, with less than a 3.5% incidence of nausea, GI upset, dysuria, and rash [14]. Methenamine can also be used in pregnancy, although it should be used with caution in mild to moderate hepatic dysfunction and avoided in mild to severe renal impairment, severe dehydration, severe hepatic impairment, or with sulfonamides owing to the potential for insoluble precipitate formation [14, 15].

Use of methenamine for UTI prophylaxis was assessed in a 2012 Cochrane Review and deemed potentially effective, although with limited evidence. The literature search for this systematic review and meta-analysis was performed in June 2012 with 13 trials (2,032 patients in total) included and the overall quality of the studies was determined to be poor. The authors concluded that the short-term use of methenamine may be effective for patients without renal tract abnormalities or neurogenic bladder dysfunction, although further large, randomized, controlled trials are needed to support efficacy, especially in the setting of long-term prophylaxis [16]. Additional systematic reviews since this publication have drawn similar conclusions; however, none has comprehensively reviewed the most recent safety and efficacy of methenamine, including data beyond randomized controlled trials [17, 18]. Given the urgent threat of growing antimicrobial resistance and renewed interest in methenamine as an antibiotic alternative for patients needing UTI prophylaxis, a systematic review of emerging evidence is necessary to delineate potential options. The objective of this review is to evaluate recently published literature regarding the efficacy and safety of methenamine for UTI prophylaxis.

Materials and Methods

Search Strategy

A search of PubMed, Embase, and CENTRAL was conducted on 8 March 2023 to identify relevant studies published after June 2012. A manual review of references from retrieved articles and reviews was also performed. The following terms were used in the literature search: methenamine (hippurate or mandelate), Hiprex, or hexamine and urinary tract infection, UTI, cystitis, pyelonephritis, bacteriuria, dysuria, or pyuria. A description of the full search strategy is included in Appendix 1. This systematic review was deemed exempt from formal review by the Institutional Review Board, adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting a systematic review, and all elements of the protocol were developed prior to conducting the review [19]. However, this review was not registered in the International Prospective Register of Systematic Reviews.

Study Selection

Studies were included for review if they assessed the use of methenamine for UTI prophylaxis in any setting and had a prospective or controlled retrospective design. Animal studies, case reports and case series, protocols without results, or studies only in abstract form were excluded. An initial screen of title and abstract was conducted for inclusion, followed by a full-text review of the remaining articles to determine final inclusion in the systematic review. Two authors (SMD and JNB) independently screened and reviewed articles, with any discrepancies being adjudicated by a third author (CBN).

Data Extraction

A standardized data extraction process was utilized to collect the following information: authors, publication date, study design, sample size, patient characteristics, treatment and comparator regimen, clinical efficacy outcomes, and adverse drug effects.

Bias Assessment

Quality of evidence for included studies was assessed using the Jadad scale for randomized, controlled trials and

the Methodological Index for Non-Randomized Studies (MINORS) for nonrandomized studies [20, 21]. The Jadad scoring system assesses the randomization, masking, and accountability of a clinical trial with a score ranging from 0 to 5, with a score ≥3 being considered high quality (Jadad) [20]. The MINORS tool is a 12-item checklist designed for the evaluation of nonrandomized studies. Each item is scored as either 0 (not reported), 1 (reported but inadequate), and 2 (reported and adequate), which can provide a maximum score of 24 for comparative studies (MINORS) [21]. Each author independently reviewed each study and the final score was determined with all authors at a consensus meeting.

Results

A total of 1,113 results were identified in the initial search of PubMed ($n = 280$), Embase ($n = 755$), and CENTRAL ($n = 78$). Of these results, 304 were excluded owing to duplication and 774 were excluded during title/abstract screening owing to irrelevance (Fig. 1). A total of 35 studies were assessed for eligibility through a full-text review. Seven studies were included in the final review and are summarized in Table 1.

