

# Evaluation of methenamine for urinary tract infection prevention in older adults: a review of the evidence

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**Abstract:** Urinary tract infections (UTI) commonly occur in older adults and can lead to more severe, life-threatening infections. Physiological factors that change with age are thought to contribute to the increased frequency of UTI recurrence in older adults. Unfortunately, there are limited methods to prevent UTI in older adults, and utilization of antimicrobial agents for prevention can have many negative consequences. Methenamine has been proposed as a useful drug for the prevention of UTI as it works as a urinary antiseptic, safely producing formaldehyde to prevent bacterial growth while avoiding bacterial resistance. The objective of this review is to evaluate the existing literature and discuss the use of methenamine in older adults for prevention of UTI. A PubMed search was conducted to identify studies evaluating the effectiveness of methenamine to prevent UTI in older adults, and 10 publications were selected based on relevant criteria. Based on the literature, methenamine appears to be a safe and effective option to prevent UTI in older adults with recurrent UTI, genitourinary surgical procedures, and potentially long-term catheterization. Studies have not evaluated the safety of methenamine in patients with impaired renal function or CrCl <30 ml/min. When selecting a treatment approach to preventing UTI in older adults with adequate renal function, clinicians may consider methenamine as a viable option.

**Keywords:** aged, antibiotic prophylaxis, methenamine, older adult, urinary anti-infective agents, urinary tract infections

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## Introduction

In the United States (US), urinary tract infection (UTI) accounts for almost 5% of all emergency department visits by adults 65 years and older.<sup>1</sup> Urinary tract infection can compromise the quality of life in older adults and can lead to hospitalization and development of more severe, life-threatening infections.<sup>1</sup> The incidence of UTI increases with age in both men and women. A study surveying approximately 30,000 women in the United States concluded that over 10% of women 65–85 years old reported having a UTI within the past 12 months, which then increased to almost 30% for women 85 years and older. The incidence of men with UTI, ages 18–24, was reported to be 0.01 per person-year, which continued to increase with age to 0.05 per person-year for men ages 65–74, and

then 0.08 per person-year for men 85 years and older.<sup>2</sup> UTIs encompass both infections of the bladder or lower urinary tract (cystitis) and upper urinary tract infections involving the kidneys (pyelonephritis).<sup>3</sup> For the purposes of this review, UTI will be used synonymously with cystitis and pyelonephritis unless one or the other was an exclusion criteria.

Common causative pathogens of UTI are Gram-negative rods, most notably *Escherichia coli* followed by *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Proteus* spp., as well as Gram-positive cocci such as *Enterococcus faecalis*, *Streptococcus agalactiae*, and *Staphylococcus saprophyticus*.<sup>4</sup> When UTI is diagnosed, clinicians typically treat based on the patient's culture and sensitivity results, or, if

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treating empirically, follow the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases guidelines for women.<sup>3</sup> No specific guidelines exist, and evidence is often lacking, for treatment and prevention of recurrent UTI in older adults. Antimicrobial resistance is often a primary concern for clinicians when pressured to consider chronic use of antimicrobial agents to prevent UTI recurrence. As such, prevention strategies utilizing antimicrobial-sparing approaches are of interest to clinicians and patients alike.

Methenamine is approved by the US Food and Drug Administration (FDA) for prophylaxis of recurrent UTI in patients age 6 years and older, and studies have demonstrated its efficacy as an antimicrobial-sparing alternative in this patient population.<sup>5</sup> Methenamine works as an antiseptic, which does not pose a risk of organisms developing resistance. In an acidic environment, methenamine is hydrolyzed to ammonia and formaldehyde. Its mechanism of action is driven by the formation of bactericidal formaldehyde, which possesses nonspecific antimicrobial activity by denaturing proteins and nucleic acid of bacteria. Methenamine is available in two salt formulations, hippurate and mandelate, which aid in providing an acidic environment to promote the formation of formaldehyde. Methenamine has little antimicrobial activity in an alkaline environment, as formation of formaldehyde does not occur until the pH of the environment falls below 6. To ensure this reaction occurs, some treatment regimens include the use of ascorbic acid to further acidify the urinary environment. Previous studies and literature reviews support the use of methenamine for prevention of recurrent UTI; however, evaluation of the drug's efficacy and safety in older adults has not been well described, especially in those and with a creatinine clearance (CrCl) < 30 mL/min.<sup>5</sup> Given the high rates of UTI recurrence in older adults, and concerns for multidrug-resistant infections, alternative antimicrobial-sparing options for older adults with UTI should be evaluated. This review article focuses on the evidence for use of methenamine to prevent UTI in older adults.

