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METHENAMINE PROPHYLAXIS FOR RECURRENT URINARY TRACT INFECTIONS IN A TERTIARY REFERRAL CENTER

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**METHENAMINE PROPHYLAXIS FOR RECURRENT URINARY TRACT
INFECTIONS IN A TERTIARY REFERRAL CENTER**

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the
requirements for the degree of

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By

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ABSTRACT

Purpose: Methenamine hippurate (MH) is a urinary antiseptic, indicated for prophylaxis of recurrent urinary tract infections (UTIs) but with only few and limited studies regarding its efficacy. To help address this knowledge gap we reviewed our experience with MH for UTI prophylaxis, focusing on women with recurrent uncomplicated UTIs.

Materials and Methods: The University of Kentucky electronic health record was queried to identify adults who were prescribed MH from the Urology clinic between January 2013 and January 2019. Charts were reviewed to assess patient-reported UTI frequency, demographics and relevant health factors. Treatment success was defined as 0-1 UTI in 6 months or 0-2 UTIs in 1 year.

Results: Of 670 patients prescribed MH, 508 did not meet inclusion criteria. The most common reasons for exclusion were complicated UTI, no return visit, treatment nonadherence and insufficient follow-up time. The primary study population was 162 women with recurrent uncomplicated UTIs: 41 age <50 and 121 age \geq 50. Success rates with MH were 83% and 77%, respectively. Success rates were not significantly associated with age, diabetes, immune suppression, high-tone pelvic floor dysfunction or (if postmenopausal) vaginal estrogen use. Exploratory study of patients using intermittent catheterization (n=30) or indwelling catheters (n=12) showed success in 67% and 50%, respectively.

Conclusions: MH had high success rates for women with recurrent uncomplicated UTIs. Patients using catheters had lower success rates. Prospective trials would strengthen the evidence to guide decisions for treatment and insurance coverage.

Abbreviations: MH-methenamine hippurate; UTI-urinary tract infection

I. INTRODUCTION

Urinary tract infection (UTI) is a common cause of bacterial infection in the United States, with a lifetime risk of 60% for women¹. Recurrent UTI is defined as >1 UTI in 6 months or >2 UTIs in one year². Recurrent UTI is a common problem; risk of UTI recurrence in a year is 30-50% among women and 12% among men¹. UTI evaluation has an estimated cost of approximately \$2 billion per year in the United States¹.