Prospective, Randomized Studies

Botros et al. performed an open-label 12-month randomized controlled study comparing methenamine 1,000 mg twice daily with trimethoprim 100 mg nightly for recurrent UTI prophylaxis. A total of 92 women with recurrent UTI enrolled (average age 72 years) and were randomized 1:1 to treatment or control, although 6 patients were excluded from per-protocol analysis owing to non-adherence or loss to follow-up, and 11 patients were reassigned groups based on adverse effects or unforeseen issues with medication interactions or access. At 1 year, there was no difference in the number of patients experiencing an episode of recurrent UTI between groups. Secondary outcomes and the per-protocol analyses for all outcomes were also not statistically significant for differences between groups. Seven patients discontinued trimethoprim and migrated to the methenamine group, whereas 4 patients discontinued methenamine and trialed trimethoprim as an alternative [22].

Tam et al. conducted a randomized, double-blinded placebo-controlled study in patients discharged with a urinary catheter following pelvic reconstructive surgery, comparing methenamine 1,000 mg twice daily plus a 450-mg cranberry with vitamin C supplement versus a cranberry supplement

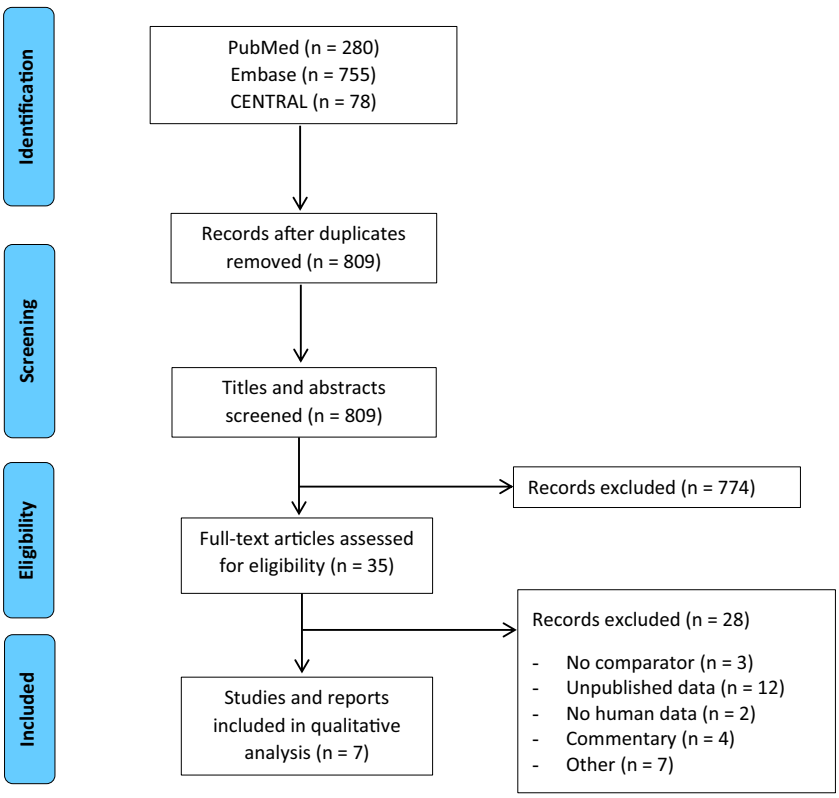

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the study selection process

Table 1 Summary of studies evaluating methenamine for urinary tract infection prophylaxis