## Methods

A *PubMed* search was conducted on September 27, 2018 to identify studies evaluating prevention

of UTI in older adults with methenamine from January 1960 through September 2018. The following search terms were used: ['methenamine' (Mesh) OR 'methenamine' OR 'hexamine' OR 'hexamethylenetetramine' OR 'urotropin' OR 'aminoform'] AND ['urinary tract infection' (Mesh) OR 'urinary tract infections' OR 'UTI' OR 'bacteriuria' OR 'pyuria' OR 'Cystitis'(Mesh) OR 'Pyelonephritis'(Mesh)] AND ['Aged' (Mesh) OR 'aged' OR 'elderly' OR 'older adult']. This search resulted in 77 articles, which were filtered for English and reduced to 60 articles. Of those 60 articles, cohort studies, randomized controlled trials, meta-analyses, and case reports were reviewed. Studies and case reports were included if they evaluated methenamine's role for prevention of UTI as well as included patients with a mean age of 58 years and older. Studies were excluded if they evaluated methenamine in combination with an antibiotic, evaluated treatment of UTI with methenamine instead of prevention, if they did not evaluate UTI events specifically, or if the study authors did not specify a mean patient age. No meta-analyses were identified in the search. Nine studies/case reports met all criteria, and an additional case series meeting all criteria was identified through references for a total of 10 studies/case reports, summarized in Table 1. The study selection process is outlined in Figure 1.

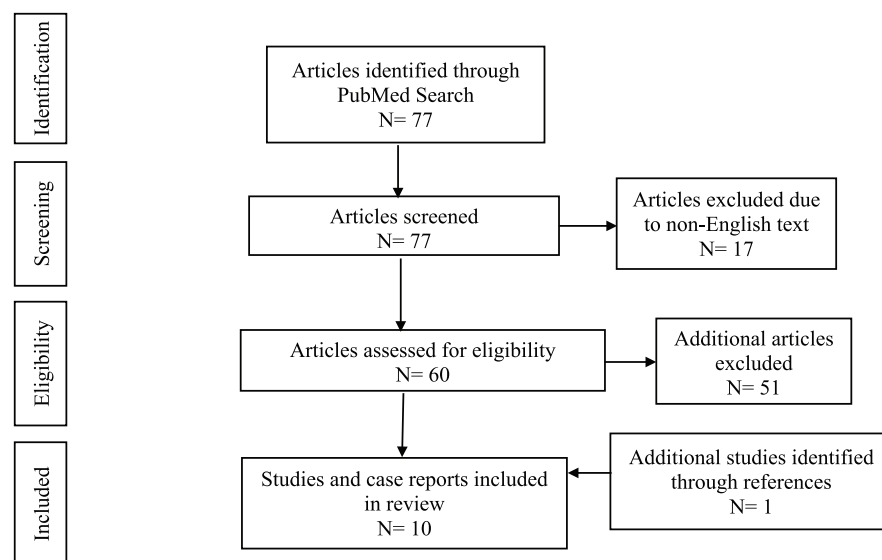
## Results

### *Recurrent urinary tract infection*

*Freeman 1968.* Freeman and colleagues evaluated the efficacy of continuous therapy with urine-sterilizing agents in 122 men with chronic UTI.<sup>6</sup> Patients were included if they had significant bacteriuria, defined by presence of > 10<sup>5</sup> organisms/ml of a single species, or two cultures with ≥ 10<sup>4</sup> organisms/ml of the same Gram-negative rod, in addition to either a positive urine sediment or a renal biopsy consistent with the diagnosis of pyelonephritis. Patients first received antibiotic therapy directed by urine culture sensitivities. On the last day of antimicrobial therapy, patients were then assigned to one of four continuous prophylactic options: sulfamethizole 0.5 g four times a day, nitrofurantoin 50 mg four times a day, methenamine mandelate 1 g four times a day, or placebo four times a day. Patients included in the analysis completed at least 13 months of