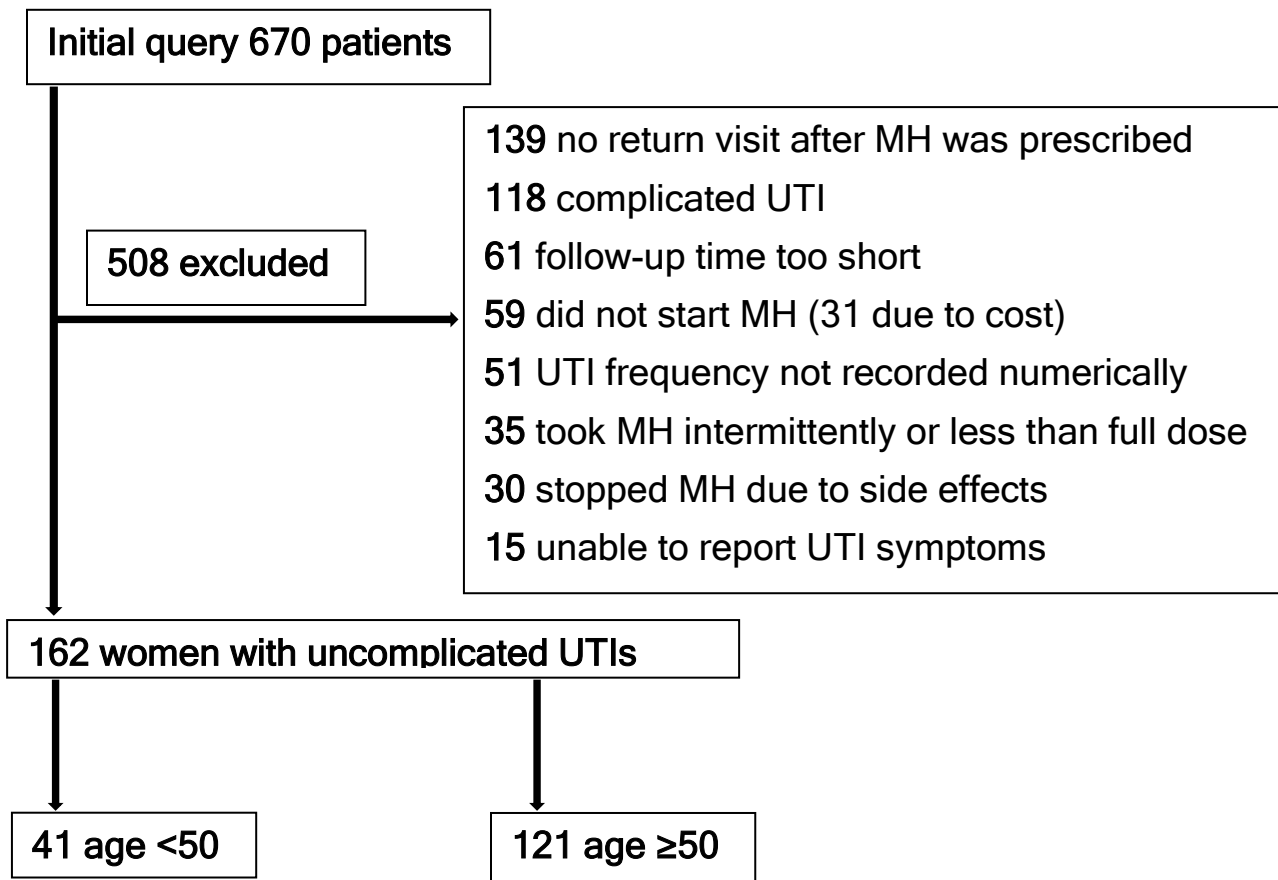
Treatment options for recurrent UTI are limited to antibiotic therapies (episodic or daily), non-antibiotic prophylactics (cranberry supplementation, methenamine hippurate), and/or vaginal estrogen replacement for post-menopausal patients. Methenamine hippurate (MH) is a non-antibiotic urinary antiseptic indicated for daily use in patients with recurrent UTI for the suppression and prevention of UTI episodes. In the acidic environment of urine, the drug is hydrolyzed to formaldehyde, which has bacteriostatic action.^{3,4,5} While it is indicated for suppression and prophylaxis of recurrent UTI,³ the evidence is limited and its use is variable among urologists. A 2012 Cochrane review noted that MH may have some benefit in decreasing symptomatic UTI for people with normal urinary tracts (RR 0.24), but the studies included in the review were of mixed quality and often short duration.⁶ In 2019 the American Urological Association published guidelines on the evaluation and treatment of recurrent UTI where a multidisciplinary guideline panel was unable to draw reliable conclusions regarding the effectiveness of MH as prophylaxis for recurrent uncomplicated UTIs in women based on the paucity of data and lack of trials.²

The aim of this capstone is to contribute more knowledge regarding the efficacy of MH as prophylaxis for recurrent UTI based on the patient reported experience of the patients at a tertiary urology practice. This was accomplished with retrospective chart review of all patients

prescribed MH spanning 6 years' experience to evaluate for treatment success. The primary outcome measure of this study is treatment success as a binary outcome with unadjusted logistic regression models to assess for associations of success with patient health factors. The secondary outcome measure of this study is magnitude of efficacy as measured by a pre-post observational analysis of difference in pre-treatment UTI frequency and on-treatment UTI frequency. As an exploratory analysis, we also reviewed the efficacy of MH among patients using intermittent catheterization or indwelling catheters.

II. MATERIALS AND METHODS

This retrospective observational study protocol was reviewed and approved by the University of Kentucky Institutional Review Board. The Ambulatory Electronic Health Record was used to identify patients age ≥ 18 years who were prescribed MH from the Urology clinic between January 2013 and January 2019. Exclusion criteria included (1) no return visit after MH was prescribed, (2) patient did not start MH, (3) patient was unable to self-report UTI symptoms, (4) on-treatment UTI frequency was not recorded numerically, (5) complicated UTI due to anatomic or neurologic abnormalities, or (6) follow-up and treatment adherence too short (<6 months) to assess the primary outcome [with the exception of patients noted to have 2 UTIs in <6 months who were included and counted as treatment failures] (Figure 1).



The primary analysis was for women with recurrent uncomplicated UTIs. Pre-MH baseline data included age, diabetes, menopausal status, immunosuppression, high-tone pelvic floor dysfunction (non-neurogenic), and, for women age ≥ 50 , use of vaginal estrogen. For return visits after starting MH, we noted treatment adherence and patient-reported number of interim UTI episodes. We used patient-reported UTIs as many of our patients live far from our center and do not come here for individual UTI episodes, making it impossible to assess UTI frequency retrospectively with billing codes or other objective measures.

Our primary outcome was binary success or failure of MH treatment based on on-treatment reported UTI frequency. We defined failure based on the standard definition for recurrent UTIs: >1 UTI in 6 months or >2 UTIs in one year. Accordingly, success was defined as 0-1 UTI in 6

months or 0-2 UTIs in one year. The primary outcome was reported as frequency of success and also fit to a series of unadjusted logistic regression models based on age, presence of pelvic floor dysfunction, diabetes mellitus, immunosuppression, and use of vaginal hormone replacement therapy (where applicable).