Author, Year	Study design	Sample size	Intervention(s)	Treatment duration	Primary outcome	Results[a]	Adverse drug reactions (%)	Quality assessment
Botros, 2022 [22]	Prospective open-label	92	MH 1 g BID TMP 100 mg daily	1 year	Culture-confirmed UTI	65.1% vs. 65.1% (P = 1.0)	Diarrhea (4), abdominal pain (2), nephrolithiasis (2)	3/5[c]
Tam, 2022 [23]	Prospective double-blind	185	MH 1 g + cranberry BID Cranberry BID	7 days	Culture-confirmed UTI or UTI requiring ABX	66.7% vs. 79.8% (P = 0.048)	Stevens-Johnson Syndrome (1)	5/5[c]
Harding, 2022 [24]	Prospective open-label	240	MH 1 g BID Usual care ABX	1 year	Symptomatic UTI episodes requiring ABX (per PY)	0.89 vs. 1.38 (90% CI: 0.15-0.84)[b]	Respiratory infection (7), abdominal pain (7), headache (6)	3/5[c]
Hollyer, 2019 [25]	Retrospective pre/post	38	MH 1 g daily + vitamin C	314 days (median)	UTI frequency (per 1000 PD)	9.16 vs. 5.01 (P = 0.0001)	Nausea (3), unspecified intolerance (3)	19/24[d]
Snellings, 2020 [26]	Retrospective pre/post	150	MH 1 g BID (median)	Until UTI recurrence	Average time to UTI (months)	3.3 vs. 11.2 (P < 0.0001)	Gastrointestinal effects (6), dysuria (2), fatigue (0.7), edema (0.7), insomnia (0.7)	20/24[d]
Sweiss, 2022 [27]	Retrospective	60	MH 1 g BID Standard of care	180 days	Rate of UTI (per 180 PD)	0.6 vs. 1.3 (P = 0.0005)	None reported	20/24[d]
Rui, 2022 [22]	Retrospective	4274	MH (variable dosing) Standard of care	2 years	Change in number of UTI ABX	- 1.75 vs. - 1.16 (P < 0.001)	Not measured	16/24[d]

[a]Efficacy assessed versus comparator

[b]Demonstrated non-inferiority

[c]Jadad assesment [20]

[d]Methodological Index for Non-Randomized Studies scale [21]

ABX, antibiotics; *MH*, methenamine hippurate; *PD*, patient days; *PY*, person year; *TMP*, trimethoprim; *UTI*, urinary tract infection

alone. A total of 182 patients (average age 61 years) were randomized to treatment (93 in methenamine arm), all of which were women. Treatment was continued until the urinary catheter was removed at follow-up, an average of 12.25 days in the methenamine group and 11.1 days in the placebo group. Standard of care perioperative antibiotics were given, and trial treatment was initiated at discharge. Incidence of UTI was defined as a positive urine culture, with or without symptoms. At the end of the study, the incidence of UTI within 1 week from surgery was lower in the methenamine plus cranberry group than in the cranberry supplement alone group. At 6 weeks post-operatively, the rate of UTI occurrence was lower in the methenamine group (72.0% vs 89.9%, $p = 0.003$) and fewer pseudomonal UTIs were noted in patients who received methenamine (9 vs 21, $p = 0.041$). When UTI was defined as positive urine culture with symptoms, no difference was seen between groups. Other secondary outcomes were not significantly different between groups. Adverse effects were not directly compared, but patient questionnaire assessment of tolerability was not significantly different between groups. One patient in the methenamine group experienced an adverse event after study completion for which methenamine could not be excluded as the potential cause [23].

Harding et al. conducted an open-label, non-inferiority randomized controlled study comparing methenamine 1,000 mg twice daily with antibiotics for recurrent UTI prophylaxis (trimethoprim 100 mg daily, nitrofurantoin 50–100 mg daily, or cephalexin 250 mg daily) in women aged 18 years or older with recurrent UTI. A total of 240 patients (average age 50 years) were enrolled and randomized 1:1 to methenamine or an antibiotic comparator. A modified intention-to-treat analysis was conducted that included only participants who were still enrolled at 6 months (205 participants [85%]; 102 on antibiotics [85%] and 103 on methenamine [86%]). Twenty-two patients (18%) who switched from methenamine to antibiotic prophylaxis and 7 patients (6%) who switched from antibiotics to methenamine. After 1 year, the number of episodes of UTI did not exceed the non-inferiority margin. Antibiotic resistance to *E. coli* at 6 or 12 months' follow-up was less common in the methenamine group (56% vs 72%), but not at 18 months (20% vs 5%). Other secondary outcomes did not demonstrate significant between-group differences. Treatment satisfaction was rated high overall, although antibiotic once-daily dosing was preferred for convenience compared with methenamine on a 0- to 100-point patient satisfaction scale (82.2 vs 91.4, $p = 0.001$). Adverse effects were not statistically significantly different between treatment and control groups in incidence or severity. Investigator-reported serious adverse effects likely related to treatment included transaminase elevations and abdominal pain, which occurred in 2 participants in the antibiotic arm [24].

