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Safety and Efficacy of Methenamine Hippurate for the Prevention of Recurrent Urinary Tract Infections in Adult Renal Transplant Recipients: A Single Center, Retrospective Study

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Abstract

Background.—Recurrent urinary tract infections (UTI) are an important cause of morbidity and mortality in renal transplant recipients (RTR).

Methods.—In this retrospective study we gathered clinical data from patients prescribed methenamine hippurate to prevent recurrent UTI pre- and post-intervention. Thirty-eight RTR 18 years old at Northwestern Memorial Hospital from 2006–2017 were included in the final analysis.

Results.—The median and range for follow-up days were 365 (299–365) pre- vs 314 (105–365) post-methenamine. Total UTI frequency (9.16 vs 5.01/1000 patient follow-up days), days of antibiotic therapy to treat UTI (215 vs 132/1000 patient follow-up days), and hospitalization due to UTI (2.64 vs. 1.07/1000 patient follow-up days) decreased while patients took methenamine. *E. coli* and *K. pneumoniae* were the most commonly identified cause of UTI both pre- and post-intervention. Drug resistant bacteria (ESBL-producing or VRE) affected three patients pre- and recurred in one of those patients plus three new patients post-methenamine. Methenamine had few adverse side effects for patients. One patient had nausea and one was intolerant.

Conclusion.—We found that methenamine is well tolerated and is useful in reducing UTI, antibiotic prescriptions, and hospitalization in RTR with recurrent UTI. Larger prospective studies are needed to confirm these findings.

Keywords

Urinary Tract Infection; Methenamine; Renal Transplant

BACKGROUND

Bacterial infections are a major source of morbidity and mortality in solid organ transplant recipients ¹. Urinary tract infections (UTI) are the most common infections that develop in adult renal transplant recipients (RTR), with approximately 25% of patients experiencing UTI within the first year post-transplant ^{2,3}. Recurrent UTI are defined as 2 UTI in any 6-month period or 3 UTI in any 12-month period and can occur as either independent inoculations of the urinary tract or as a persistent infection with a foreign body *in situ* (i.e., stone, stent or drain) or tissue (i.e., prostatitis, pyelonephritis, or abscess) ⁴. Recurrent UTI have been associated with significant morbidity, worse graft outcomes (1.4 times greater risk of graft failure) and increased mortality (1.9 times greater risk of death) compared to patients with single episodes of UTI post-transplant ^{5,6}. Mortality is particularly increased (1.5 times higher) among those with infections due to multidrug-resistant Gram-negative organisms ^{5,6}.

Given the negative impact of recurrent UTI on graft survival and patient mortality, aggressive approaches to uncover resolvable sources of infection should always be considered in patients with recurrent UTI. This involves looking for anatomical or functional abnormalities in the urinary tract that could lead to obstruction, such as strictures, stenosis, renal calculi, or complex cysts using radiographs, ultrasound, or computerized tomography. Further investigation may also require other imaging such as CT-PET for patients with suspected polycystic kidney disease, cystoscopy for patients with potential abnormalities of the urethra and bladder, and voiding cystourethrography for patients with suspected vesicoureteral reflux ⁶. Bladder dysfunction and outflow tract obstruction may also be diagnosed using urodynamic studies ⁶. However, even with comprehensive investigation, there is often no obvious abnormality contributing to a patient's frequent infections.

After establishing that there are no clear correctable factors causing recurrent UTI, management often involves simply treating a UTI based on antibiotic susceptibility as it arises, yet frequent and repeated administration of antibiotics predisposes patients to infections by drug-resistant organisms ^{5,7,8}. Such an approach to treating recurrent UTI often results in infections caused by multidrug-resistant (MDR) organisms compared to patients with single episodes; reported percentages of UTI caused by MDR bacteria range from 53–81% in patients with recurrent UTI ^{5,9–11}. MDR bacteria include those that have developed resistance to multiple antimicrobial drugs, and includes methicillin-resistant *Staphylococcus aureus* (MRSA), or extended-spectrum beta-lactamases (resistant to cephalosporins and monobactams) gram negative rods.