The secondary analysis of this population included those subjects that self-reported pre-treatment yearly UTI frequency numerically (in addition to on-treatment UTI frequency). For these subjects we performed a pre-post observational analysis to compare the UTI frequencies pre-treatment vs. on-treatment. The pre- and on-treatment yearly UTI frequency was analyzed using paired-profile T-testing of the means.

As an exploratory analysis, we evaluated success in patients who were using intermittent catheterization or indwelling catheters, mostly for neurogenic lower tract dysfunction, but otherwise met inclusion criteria. Pre-MH baseline data for this exploratory analysis included age, sex, diabetes, immunosuppression, etiology of urinary retention and type of catheter (intermittent, indwelling urethral or suprapubic). For return visits after starting MH, we noted treatment adherence and number of interim UTI episodes.

Data were analyzed using Statistical Analysis System (SAS) version 9.4.

III. RESULTS

Demographics

Initial electronic health record query found 670 patients aged ≥ 18 who were prescribed MH during the study period. Of these, 508 were excluded (Figure 1). The primary study population included 162 women with recurrent uncomplicated UTIs. Of these, 25% were age < 50 and 75% were age ≥ 50 . Baseline demographics for the overall sample are presented in Table 1.

Table 1			
Women with Recurrent Uncomplicated UTIs			
	Total n=162	Age <50 n=41	Age ≥50 n=121
Age (mean +/- SD)	57.9 +/- 17	34.8 +/- 9.8	65.8 +/-10.6
Diabetes mellitus (n, %)	40 (25%)	7 (17%)	33 (28%)
Immunosuppressed (n, %)	24 (15%)	4 (10%)	20 (17%)
High-tone pelvic floor (n, %)	47 (29%)	15 (37%)	32 (26%)
Vaginal estrogen use (n, %)	n/a	n/a	94 (78%)

Primary Analysis

Of the 162 women included in our analytic sample, 127 (78%) had success with MH therapy. Odds of success did not differ by the two age groups as a proxy for menopausal status (p=0.42); however, given our a-priori expectation that postmenopausal women could be more likely to fail, we present all analyses stratified by this age distinction. Of the age <50 group, 34 (83%) reported success. In logistic regression models, odds of MH success did not differ by the presence or absence of the following variables: presence of diabetes, immunosuppression, or high-tone pelvic floor dysfunction (Table 2).

Of the age ≥50 group, 93 (77%) reported success. In logistic regression models, odds of MH success did not differ by the presence or absence of the following variables: presence of diabetes, immunosuppression, high-tone pelvic floor dysfunction, or use of vaginal estrogen (Table 2).

Table 2				
Associations between MH Success and Presence of Diabetes Mellitus, Immunosuppression, High-Tone Pelvic Floor or Vaginal Estrogen				
Age <50 n=41	Success Rates			
Variable	Present	Absent	Odds Ratio for Treatment Success*	P
Diabetes mellitus	6 of 8 (75%)	29 of 34 (85%)	0.43 (0.06-2.87)	0.38
Immunosuppression	3 of 4 (75%)	32 of 38 (84%)	0.58 (0.05-6.57)	0.66
High-tone pelvic floor	13 of 15 (87%)	21 of 26 (81%)	1.55 (0.26-9.17)	0.63
Age ≥50 n=121	Success Rates			
Variable	Present	Absent	Odds Ratio for Treatment Success*	P
Vaginal estrogen HRT	73 of 94 (78%)	20 of 27 (74%)	1.22 (0.45-3.27)	0.70
Diabetes mellitus	24 of 33 (73%)	69 of 88 (78%)	0.73 (0.29-1.84)	0.51
Immunosuppression	14 of 20 (70%)	79 of 101 (78%)	0.65 (0.22-1.89)	0.43
High-tone pelvic floor	22 of 32 (69%)	64 of 81 (79%)	0.56 (0.22-1.38)	0.21

* Risk ratio +/- 95% confidence interval

Secondary Analysis

The study population included 85 women (28 age <50, 57 age ≥50) who provided a numeric estimate of pre-treatment UTI frequency. To validate the use of paired-profile T-testing, these data were assessed for normalcy using Q-Q plots of paired profile differences in yearly UTI frequency (Supplementary Figures 1a-b). In both groups, UTI frequency decreased significantly after starting MH (Table 3). Data are visualized as paired profile figures in Supplementary Figures 2a-b.