Retrospective Studies

Hollyer et al. conducted a retrospective, pre/post study of methenamine use for recurrent UTI prophylaxis in patients with renal transplant. A total of 38 patients were included. UTI was defined as the presence of related symptoms, laboratory evidence for infection, and requiring antibiotic treatment. Methenamine was dosed 1,000 mg daily and co-administered with a vitamin C supplement. After a median duration of 314 days, methenamine significantly reduced the rate of UTI occurrence, decreased days of antibiotic use (132 out of 1,000 vs 215/1,000 patient follow-up days, $p = 0.0022$), and decreased hospitalizations related to UTI (1.07 out of 1,000 vs 2.64/1,000 patient follow-up days, $p = 0.0456$). Minimal adverse effects were reported. Adherence to treatment was not assessed, although 1 patient discontinued methenamine owing to adverse effects [25].

Snellings et al. conducted a retrospective, pre/post study of methenamine in adults aged 60 and older prescribed methenamine for recurrent UTI prophylaxis in a primary care setting. Recurrent UTI was defined as 2 or more UTIs in a 12-month period prior to methenamine initiation; UTIs were defined by antibiotic prescription or a visit coded for UTI. A total of 150 patients (average age 77 years) were included in the study and evaluated for time to next UTI pre/post methenamine initiation (88.7% of study patients on methenamine 1,000 mg twice daily). The average time to recurrent UTI was significantly longer after methenamine initiation compared with prior to methenamine initiation (3.3 months vs 5.5 months, $p = 0.0004$). Several patients with CrCl < 30 ml/min were also observed to have a similar delayed time to next UTI without a greater rate of adverse effects, although the manufacturer's label advises avoidance in this degree of renal impairment. Adverse effects were reported in 16 patients and led to discontinuation of methenamine in 15 patients [26].

Sweiss et al. performed a retrospective, controlled study of methenamine for recurrent UTI prophylaxis in patients with kidney or liver–kidney transplantation. Patients older than 18 (average age 58 years) with past kidney or liver–kidney transplant and recurrent UTI who received methenamine 1,000 mg twice daily for UTI prophylaxis were matched 1:1 with controls who did not receive methenamine. Over 180 days post-initiation of methenamine, a reduction in the rate of recurrent UTI was seen with the use of methenamine. Additionally, decreased antibiotic exposure by approximately 3 days and a decreased rate of multi-drug-resistant organism isolation was seen in patients receiving methenamine. Data regarding tolerability/safety were not reported [27].

Rui et al. performed a retrospective, case-controlled study of methenamine use in women aged over 40 years of age with

recurrent UTI. Recurrent UTI was estimated based on previous antibiotic prescription history. Data were collected from a national Norwegian prescription database and assessed for the number of subsequent prescriptions for antibiotics after methenamine initiation in 2,137 women on methenamine and 2,137 controls (matched for age ± 10 years and number of antibiotic prescriptions prior to treatment start). After 2 years, greater decreases in the number of antibiotic dispensations were seen in the methenamine group compared with controls. Data on adverse effects, treatment discontinuation, and methenamine dosing strategies were not reported [28].