To prevent recurrent UTIs, some clinicians rely on suppressive antibiotics to prevent recurrent UTI from developing. While use of suppressive antibiotics is often effective in reducing UTI incidence, it contributes to increasing antibacterial resistance and is not an option for patients with recurrent UTI caused by MDR organisms ^{7,12}. In addition, growing evidence suggests that prolonged antibiotic exposure can have adverse consequences on the human body, such as altering the gut microbiome ¹³.

Methenamine was first introduced as a urinary antiseptic in 1899, and it is an organic compound that when taken orally travels to the bladder and decomposes in the acidic environment to form formaldehyde and ammonia¹⁴. Formaldehyde inactivates microorganisms by non-specifically alkylating the amino and sulfhydryl groups of proteins and ring nitrogen atoms of purine bases¹⁴. As such, methenamine is a non-antibiotic agent that may reduce the frequency of recurrent UTI.

While there is a paucity of data for using methenamine in transplant recipients, there is published data documenting the efficacy of methenamine in reducing recurrent UTI in non-transplant patients. A meta-analysis of thirteen mixed quality studies (2032 participants) concluded that methenamine may be effective in preventing cystitis in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89), and also reported that overall the rate of adverse events from methenamine, while poorly described, was low¹⁵. While methenamine fell out of favor in the 1990s due to concerns of side effects, including hemorrhagic cystitis, it offers an appealing alternative to conventional targeted preventative antibiotics as it should be effective and reduce pressure on antibacterial resistance emergence¹⁶. Due to its low side effect profile and potential for benefit, in 2006 our Transplant Infectious Disease clinicians began to prescribe methenamine to prevent recurrent UTI in our renal transplant population.

The present study is the first retrospective analysis of the efficacy of methenamine in preventing recurrent UTI in adult renal transplant recipients.

PATIENTS AND METHODS

Study population and design

After IRB approval, the medical records of adult RTR 18 years old at Northwestern Memorial Hospital (Chicago, IL) between January 2006 and April 2017 who were treated with methenamine hippurate for recurrent UTI were retrospectively studied. Inclusion criteria required that a patient have a documented history of at least two UTI in the six months or three UTI in the year preceding initiation of methenamine. If there was no note of UTI or documentation of only one UTI in the medical record in the year before initiation of methenamine then the patient was excluded. Patients who met inclusion criteria based on UTI history were then screened up to a year past the initial methenamine prescription date and must have had at least 1 note discussing the patient's experience while on methenamine. Those without any follow-up notes in the medical record while on methenamine were excluded.

Patients were identified through a search of the Northwestern Medicine Enterprise Data Warehouse (EDW), a joint initiative between the Northwestern University Feinberg School of Medicine and Northwestern Memorial Healthcare Corporation that serves as a single repository for all clinical and research data including patient electronic health records. Data on individual patients was then gathered from health records through evaluation of the three electronic medical record (EMR) programs at Northwestern: a center-specific organ transplant tracking record (OTTRTM), Cerner PowerChart®, and the EHR provided by Epic Systems Corporation. Data was obtained from EMR records at Northwestern Memorial

Hospital as well as scanned records and notes from outside hospitals that were uploaded into the Northwestern EMRs. Follow-up for each patient was divided into pre-treatment, defined as the year prior to methenamine treatment or from the time of transplant to the start of methenamine if this occurred less than a year before initiation of methenamine, and post-treatment, which was collected up to one year following initiation of methenamine or until discontinuation of methenamine if this occurred less than a year following the start of treatment.

Definitions

UTI events were divided into two separate categories due to the variability of information provided by the medical record. We first created a 'medical record note plus primary documentation' category, which included UTI where we could find lab results of a positive urine culture ($>100,000$ CFU/ml), a description of patient symptoms (such as frequency, urgency, or dysuria), lab results of a urinalysis indicative of infection (positive leukocyte esterase, WBC $>10/\text{microL}$ $\pm$ positive nitrite), and a record of antibiotic treatment (name and duration). A urinalysis was marked as 'squamous positive' and not included if records of squamous cells were indicated as '+', '3+' or ' >28 '.

When patients had a recorded UTI event, but one or more of the clinical indicators we used in the 'medical record note plus primary documentation' category did not have primary documentation (e.g. we found a note referencing a positive culture, but we could not find the associated lab document showing $>100,000$ CFU/ml), the UTI event was recorded in the 'medical record note only' category.