**Table 1.** Summary of clinical studies investigating methenamine for prevention of UTIs in older adults.

First author	Study design	Methenamine dose and duration	Number of patients	Mean age in years (range)	Incidence of UTI or bacteriuria (methenamine versus placebo, when applicable)	Renal function of patients
<b>Recurrent UTI</b>						
Freeman <sup>6</sup>	Randomized Controlled Trial	Methenamine mandelate 1 g QID × 25 months	122	(20–89) with 58% >60 years	25% versus 86%	Patients excluded if CrCl <41 ml/min
Freeman <sup>7</sup>	Randomized Controlled Trial	Methenamine mandelate 1 g QID × 2 years	249	59 (21–83)	9% versus 40% ( $p < 0.001$ )	6% of patients had renal failure <sup>§</sup>
Bohensky <sup>8</sup>	Case Series	Methenamine mandelate 2 g QID × 25 days	90	81.5 (67–102)	28%*	NR
Parvio <sup>9</sup>	Case Series	Methenamine hippurate 1 g BID × 6 months	52	84.7 (65–96)	42.5%*	NR
McAllister <sup>10</sup>	Case Reports	Methenamine hippurate 500 mg BID	4	89	Not applicable	Various <sup>‡</sup>
<b>Genitourinary Surgical Procedures</b>						
Schiotz <sup>11</sup>	Randomized Controlled Trial	Methenamine hippurate 1 g BID × 5 days	145	58.3 (30–87)	2.7% versus 13.9% ( $p = 0.03$ )	NR
Tyreman <sup>12</sup>	Randomized Controlled Trial	Methenamine hippurate 1 g night before surgery, 1 g BID day of surgery, 1 g TID × 5 days after surgery	109	65 (63–67)	2.2% versus 28.6% ( $p < 0.001$ )	NR
Wesolowski <sup>13</sup>	Randomized Controlled Trial	Methenamine mandelate 3–4 g daily	75	67 (54–80)	40% versus 66.6%	NR
<b>Long-term Catheterization</b>						
Kostiala <sup>14</sup>	Randomized Controlled Trial	Methenamine hippurate 1 g BID + 0.5 g ascorbic acid TID × 8 days	123	75	39% versus 100% at 1 week 77% versus 100% at 2 weeks Both 100% at 6 weeks	Patients excluded if SCr >1.5 mg/dl
Norrman <sup>15</sup>	Prospective Cohort Study	Methenamine hippurate 1 g BID × 4 months	22	75 (70–80)	18.2% versus 77.3%	NR
<p>*Methenamine only.  <sup>§</sup>Defined as SCr &gt;2 mg/100 ml.  <sup>‡</sup>One patient had a CrCl of 37 ml/min, one had a CrCl of 43 ml/min, one had ESRD with a CrCl of 8 ml/min, one not reported.            BID, twice daily; NR, not reported; QID, four times daily; SCr, serum creatinine; TID, three times daily; UTI urinary tract infection.</p>						



**Figure 1.** Article selection flowchart.

therapy, continued for up to 25 months. Patients with a creatinine clearance  $< 41$  ml/min and gout were excluded from the methenamine group to avoid acid load or precipitation of urate crystals in the urine. Outcomes of continuous prophylaxis were recorded by two means: responders (sterile urine culture or  $< 1000$  organisms/ml) and culture results. Results of continuous therapy revealed that prophylaxis with methenamine mandelate was associated with the greatest number of responders amongst all groups. Compared with placebo, methenamine demonstrated a significant increase in responders (75% versus 14%;  $p < 0.001$ ) as well as negative cultures (46% versus 3%;  $p < 0.0005$ ). When compared with other antimicrobial agents evaluated, methenamine was shown to have significantly more responders to therapy than nitrofurantoin (75% versus 43%;  $p < 0.05$ ) and sulfamethizole (75% versus 46%;  $p < 0.05$ ). However, there were no differences in negative cultures between agents. There were three cases of adverse events reported in patients receiving methenamine which included abdominal cramps and diarrhea, dyspnea, and severe dysuria, and one severe case that consisted of generalized edema, urticaria, and dyspnea.