Table 3			
UTI Frequencies Before and During Treatment with MH for Women with Recurrent Uncomplicated UTIs			
Group	UTIs/year MH (mean +/- SD)		P-value
	Pre-treatment	On-treatment	
Age <50 (n=28)	10.13 +/- 5.24	0.90 +/- 1.18	<0.0001
Age ≥50 (n=57)	5.87 +/- 3.06	1.41 +/- 2.19	<0.0001

Side effects

Our initial review identified 30 patients who stopped MH due to side effects. The most frequent side effects were GI upset (14 patients) and bladder/urethral/vaginal irritation (8 patients). For an approximate estimate of side effect frequency, we set the denominator as our study population (162) + patients who stopped MH due to side effects (30) + patients who met inclusion criteria except for inconsistent MH adherence (35) or follow-up too short (61). With this estimated denominator of 288 patients, our side effect rates were 10% overall, 4.9% for GI side effects and 2.8% for bladder/urethral/vaginal irritation.

Exploratory analysis of patients using catheters

Twelve patients had indwelling catheters (6 urethral, 6 suprapubic). Success rates were 50% for the group overall, 33% with urethral catheters and 67% with suprapubic catheters. Thirty patients were using intermittent catheterization. Of these, 20 (67%) reported success. While small numbers preclude statistical comparison, for interest we tabulated success rates among patients with different etiologies for their urinary retention (Table 4).

Table 4
Success Rates of MH for Patients Using Intermittent Catheterization

Etiology of urinary retention	Success (n)	Failure (n)	Success rate
Spinal cord injury	6	5	54%
Spina bifida	5	0	100%
MS	2	0	100%
Diabetes mellitus	0	2	0%
Other neurogenic	1	2	33%
Non-neurogenic	6	1	86%

IV. DISCUSSION

MH was introduced as a urinary antiseptic in 1899.⁵ It is indicated for prophylaxis of recurrent urinary tract infections, but prior evidence was generally of low quality.^{2,6} A 2012 Cochrane review noted MH may have some benefit in decreasing symptomatic UTI for people with normal urinary tracts, but the studies had mixed quality and often short duration.⁶ Six years later, with no interim trials of MH to add, a multidisciplinary guideline panel was unable to draw reliable conclusions regarding its effectiveness.²

The literature review for the guideline ended September 2018. Since that date, two retrospective studies of MH have been published.^{5,8} Hollyer et al. reported their experience with 38 kidney transplant recipients, using the outcome UTI frequency per 1000 person-days. Mean UTI frequency decreased from 9.2 before MH to 5.0 with MH. Mean number of hospitalizations for UTI decreased from 2.6 to 1.1. The other study by Snellings et al. included 150 primary care

patients (133 women) age 60 years or older.⁸ Average time between UTIs was 3.3 months before MH; this increased to 11.2 months with MH. The authors noted 33 patients (22%) were free of UTI after starting MH.

Our study, using a binary outcome of success/failure, showed a high success rate for women with recurrent uncomplicated UTIs. We expected that lack of vaginal estrogen would significantly decrease the success rate, but this turned out not to be the case. Success rates were 74% for women age ≥ 50 not using vaginal estrogen, 79% for women age ≥ 50 using vaginal estrogen and 83% for women age < 50 . We also found no significant association between success rates and other UTI risk factors (diabetes, immune suppression, or high-tone pelvic floor dysfunction). The lack of associations may reflect insufficient statistical power, or may indicate that MH has efficacy even if these risk factors are present. In support of the latter expectation, a retrospective study of renal transplant recipients showed decreased UTI frequency after starting MH.⁵

The MH package insert described side effects in less than 3.5% of patients, most commonly nausea, upset stomach, dysuria, and rash.³ Our estimated side effect rates were 10% overall, 4.9% for GI side effects and 2.8% for bladder/urethral/vaginal irritation. These are similar to the side effect rates in recent reports. Among the 150 patients in the study by Snellings et al,⁸ side effect rates were 10.7% overall, 6% for GI side effects and 3% for dysuria. Hollyer et al.⁵ noted side effects in two of their 38 patients (5.3% overall, 2.6% GI and 2.6% unknown).

Our findings, combined with the other recent publications, increase the evidence base to support the efficacy of MH for prophylaxis in women with recurrent uncomplicated UTIs. Of course, these are all retrospective reviews. It will be interesting to see the results of a randomized non-inferiority trial currently in progress, comparing MH vs. antibiotic prophylaxis for recurrent uncomplicated UTIs in women.^{4,7}

While uncomplicated UTIs were our primary focus, we also considered patients using catheters. The 2012 Cochrane review included only one trial of MH in this population. That trial (SINBA) was randomized with four arms: MH, cranberry tablets, both or placebo.⁹ Subjects were spinal cord-injured patients with stable bladder management (indwelling catheter, intermittent catheterization or spontaneous voiding). The primary outcome was time to the next symptomatic UTI after starting the study. Kaplan-Meier curves turned out to be similar for MH vs. placebo and for cranberry tablets vs. placebo, indicating no benefit from MH or cranberry tablets in this patient population. Type of SCI, duration of SCI and type of bladder management were not associated with outcome.