All UTI events during the pre- and post-methenamine periods were recorded. UTIs were not further subdivided into cystitis vs. pyelonephritis as there was a paucity of clinical symptom detail in the medical record to differentiate between the two. When culture data was negative ($<100,000$ CFU/ml) with other indicators of infection, such as symptoms, a positive urinalysis, and treatment, this was recorded as a culture-negative treated UTI. When patient had no symptoms but a positive urine culture ($>100,000$ CFU/ml), this was defined as asymptomatic bacteriuria (ASB). These events were also subdivided into treated and untreated ASB based on whether or not there were records of the patient receiving antibiotics to treat the positive urine culture.

Study procedures

Antibiotic prescription information was gathered from inpatient hospital records, notes from physicians, discharge summaries, and from prescription fill records from the patient's EMR pharmacy data. When a note about the length of antibiotic therapy, or other information about the duration of antibiotic exposure (such as data gathered from prescriptions fills) was absent, then a standard length of treatment was recorded, derived from standard drug dosing charts in Epic. If patients were taking multiple antibiotics on the same day, this was still only counted as 1 day.

Blood test data including WBC count, hemoglobin, platelet, serum creatinine and estimated GFR were recorded from lab results first from the date closest to start of methenamine and then the date closest to the end date of methenamine therapy.

Methenamine was dosed as a 1g oral daily tablet with vitamin C. While short-term dosing for methenamine is recommended BID, to allow for better compliance and ease for patients we prescribed methenamine daily¹⁷. We did not have any reliable way to assess medication compliance of patients in our study. Because an acidic urine is required for the conversion of methenamine into formaldehyde, and some pathogens that split urea and cause a more basic urine pH will have lower levels of formaldehyde, methenamine is also given with ascorbic acid to help acidify the urine¹⁸. When patients had a breakthrough UTI, methenamine was stopped and appropriate antibiotics based on the culture data were utilized. After the infection was cleared, methenamine was restarted. In patients also taking TMP-SMX prophylaxis, in order to avoid the possibility of crystalluria due to cross reaction with sulfonamides, patients were instructed to take methenamine at least 12 hours after TMP-SMX. TMP-SMX prophylaxis was given to patients as 400 mg/80 mg tablets to be taken Monday, Wednesday and Friday while also on methenamine. The standard outpatient follow-up for patients newly prescribed methenamine was a one- and five-month visit. However, this was variable depending on whether or not patients had issues that required earlier follow-up, such as drug side effects or intercurrent infections.

Statistical analysis

Because the underlying distribution of our data is unknown, we used the nonparametric Wilcoxon rank sum test for group comparisons in R version 1.0.143¹⁹. Specifically, we used a modified zero-inflated Wilcoxon signed-rank test given the number of data categories including values of zero²⁰. The threshold of statistical significance was established at $p < 0.05$ for all tests.

When calculating rates for UTI, hospitalizations, and length of antibiotic therapy, because follow-up time for patients in the pre- and post-methenamine periods was not always 365 days, we normalized all patient data by dividing each variable by the follow-up time.

RESULTS

The initial EDW search identified 61 patients, and 38 met inclusion criteria. Thirteen patients had insufficient data in their EMR records, and 10 failed UTI inclusion criteria, as they had no data of UTI (3) or only one documented UTI (7) in the pre-methenamine period. Of the 38 patients included, over half were Caucasian women and the median age was 50 years (See Table 1 for detailed demographics). Nine of the enrolled subjects had a history of previous renal transplant, and 13 had the presence of a second organ transplant in addition to kidney. Median time from transplant to methenamine start was 1192 days, while median duration of methenamine treatment was 314 days. In both the pre- and post-methenamine time period, about 30% of patients had a GFR > 60 ml/min/1.73m², while the rest with GFRs < 60 ml/min/1.73m² had values close to 40 ml/min/1.73m².

Twenty-four (63%) patients had a urology consult to evaluate for recurrent UTI (Supplemental Table 1). Of these consults, half had no pathology found that would affect UTI risk. Seven patients had evidence of nephrolithiasis, two patients had fistulas (colovesical, rectovaginal), and one patient had mild vesicoureteral reflux (retrograde passage of urine and potentially bacteria from the bladder into the upper urinary tract).