*Freeman 1975.* Expanding on the results of the 1968 study above, Freeman and colleagues evaluated 249 men with symptomatic bacteriuria (defined as  $> 10^5$  organisms/ml) in a prospective study of four continuous prophylactic regimens

for 25 months: sulfamethizole 0.5 g four times daily, nitrofurantoin 50 mg four times daily, methenamine mandelate 1 g four times daily, or placebo.<sup>7</sup> Patients were required to show evidence of 'tissue infection' defined by positive urine sediment or a renal biopsy consistent with the diagnosis of pyelonephritis. The primary outcome was UTI recurrence and exacerbations, defined as clinical infection involving inflammation of the urinary tract organs, febrile episodes requiring antibiotic therapy, or both.<sup>7</sup> Of the 249 patients initially evaluated, 165 completed 25 months of therapy, and an additional 65 patients continued follow up for as long as 123 months at the time of publication. The results showed a beneficial effect of continuous therapy at delaying recurrence of bacteriuria, particularly with nitrofurantoin and methenamine mandelate. When compared with placebo, methenamine was associated with significantly more negative cultures, 69% versus 43% ( $p < 0.001$ ). Methenamine also significantly reduced the recurrence of bacteriuria at up to 25 months when compared with placebo ( $p < 0.05$ ). However, the rate of interim antimicrobial therapy for acute exacerbation of UTI was not significantly different (38% with methenamine versus 48% with placebo,  $p > 0.05$ ). While the methenamine group required a relatively greater number of interim antibiotic courses during the 25-month follow-up period compared with the sulfamethizole and nitrofurantoin groups (0.59 courses per patient versus 0.16 and 0.39, respectively; no

statistical analysis performed), it remained significantly less than placebo (0.59 *versus* 0.96 courses per patient;  $p < 0.05$ ). The authors concluded that continuous therapy with methenamine may delay, but not prevent, the recurrence of bacteriuria. Recurrence of bacteriuria in the methenamine group remained statistically significant when compared with placebo ( $p < 0.05$ ) for 6 months longer than the nitrofurantoin group. In regards to safety, there were three cases of adverse events reported in patients receiving methenamine, which included skin eruption, dyspnea and dysuria, and severe diarrhea.

*Bohensky.* Bohensky evaluated whether methenamine mandelate could prove an acceptable, well-tolerated drug to control and prophylaxis against asymptomatic bacteriuria in hospitalized elderly patients.<sup>8</sup> This study included 95 patients, most catheterized, and not undergoing treatment for acute UTI at the time of inclusion. Prior to, and during, the study period, patients underwent urinalysis to detect presence of bacteriuria through microscopic examination and triphenyl tetrazolium chloride (TTC) test. Bacteriuria was defined by a positive TCC test indicated by a color change occurring in the presence of high concentrations of urinary tract pathogenic organisms (organism concentrations not specified by the authors). Five patients discontinued therapy due to taste preferences. Of the 90 patients who completed the study, 65 tested positive and 25 tested negative for UTI prior to therapy with methenamine. All patients received 10 ml of methenamine mandelate suspension (1 g methenamine from 100 mg/ml suspension) four times a day for 3.5 weeks for either treatment (positive TTC) or prophylaxis (negative TTC) of UTI. If their urine was alkaline, acidification was achieved by adding ascorbic acid 2 g orally daily during the 3.5 week period. A urinalysis was completed before and during the study at 2 weeks and 3.5 weeks. Methenamine mandelate reduced the number of patients with bacteriuria, with 47 (72%) of the patients with a positive urinalysis prior to therapy converting to a negative urinalysis at the end of the 3.5 week period. However, of the 25 patients without significant bacteriuria prior to methenamine therapy, 13 had a positive urinalysis at the end of the 3.5 week period. No statistical analysis was performed on these data. Elaboration of bacteriuria resulting in either asymptomatic or symptomatic UTI was not

discussed by the authors, nor was the occurrence of bacteriuria in those patients with a negative TTC prior to starting methenamine for prophylaxis. Additionally, no adverse events were reported.

*Parvio.* Parvio evaluated the efficacy of methenamine hippurate in 52 older females with chronic UTI.<sup>9</sup> All patients were hospitalized in a long-term care facility for at least 2 years, and had a history of recurrent UTI. In the 6 months preceding the trial, all patients had received short courses of antimicrobial therapy for the treatment of UTI, in addition to long-term prophylactic antimicrobial therapy replaced by methenamine hippurate at the start of the study. Urinalysis was performed and patients were treated with antimicrobial agents based on culture and sensitivities to ensure eradication prior to prophylaxis with methenamine hippurate. Rates of re-infection during the 6-month course of therapy with methenamine hippurate 1 g twice daily was compared with infection rates documented in the 6 months preceding the trial. In addition, a daily dose of 2–4 g of oral ascorbic acid was administered in patients with a urine pH > 5. For analysis, patients were divided into three groups based on degree (normal, partial, total) of incontinence and immobility. Prophylaxis with methenamine hippurate was associated with a lower rate of re-infection (reported as total re-infection cases per person in each group over 6 months) compared with no therapy in all three patient groups: normal (0.45 *versus* 2.82), partial (0.58 *versus* 4.33), and total (0.29 *versus* 5.24). No statistical analyses were provided for these results. Parvio reported that of the 40 patients who completed the 6 months of therapy, only 17 (42.5%) cases of re-infection occurred, objectively less than during the 6 months without therapy, which was not quantified in the study. The only recorded side effects were mouth soreness in two patients and abdominal pain in one; no serious adverse events were observed.