Inspecting the Kaplan-Meier curves in the SINBA trial, slightly >50% of patients had no UTIs at 6 months. Thus, success rates for our spinal cord-injured patients using intermittent catheterization (54%) or our patients with indwelling catheters (50%) were similar to those in the SINBA trial's MH and placebo groups. Thus, our findings agree with the prior trial and indicate no benefit for MH in the setting of indwelling catheter or spinal cord injury. With indwelling catheters, the lack of benefit is consistent with the drug's mechanism of action: MH requires a dwell time in the bladder for conversion to formaldehyde.

In contrast to spinal cord-injured patients, our patients with non-neurogenic urinary retention had a higher success rate (86%). This may simply be an artifact of small patient numbers, but a true difference is plausible. Most non-neurogenic retention involves low-pressure, high capacity bladders. MH may be more effective in this setting, compared to the high-pressure, low capacity bladders typical for patients with chronic spinal cord injury.

Our high success rate with spina bifida was likely due to patient selection. Patients with unsafe bladders (and thus more refractory UTIs) would have undergone augmentation cystoplasty or urinary diversion, which were exclusion criteria for this study.

Our study was limited by the retrospective design. Our tertiary center serves a large geographic area, and travel difficulties impair patients' ability to return for follow-up. (The recent widespread adoption of telemedicine is already helping to mitigate the travel limitations.) In addition, our retrospective study depended on electronic notes to provide numeric estimates of UTI frequency. We also depended on patient recollection of UTI frequency. We have no doubt that women with uncomplicated UTIs can recognize individual episodes accurately. In fact, self-reported UTIs will be the primary outcome in the ongoing trial of MH vs. antibiotics.⁷ However, patient memory for the frequency of episodes may not always be accurate. This may have skewed the pre-treatment UTI frequency in our secondary analysis, but we have confidence in our primary outcome of on-treatment success because they were followed more closely in real time.

V. CONCLUSION

In this retrospective review from our tertiary care center, approximately 79% of women with recurrent uncomplicated UTIs had successful resolution with MH treatment. Further our secondary analysis shows that there is a statistically significant reduction in yearly reported UTI frequency, regardless of if the reduction is significant enough to meet treatment success criteria. These findings, combined with two other retrospective studies, support further investigation and consideration of MH as an antibiotic-sparing alternative for women with recurrent uncomplicated UTIs. Given the substantial costs associated with the evaluation and treatment of UTI in the United States, and prevalence of recurrent UTI, it is important for clinicians to

consider strategies like methenamine hippurate. These data demonstrate this treatment as an excellent option to reduce the UTI burden of these patients as well as an alternative to antibiotics which have may have substantial impacts with regard to side effects, cost, and antibiotic resistance of the infectious organisms.

VI. REFERENCES

1. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am* **28**: 1, 2014.
2. Anger J, Lee U, Ackerman AL, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. *J Urol* **202**: 282, 2019
3. HIPREX (methenamine hippurate tablets USP) [package insert]. Parsippany, NJ: Validus Pharmaceuticals; 2017.
4. Sihra N, Goodman A, Zakri R et al. Nonantibiotic prevention and management of recurrent urinary tract infection. *Nature Reviews* **15**: 750, 2018.
5. Hollyer I, Varias F, Ho B et al. Safety and efficacy of methenamine hippurate for the prevention of recurrent urinary tract infections in adult renal transplant recipients: A single center, retrospective study. *Transpl Infect Dis.* **21**(3): e13063, 2019.
6. Lee BS, Bhuta T, Simpson JM et al. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev.* Issue 10: CD003265, 2012.
7. ISRCTN registry. Alternatives to prophylactic antibiotics for the treatment of recurrent urinary tract infection in women. *BMC* <http://www.isrctn.com/> ISRCTN70219762 (2016).
8. Snellings MS, Linnebur SA, Pearson SM et al. Effectiveness of methenamine for UTI prevention in older adults. *Ann Pharmacother.* **54**: 359, 2020.
doi:10.1177/1060028019886308
9. Lee BB, Haran MJ, Hunt LM et al. Spinal-injured neuropathic bladder antiseptis (SINBA) trial. *Spinal Cord.* **45**: 542, 2007