In the pre-methenamine period, three patients total had an average of 55 days of suppressive antibiotic therapy. One patient was given doxycycline, one was given fosfomycin, and one was given cefpodoxime. The patient on fosfomycin failed suppressive antibiotics by having a breakthrough UTI. No patients had any record of suppressive antibiotics in the post-methenamine period.

Pre-methenamine period

Enrolled patients had a median patient follow-up time of 365 days. Most patients were maintained on a standard immunosuppression regimen made up of tacrolimus and mycophenolate mofetil; few received corticosteroids (See Table 1). Sixty-three percent of patients had records of receiving TMP-SMX prophylaxis for *P. jirovecii* for more than 12 months in the post-transplant period, while eight (21%) had a sulfa allergy and never took TMP-SMX. Twenty-one (55%) patients were on TMP-SMX prophylaxis throughout their pre-methenamine period.

A total of 111 UTI events were recorded in the pre-methenamine period. The rate of UTI per 1000 patient follow-up days in the pre-methenamine period was 9.16 (3.63 UTI in the 'medical record note plus primary documentation' category and 5.53 UTI in the 'medical record note only' category).

The most common bacterial species identified in cultures in pre-methenamine UTI were *E. coli*, and *K. pneumoniae*. Two patients had a UTI caused by ESBL-*E. coli* and one had UTI caused by ESBL-*K. pneumoniae*.

The most common antibiotics prescribed for UTI were ciprofloxacin, cephalexin, and ceftriaxone. The median antibiotic length of therapy per treatment episode of UTI was 14 days.

Correcting for follow-up time, the rate of hospitalization due to UTI in the pre-methenamine period was 2.64 per 1000 patient follow-up days, while hospitalization for other reasons was 3.72 per 1000 patient follow-up days.

Post-methenamine period

Enrolled patients had a median follow-up time of 314 days after starting methenamine. The total number of UTIs recorded in the post-methenamine period was 47. The rate of UTI per 1000 patient follow-up days was 5.01 (1.91 UTI in the 'medical record note plus primary documentation' category and 3.09 UTI in the 'medical record note only' category).

Eighteen out of our 38 patients (47%) had no UTI in the post-methenamine period, while 9 (24%) additional patients had a reduced rate of UTI post-methenamine.

The most common bacterial species identified in cultures in post-methenamine UTI were also *E. coli*, and *K. pneumoniae* (See Supplemental Table 1). One patient with ESBL-*E. coli* UTI in the pre-methenamine period and two new patients had ESBL-*E. coli* UTI, and one new patient had a VRE UTI. Ten patients had UTIs in the pre- and post-methenamine periods caused by the same bacterial species.

The most common antibiotics prescribed for UTI were ciprofloxacin, cephalexin, and nitrofurantoin. The median antibiotic length of therapy per treatment episode of UTI was 9 days.

Correcting for follow-up, the number of hospitalizations due to UTI in the post-methenamine period was 1.07 per 1000 patient follow-up days, while hospitalization for other reasons was 2.03 per 1000 patient follow-up days.

Eighteen of the initial 21 patients on TMP-SMX prophylaxis maintained it in the post-methenamine period, while three patients had reduced TMP-SMX exposure, and one patient had new TMP-SMX prophylaxis compared to the pre-methenamine period (See Supplemental Table 1).

Methenamine was generally well tolerated. Only two patients in our sample experienced adverse effects. One patient experienced nausea after taking methenamine, but continued treatment despite the side effect. One patient was noted to be 'intolerant' and discontinued methenamine, but further details were not found in the medical record.

According to the manufacturers, methenamine should not be used in patients with severe renal failure (GFR<10 ml/min) due to the risk of toxic serum levels ¹⁴. In our study no patient had a GFR <10 ml/min.

Comparison

When we compared the total UTI rate between the pre- and post-methenamine periods, we found that UTIs were significantly lower in the post-treatment period (see Table 2). When we subdivided our total UTI data into its two composite categories, we found that UTIs in the 'medical record note only' category were significantly decreased post-methenamine ($p = 0.0034$), while UTIs in the 'medical record note plus primary documentation' category were not significantly different with the use of methenamine ($p = 0.0888$).