Discussion

This systematic review assessed recent evidence regarding the use of methenamine for UTI prophylaxis across a variety of settings, with a broad search strategy focused on recently published literature. Three prospective, randomized trials ($n = 517$) and 4 retrospective studies ($n = 4{,}522$) were included in this analysis, representing multiple different clinical settings [22–28]. Two of the 3 prospective trials were similar in terms of comparator, duration, outcome, and setting of care. These studies demonstrated similar efficacy of methenamine compared with antibiotic prophylaxis, although options for antibiotic prophylaxis were broader in Harding et al. [24] than in Botros et al [22]. The setting, treatment, and duration of use in Tam et al. differed from those of other trials reviewed, but demonstrated methenamine efficacy and safety in UTI prevention following pelvic floor reconstructive surgery [23].

The four retrospective studies demonstrated consistently positive conclusions that support the benefits seen in prospective trials. Among the retrospective studies reviewed, there was less potential for selection bias owing to the pre/post design in Snellings et al. and Hollyer et al. [25, 26]. Snellings et al. also presented preserved benefits of methenamine on UTI prophylaxis in patients with CrCl < 30 ml/min, albeit in a small subset of the study population [26]. Additionally, there appears to be the potential for lower rates of antibiotic resistance, which were found in 2 of the studies included [23, 27]. However, this finding was not maintained at 18 months in Harding et al. [24]. The overall findings from this systematic review suggest the long-term efficacy of methenamine for prophylaxis against UTI for up to 2 years and in multiple clinical settings.

Methenamine 1,000 mg twice daily was the most common dosing strategy regardless of clinical practice setting and was utilized in the majority of studies [22–24, 26, 27]. Co-administered medications, such as cranberry and vitamin C supplementation, were variable between trials. Adherence was not formally measured in the majority of trials included in this review, so it is difficult to assess the impact of twice-daily dosing compared with treatments dosed once daily. Overall, there were similar rates of adverse effects, including when compared with prophylactic antibiotics. It is reassuring that methenamine does not appear to lead to additional safety risks compared with prophylactic antibiotics. In addition, Snellings et al. demonstrated no increased safety risks when methenamine was used in patients with renal impairment (CrCl < 30 ml/min), although this was a small subset of the trial population [26].

The studies reviewed in this systematic review are limited by several factors. The inclusion of observational data in the retrospective studies and the lack of blinding in 2 of the 3 prospective trials introduces the potential for bias. The search strategy used for this review, although ideally providing a comprehensive review of recent evidence, does not include studies published before June 2012. There is also significant heterogeneity in concomitant treatment, clinical settings, and outcome measures between the studies included, preventing the completion of a quantitative systematic review and making comparisons between studies difficult. In addition, data on specific patient populations such as men and those with neurogenic bladder dysfunction are limited, as is adherence data from the studies included. Last, there was significant crossover (up to 18%) of patients in 2 of the 3 prospective trials [22, 23].

Future studies with increased standardization of methenamine dosing, limited concomitant medications, and blinded comparator groups may better assess the risks and benefits of methenamine for UTI prophylaxis. Longer study durations may also further inform the safety profile of methenamine and assess for potential impacts on multi-drug-resistant organism development, particularly because the benefits of decreased antibiotic use on drug-resistant organism development and rates of resistant organisms are likely not fully realized with shorter study durations.

Conclusion

The studies included in this systematic review demonstrate the efficacy of methenamine for UTI prophylaxis in a variety of clinical settings. The rate of adverse effects seen with methenamine appears to be comparable with that of existing treatments but with the potential added benefit of preventing other harms associated with antibiotics (e.g., resistance development). Methenamine may be considered a viable antibiotic-sparing agent in individuals at increased risk for UTI when nonpharmacological strategies fail or are not desired, although further evidence is needed to confirm risks and benefits of longer-term use as well as use in populations not represented in the studies reviewed.

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Declarations

Conflicts of Interest None.

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