VII. SUPPLEMENTARY FIGURES

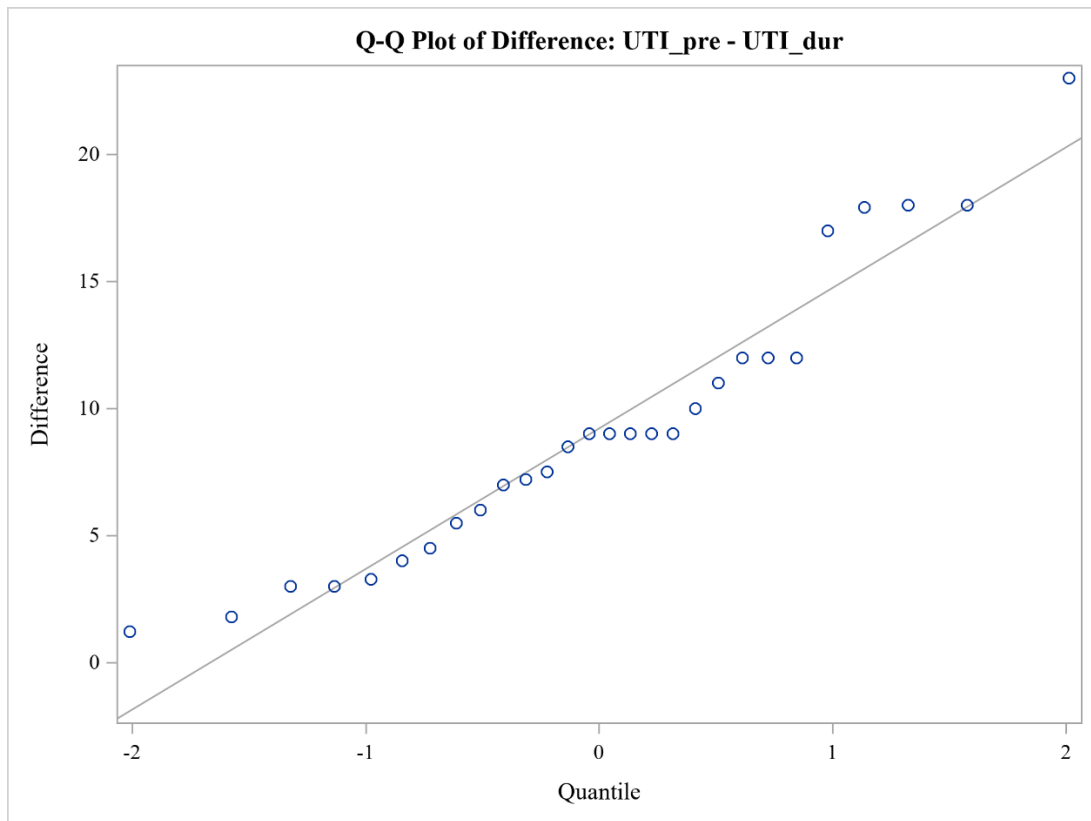


Figure S1a. Q-Q plot of pre-MH treatment and on-MH treatment yearly UTI frequency for women age <50 with recurrent UTI