There was also a reduction in length of antibiotic therapy to treat UTI in the post-methenamine period. Excluding the three patients who received suppressive antibiotic prior to treatment with methenamine period, we demonstrated similar decreases in UTIs ($p<0.0001$) as well as length of antibiotic therapy to treat UTI ($p=0.0107$). The number of antibiotics that patients were prescribed for non-UTI infections was not significantly different pre- vs post-methenamine.

Hospitalizations due to UTI were significantly reduced post-methenamine, although hospitalizations due to other causes were not significantly different between periods. We also compared WBC count, hemoglobin, platelets, creatinine, and GFR pre- and post-methenamine and found no significant differences.

DISCUSSION

To our knowledge this is one of the first studies of the safety and efficacy of methenamine in the prevention of recurrent UTI in renal transplant recipients. Methenamine was associated with a 45% reduction in UTI, a 42% reduction in length of antibiotic therapy to treat a UTI,

and a 59% reduction in hospitalizations as a result of UTI. The use of methenamine was generally well tolerated with only one patient requiring discontinuation of therapy.

The results of our study agree with the previous meta-analysis in non-transplant patients, which concluded that methenamine is effective in reducing UTI. This meta-analysis also stated that methenamine did not appear to work in patients with neuropathic bladder¹⁵. In our study, we had two patients with documentation of neurogenic bladder and similarly both did not see any improvement in their UTI frequency while on methenamine. The limited efficacy in patients with specific bladder defects should be a focus of future studies to see if these patients should use alternative preventative strategies.

Unlike other previous work, our study also collected data on antibiotic prescriptions and hospitalization while on methenamine. We found that hospitalizations due to UTI and antibiotic prescriptions to treat UTI were significantly decreased while patients took methenamine.

What was not addressed in this study but may be of great clinical relevance is the safety of methenamine usage in the long-term. While formaldehyde has been well-studied in human carcinogen epidemiology involving lifetime occupational exposures, studies involving long-term exposure to methenamine have not been established²¹. A risk assessment report by the Federal Institute for Occupational Safety and Health in Germany noted that in the absence of research on methenamine, the only relevant study involved formaldehyde administered via drinking water to rats over several years where there was found to be no increased tumor incidence in any organ²². The report concluded that the formation of formaldehyde due to the pH dependent cleavage of methenamine in body compartments should be of no concern with respect to carcinogenicity²³. However, some clinicians are still concerned that continuous exposure of the bladder epithelium to formaldehyde may increase lifetime risk of cancer²⁴. In addition, this effect may be even more important to consider in patients taking immunosuppressive medications given their already increased risk for developing malignancy²⁵.

In addition to long-term outcomes, there is also the potential safety concern of acute methenamine toxicity. Of the studies included in a 2012 Cochrane review of methenamine for the prevention of UTI in non-transplant patients, the longest follow-up time was one year, and methenamine doses ranged from 1–4g/day. Out of the total 2032 participants included in the review, the most common adverse event was nausea in 12 patients, followed by constipation, rash, and single instances of diarrhea, sore throat, and stinging in the bladder¹⁵. In addition to these mild side effects, painful and frequent micturition, albuminuria, hematuria have been reported to result from doses of 4 to 8 g/day for longer than 3–4 weeks²⁶. Overdose reports in the literature are limited, but one study reported that a child who accidentally took 8 grams of methenamine developed hemorrhagic cystitis, mild metabolic acidosis, elevated BUN, and lower urinary tract irritation¹⁶. The patients in our study took 1g daily doses of methenamine, which based on previous literature is likely too low to have any serious side effects. However, given that there are few studies that have followed patients taking methenamine for even just one year, outcomes from longer

Overall, we found that methenamine reduces recurrent UTI in adult RTR, results in fewer hospitalizations for UTI, and decreases antibiotic use. While our study was too small to detect differences in antibacterial resistance over time, reduced antibiotic use should reduce pressure contributing to increased antibiotic-resistance genes in bacteria. Methenamine was well tolerated with few side effects or discontinuations documented. Identification of therapies that decrease recurrent UTI in RTR should improve outcomes and quality of life for patients, and methenamine appears to be a safe and effective non-antibiotic approach for prevention of recurrent UTI. Future prospective studies are needed to confirm these findings.

Refer to Web version on PubMed Central for supplementary material.