*McAllister and Allwood.* Four case studies summarized by McAllister and Allwood provide some additional limited data for the safety and efficacy of methenamine hippurate to treat complicated UTI in older adults.<sup>10</sup> The UTIs in the case studies were untreatable with oral antimicrobial agents due to pathogen multi-drug resistance or were contraindicated in the setting of ESRD. As a

result, methenamine hippurate was utilized as a treatment for their complicated UTI, and the recurrence rate was documented. All four patients had a history of recurrent UTI as defined by  $\geq 3$  occurrences within 1 year or  $\geq 2$  occurrences in a 6-month period. Each patient was treated with methenamine hippurate 500 mg twice daily, supplemented by ascorbic acid 1 g twice daily in three of the four cases. In each case report, the patient's UTI improved, and they did not experience symptomatic UTI recurrence during the duration of methenamine hippurate treatment, which ranged from 1 to 6 months. No adverse effects were reported by the authors for any of the four cases.

#### *Genitorurinary surgical procedures*

*Schiotz and Guttu.* Schiotz and Guttu found that methenamine hippurate significantly reduced the incidence of postoperative bacteriuria and UTI when given prophylactically to surgical patients.<sup>11</sup> The study included patients admitted for elective gynecologic laparotomy or vaginal plastic surgery who received Foley catheter placement without antibiotic prophylaxis. Methenamine hippurate was administered at 1 g twice daily for 5 days, with the first dose given the night prior to surgery and the last dose given on postsurgery day 4. Methenamine hippurate was associated with a significant reduction in both postoperative, symptomatic UTI (2.7% versus 13.9%,  $p = 0.03$ ) and postoperative, asymptomatic bacteriuria (30.1% versus 50.0%,  $p = 0.02$ ) compared with placebo. No major adverse events were noted.

*Tyreman.* Tyreman and colleagues found that prophylactic methenamine hippurate significantly reduced the rate of bacteriuria (defined as  $>10^5$  organisms/ml of urine) at 3 days post-op in 94 patients undergoing surgery for uterovaginal prolapse with subsequent placement of an indwelling catheter.<sup>12</sup> Of the original 109 patients, 15 were excluded due to bacteriuria prior to surgery. The remaining patients were randomized to receive either methenamine hippurate prophylaxis ( $n = 45$ ) or no prophylaxis ( $n = 49$ ). Patients in the methenamine hippurate group received 1 g the night before surgery, then 1 g twice daily on the day of surgery, and 1 g three times daily for 5 days following surgery. Compared with no therapy, methenamine hippurate was associated with a significant reduction in the incidence of

bacteriuria: only 1 (2.2%) patient developed symptomatic bacteriuria compared with 14 (28.6%) in the placebo group ( $p < 0.001$ ). No side effects from methenamine hippurate were reported.

*Wesolowski.* A study by Wesolowski and colleagues investigated the relative efficacy of four antibacterial agents for prophylaxis of UTI in men undergoing prostatectomy.<sup>13</sup> The study included 75 men who were assigned to receive either nitrofurantoin 100 mg orally daily, methenamine mandelate 3–4 g orally daily, sulfamethoxazole/trimethoprim 800/160 mg orally twice daily, chloramphenicol 1 g intramuscularly twice daily, or no therapy. Prophylaxis was started 1 day prior to the surgery and continued until 3 days after removal of the indwelling catheter (total mean time to removal: 11 days). UTI was observed in 53% of patients. When comparing groups, nitrofurantoin, and methenamine mandelate were associated with less frequent UTI after prostatectomy (33.3% and 40%, respectively), while sulfamethoxazole/trimethoprim and chloramphenicol (53.3% and 66.6%, respectively) had infection rates similar to no therapy (66.6%). No further statistical analysis was provided for the results.