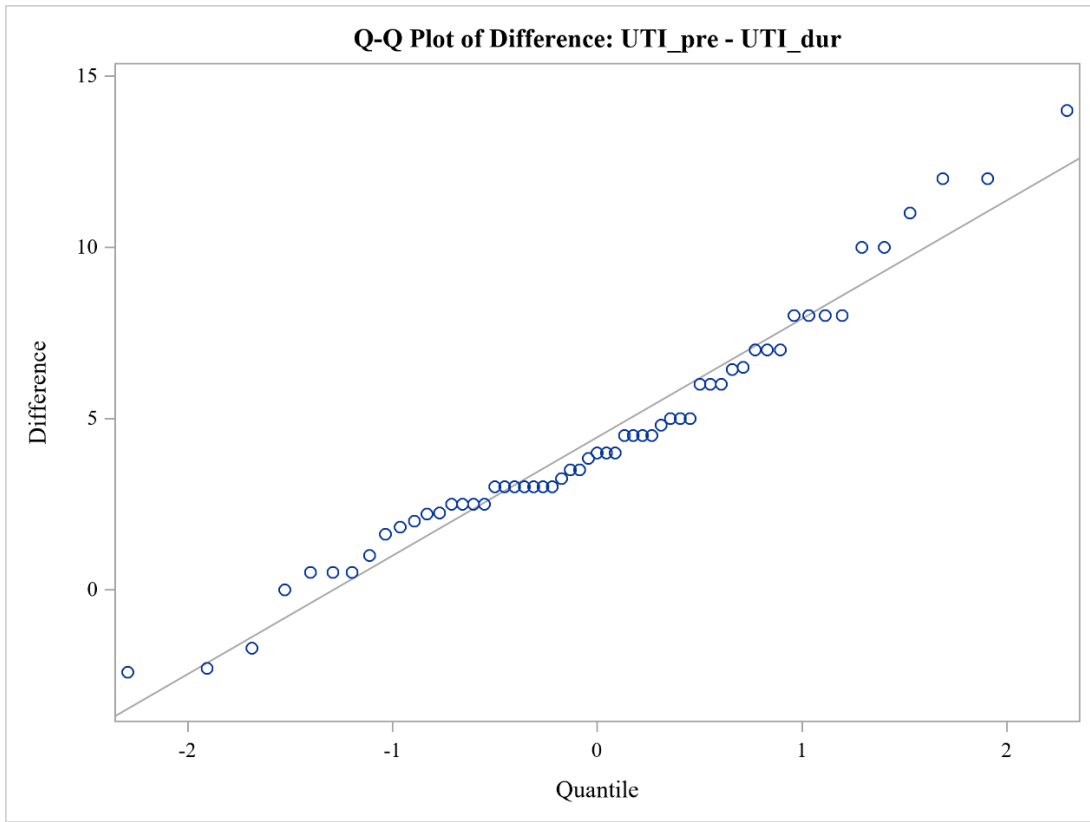


Figure S1b. Q-Q plot of pre-MH treatment and on-MH treatment yearly UTI frequency for women age ≥ 50 with recurrent UTI