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References

Bibliography

1. Fishman JA. Infection in Organ Transplantation. *Am J Transplant*. 2017;17(4):856–879. [PubMed: 28117944]
2. Ariza-Heredia EJ, Beam EN, Lesnick TG, Kremers WK, Cosio FG, Razonable RR. Urinary tract infections in kidney transplant recipients: role of gender, urologic abnormalities, and antimicrobial prophylaxis. *Ann Transplant*. 2013;18:195–204. [PubMed: 23792521]
3. Lee JR, Bang H, Dadhania D, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. *Transplantation*. 2013;96(8):732–738. [PubMed: 23917724]
4. Parasuraman R, Julian K, Practice ASTIDCo. Urinary tract infections in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:327–336. [PubMed: 23465025]
5. Britt NS, Hagopian JC, Brennan DC, et al. Effects of recurrent urinary tract infections on graft and patient outcomes after kidney transplantation. *Nephrol Dial Transplant*. 2017;32(10):1758–1766. [PubMed: 28967964]
6. Mitra S, Alangaden GJ. Recurrent urinary tract infections in kidney transplant recipients. *Curr Infect Dis Rep*. 2011;13(6):579–587. [PubMed: 21870039]
7. Singh R, Bemelman FJ, Hodiament CJ, Idu MM, Ten Berge IJ, Geerlings SE. The impact of trimethoprim-sulfamethoxazole as *Pneumocystis jiroveci* pneumonia prophylaxis on the occurrence of asymptomatic bacteriuria and urinary tract infections among renal allograft recipients: a retrospective before-after study. *BMC Infect Dis*. 2016;16:90. [PubMed: 26912326]
8. Memikoglu KO, Keven K, Sengul S, Soypacaci Z, Erturk S, Erbay B. Urinary tract infections following renal transplantation: a single-center experience. *Transplant Proc*. 2007;39(10):3131–3134. [PubMed: 18089338]
9. Bodro M, Sanclemente G, Lipperheide I, et al. Impact of antibiotic resistance on the development of recurrent and relapsing symptomatic urinary tract infection in kidney recipients. *Am J Transplant*. 2015;15(4):1021–1027. [PubMed: 25676738]
10. Lim JH, Cho JH, Lee JH, et al. Risk factors for recurrent urinary tract infection in kidney transplant recipients. *Transplant Proc*. 2013;45(4):1584–1589. [PubMed: 23726625]
11. Silva C, Afonso N, Macario F, Alves R, Mota A. Recurrent urinary tract infections in kidney transplant recipients. *Transplant Proc*. 2013;45(3):1092–1095. [PubMed: 23622634]
12. Rafat C, Vimont S, Ancel PY, et al. Ofloxacin: new applications for the prevention of urinary tract infections in renal graft recipients. *Transpl Infect Dis*. 2011;13(4):344–352. [PubMed: 21299776]
13. Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology*. 2010;156(Pt 11):3216–3223. [PubMed: 20705661]
14. Bartlett JG, Auwaerter PG, Pham PA, eds. *Johns Hopkins ABX Guide 2012*. Jones & Bartlett Publishers; 2011.
15. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10:CD003265.
16. Ross RR Jr., Conway GF. Hemorrhagic cystitis following accidental overdose of methenamine mandelate. *Am J Dis Child*. 1970;119(1):86–87. [PubMed: 5410299]
17. Methenamine. Lexi-Comp, Inc.; 2018. http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7265. Accessed September 28th, 2018.
18. Nahata MC, Cummins BA, McLeod DC, Butler R. Predictability of methenamine efficacy based on type of urinary pathogen and pH. *J Am Geriatr Soc*. 1981;29(5):236–239. [PubMed: 7014695]
19. R Core Team. R: A language and environment for statistical computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2017.
20. Wang W, Chen EZ, Li H. Zero-Inflated (Wilcoxon and Kruskal–Wallis) Rank Test. 2015; <https://github.com/chvlyl/ZIR>. Accessed June, 12, 2018.