#### *Long-term catheterization*

*Kostiala.* In a study performed by Kostiala and colleagues, prior to undergoing long-term catheterization (mean 81 days), 123 patients were given either methenamine hippurate 1 g twice daily ( $n = 40$ ), nitrofurantoin 50 mg three times daily ( $n = 42$ ), or no therapy ( $n = 41$ ).<sup>14</sup> Patients in the nitrofurantoin and methenamine hippurate groups were also given ascorbic acid 0.5 g three times daily. Patients were included if they had a serum creatinine level  $\leq 150 \mu\text{mol/l}$  or  $\leq 1.7 \text{ mg/dl}$  and no acute or chronic UTI. Urine collection was done weekly on a prefixed day during the first 3 months of catheterization and every 2 weeks thereafter. Nitrofurantoin and methenamine hippurate delayed the appearance of bacteriuria at 1 week postcatheterization compared with no therapy, with 30%, 39%, and 79% of patients infected ( $\geq 10^4$  organisms/ml), respectively. The corresponding percentages of bacteriuria at 2 weeks were 58%, 77%, and 100% for nitrofurantoin, methenamine hippurate, and no therapy, respectively; however, nearly all patients in each group

had bacteriuria at 6 weeks. While the authors noted that patients in the methenamine hippurate group needed significantly fewer antimicrobials to treat symptomatic UTI than the group receiving no therapy, no statistical data for these results was reported. Additionally, no adverse events in the methenamine hippurate group were reported.

*Norrman and Wibell.* Norrman and Wibell showed a reduction in the incidence of symptomatic UTI in patients with indwelling catheters taking methenamine hippurate.<sup>15</sup> Although this study was designed to evaluate the incidence of catheter blockage, the authors were also able to secondarily note the incidence of symptomatic UTI. The trial included 29 elderly women (of which 22 were reported on), who had an indwelling Foley catheter and significant bacteriuria ( $> 10^5$  organisms/ml). Patients received methenamine hippurate 1 g twice daily for a mean of 120 days, followed by no therapy (control period) for a mean of 131 days. Urine cultures were performed monthly. The time period with methenamine hippurate was associated with less UTI than during the control period (18.2% versus 77.3%) as well as fewer number of episodes and total days of antibiotic treatment for clinical infection (8 versus 22 episodes and 137 versus 406 days, respectively); however, no further statistical analyses were reported. In addition, rates of catheter replacement (per patient day) were significantly lower during the methenamine hippurate therapy period than the control period (0.0256 versus 0.0398,  $p < 0.01$ ). No adverse effects with methenamine hippurate were reported.

## Discussion

Methenamine is FDA-approved for prophylaxis of recurrent UTI in patients when long-term therapy is necessary.<sup>16</sup> There are two methenamine formulations available that vary in dose: methenamid hippurate and methenamine mandelate. Methenamine hippurate is dosed 1 g twice daily for prophylaxis, whereas methenamine mandelate is dosed 1 g four times daily. The clinical trials that brought both forms of methenamine to market included an insufficient number of patients age  $\geq 65$  to assess response differences in this population, and the manufacturer recommends methenamine hippurate and mandelate be used cautiously in older adults. Based on the available literature including older adults, we

have extracted data for patients 58 years and older to summarize our findings of the role of methenamine hippurate or mandelate for prevention of UTI in older adults.

## Recurrent UTI

The studies included in this review that evaluated effectiveness of methenamine hippurate or mandelate in recurrent UTI prevention collectively resulted in positive results, with each showing a reduction in incidence of UTI or bacteriuria. The doses ranged from 500 mg twice daily to 1 g four times daily. Although the studies were able to show positive results, a collaborative recommendation for use of methenamine as a preventative strategy at doses lower than the FDA-approved doses remains unclear. The safety of methenamine hippurate and mandelate was demonstrated across each of these studies across different doses, durations, and in combination with or without ascorbic acid. All studies reviewed reported reduced rates of bacteriuria, but not all documented the incidence of symptomatic UTI. Bacteriuria may be a risk factor for UTI but does not always lead to a symptomatic UTI. The FDA approval for methenamine does not provide specific guidance on duration of therapy. Each study discussed above included a different duration of therapy and time period for follow-up. In the 1975 study by Freeman and colleagues, patients were followed for 25 months, with continued follow up for up to 10 years (data not reported). Results showed that methenamine mandelate was successful in delaying recurrence of UTI until 25 months, which is the longest time period reported when compared with other studies evaluating patients with recurrent UTI.<sup>6</sup> However, in all of the studies, once methenamine was discontinued, incidence of bacteriuria or UTI were more common.