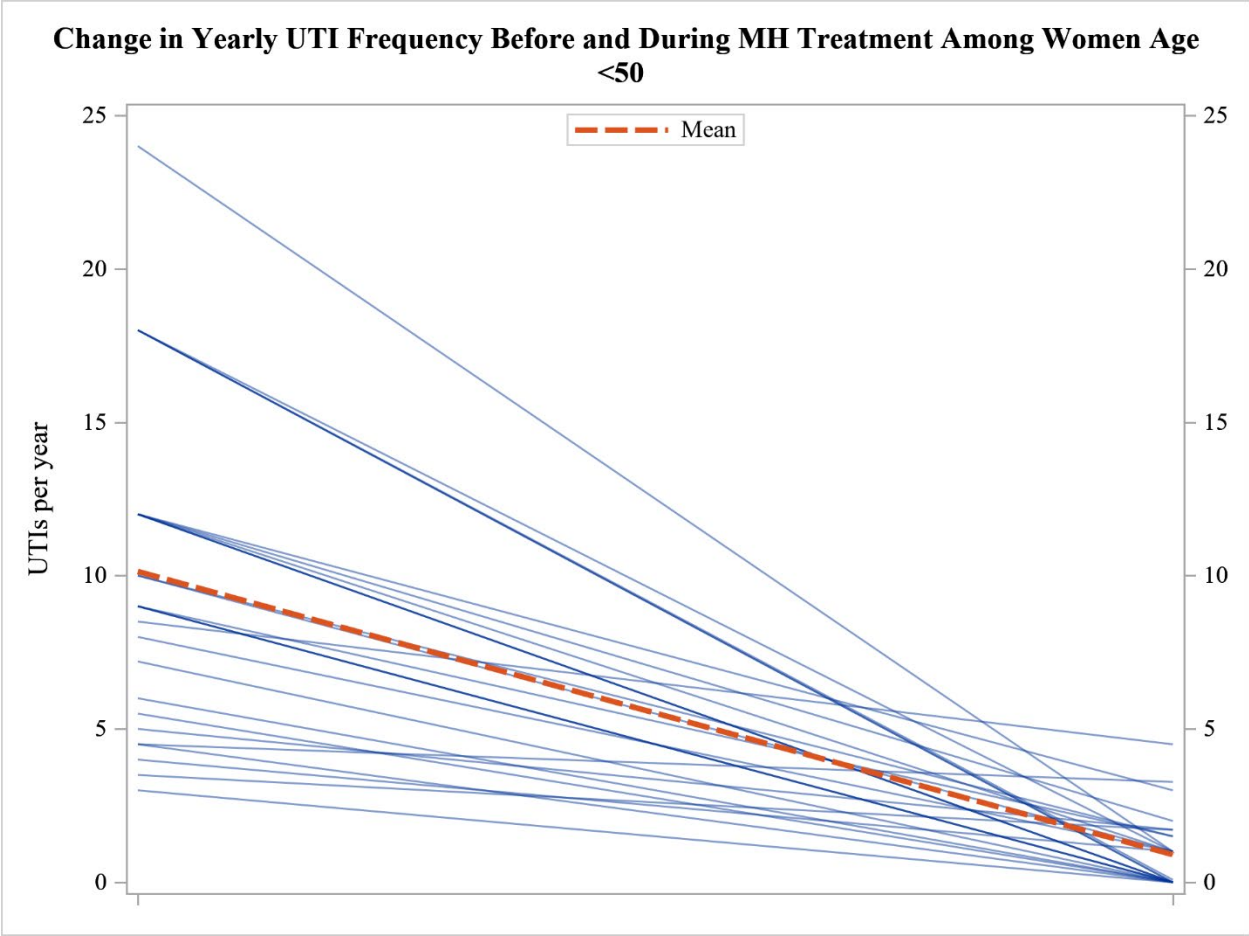


Figure S2a. Paired profiles of pre- and on-treatment UTI frequency for women age <50 taking methenamine hippurate for recurrent UTI

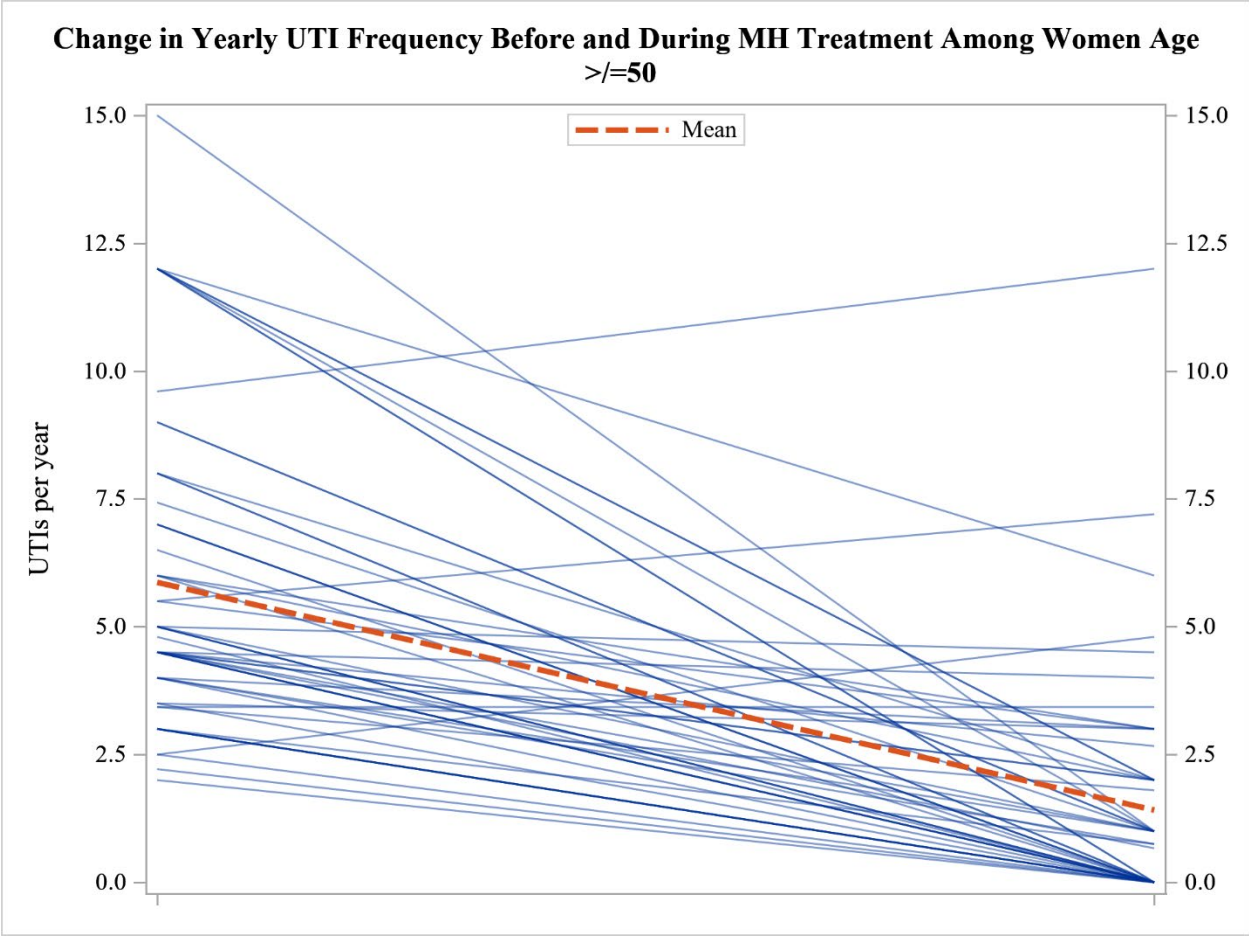


Figure S2b. Paired profiles of pre- and on-treatment UTI frequency for women age ≥ 50 taking methenamine hippurate for recurrent UTI