21. Swenberg JA, Moeller BC, Lu K, Rager JE, Fry RC, Starr TB. Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment. *Toxicol Pathol.* 2013;41(2):181–189. [PubMed: 23160431]
22. Til HP, Woutersen RA, Feron VJ, Hollanders VH, Falke HE, Clary JJ. Two-year drinking-water study of formaldehyde in rats. *Food Chem Toxicol.* 1989;27(2):77–87. [PubMed: 2714719]
23. EFSA ANS Panel (EFSA Panel Food additives and Nutrient Sources added to Food). Scientific Opinion on the re-evaluation of hexamethylene tetramine (E 239) as a food additive. *EFSA Journal.* 2014;12(6):39.
24. Chung K-T. The Etiology of Bladder Cancer and its Prevention. *Journal of Cancer Science & Therapy.* 2013;5(10):346–361.
25. Engels EA, Pfeiffer RM, Fraumeni JF Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA.* 2011;306(17):1891–1901. [PubMed: 22045767]
26. Goodman LS, Brunton LL, Chabner B, Knollmann BrC. Goodman & Gilman's pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.

Table 1.**Study Participant Demographics**

Age of recipient, years, median (25%Q, 75%Q)	50 (40, 58)
Race/ethnicity, n (%)	
Black or African American	4 (11)
Hispanic or Latino	7 (18)
White or Caucasian	25 (66)
Unidentified	2 (5)
Female sex, n (%)	32 (84)
Previous renal transplant, n (%)	9 (24)
Presence of 2nd organ transplant, n (%)	13 (34)
Neurogenic bladder, n (%)	2 (5)
Primary etiology of end stage renal disease, n (%)	
Diabetic nephropathy	18 (47)
Hypertensive nephrosclerosis	3 (8)
Graft failure	4 (11)
Nonalcoholic steatohepatitis	2 (5)
Systemic Lupus Erythematosus	2 (5)
Chronic glomerulonephritis	2 (5)
Other	7 (18)
GFR pre-methenamine	
>60 ml/min/1.73m2, n (%)	11 (29)
<60 ml/min/1.73m2, n (%)	27 (71)
<60 ml/min/1.73m2, median ml/min (minimum ml/min)	45 (21)
GFR post-methenamine	
>60 ml/min/1.73m2, n (%)	12 (32)
<60 ml/min/1.73m2, n (%)	26 (68)
<60 ml/min/1.73m2, median ml/min (minimum ml/min)	41 (17)
Follow-up days pre-methenamine	
Total for all patients, thousand days	12.1
Individual patients, median (25%Q, 75%Q)	365 (299, 365)
Follow-up days post-methenamine	
Total for all patients, thousand days	9.8
Individual patients, median (25%Q, 75%Q)	314 (105, 365)
Days from transplant to methenamine start, median (25%Q, 75%Q)	1192 (300, 2433)
Total days of methenamine treatment, median (25%Q, 75%Q)	314 (105, 566)
Immunosuppressive regimen, n (%)	
Mycophenolic acid	35 (92)
Tacrolimus	26 (68)
Sirolimus	4 (11)

Prednisone	9 (24)
Azathioprine	2 (5)
Cyclosporine	3 (8)

Table 2.

Comparison of Key Outcomes Pre- and Post-Methenamine Suppression

	Pre-methenamine	Post-methenamine	p-value
UTI rate, n/1000 follow-up days	9.16	5.01	0.0001
Length of antibiotic therapy to treat UTI, n/1000 follow-up days	152	88	0.0022
Length of antibiotic suppressive therapy, n/1000 follow-up days	13.7	0	<0.0001
Length of therapy for non-UTI antibiotics, n/1000 follow-up days	69	83	0.8655
TMP-SMX prophylaxis length of therapy, n/1000 follow-up days	849	895	0.7080
Hospitalizations due to UTI, n/1000 follow-up days	2.64	1.07	0.0456
Hospitalizations (other cause), n/1000 patient days	3.72	2.03	0.1244
Untreated ASB, n/1000 follow-up days	0.58	0.85	0.1344
Treated ASB, n/1000 follow-up days	0.66	0.85	0.2290
Culture negative treated UTI, n/1000 follow-up days	0.83	0.96	0.8062
Creatinine, median	1.24	1.21	0.8723
GFR ml/min/1.73m ² , median	50.5	51.0	0.9942
Urinary pH, median	5.50	6.00	0.3203
MDR organisms isolated, % of positive bacteria cultures	0.08	0.07	0.6145