## Genitorurinary surgical procedures

While not FDA-approved for this indication, prophylaxis with methenamine hippurate or mandelate was shown to be effective at preventing UTI in patients undergoing genitorurinary surgery; however, timing of methenamine dosing differed among the studies. All three studies included dosed methenamine before, during, and after surgery; however, the duration postsurgery differed as Schiotz and Guttu, and Tyreman and

colleagues had a finite duration postsurgery and Wesolowski and colleagues ceased therapy with methenamine mandelate 3 days after catheter removal. The dose and regimen also differed amongst the studies. Tyreman and colleagues chose to evaluate methenamine hippurate with a dose escalating regimen, whereas Schiotz and Guttu, and Wesolowski and colleagues both kept the dose of methenamine consistent throughout the duration therapy. In spite of the differences amongst treatment dose and regimen, all three studies were able to successfully demonstrate that methenamine hippurate or mandelate are effective options for UTI prophylaxis in patients receiving genitourinary surgery.

#### *Long-term catheterization*

Long-term catheterization has been associated with increased risk of UTI.<sup>14</sup> In the two studies evaluated, both provided positive results that supported methenamine hippurate 1 g twice daily as an effective off-label prophylactic option to prevent UTI in some patients with long-term need for catheterization. While methenamine hippurate may not be as effective at preventing UTI in patients with catheters compared with patients with recurrent UTI or postgenitourinary surgery, these studies demonstrated that it can delay acute occurrence of UTI postcatheterization in some patients and decrease the future rate of UTI. In addition, methenamine hippurate was found to be antibiotic-sparing, a quality that may attenuate the development of antibiotic resistance in patients with recurrent UTI.

One important point to consider in older adults is that the use of both forms of methenamine are contraindicated in patients with renal or hepatic impairment, or severe dehydration.<sup>16</sup> As the mechanism of action is entirely dependent on reaching the bladder, patients who are dehydrated or have significant renal insufficiency may not benefit from its use and may potentially experience an increased incidence of adverse events due to formaldehyde production.<sup>17</sup> In our review, we found no clinical studies investigating use of methenamine hippurate or mandelate in patients with impaired renal function. There were a few case reports of patients with end-stage renal disease (ESRD), but these do not provide conclusive evidence for using methenamine hippurate in this patient population. It is also possible that studies

in patients with renal impairment were conducted but were never published.

Additional limitations of this review included the reporting of case studies, which could introduce bias and may impact the validity of the findings. Many of the studies were of low quality and did not include statistical analysis to evaluate the significance of the rate of bacteriuria or UTI occurrence.

Although this review highlights studies supporting the role of methenamine hippurate and mandelate in preventing UTI in certain high risk patients, it is unclear whether doses lower than FDA approved doses can be recommended in older adults. This is an important consideration as an over-the-counter product, Cystex<sup>®</sup>, is now available, containing methenamine 162 mg per tablet in combination with sodium salicylate. The product is recommended for adults up to age 60 years with dosing instructions of two tablets three times a day or a total daily dose of 972 mg of methenamine. Additionally, given the product is over-the-counter, it is not regulated by the FDA, leading to potential product variability. Questions also still remain regarding length of prophylaxis for recurrent UTI, postoperative procedures, and catheterization. The available data, however, suggest that methenamine may be a safe and effective drug for the prevention of UTI in older adults with adequate renal function. The most commonly reported side effects of methenamine are nausea, upset stomach, dysuria, and rash, each reported to occur in less than 3.5% of patient's treated.<sup>16</sup> Methenamine is converted to formaldehyde in the stomach and urine, which may be the cause of gastrointestinal side effects as well as dysuria.<sup>17</sup>

#### **Conclusion**

This review provides evidence demonstrating the efficacy of methenamine in the prevention of UTI in older adults, as well as its tolerability and safety profile. There are limited data for the use of methenamine in older adults, especially with impaired renal function; however, this review provides evidence supporting the use of methenamine for prevention of UTI in different populations of adults 58 years and older. Further research is needed to establish the effective dose and duration of methenamine for prevention of UTI in older adults.



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