# Methenamine Hippurate (Hiprex) versus Nitrofurantoin for recurrent lower urinary tract infection in women: An open-label non-inferiority multi-centre randomised controlled trial

**Aim:**

The aim of this study is to assess and compare the efficacy of methenamine hippurate with oral prophylactic antibiotics in women with recurrent urinary tract infection.

**Background:**

Lower urinary tract infections present with cystitis and/or urethritis. Symptoms include frequent urination, urgency, dysuria, suprapubic pain, turbid or foul smelling urine, haematuria, fever and non-specific lower back pain. (1) Evidence of two or more infections in six months or three or more in one year is referred to as of recurrent UTI (rUTI). (2-7)

In a study of healthy college age women who were followed for 6 months after an index UTI almost 30% had at least one symptomatic recurrence. (8) In another study of 179 Finnish women who were followed for 1 year after an index Escherichia coli UTI, 44% had a least one UTI and 5% had more than three rUTIs. (9)

Symptomatic rUTI can be particularly distressing for patients. Each episode of UTI is associated with days of lower urinary tract symptoms, general malaise, and restrictions on everyday activities and days lost from work and often hospitalisation in elderly patients. (10)

Methenamine hippurate (Hiprex) is often used in the prevention of UTI. It is frequently used for prolonged periods because, unlike conventional antibiotics, acquired resistance does not appear to develop. Given the problems of increasing antibiotic resistance, Hiprex may be especially useful in populations susceptible to recurrent UTI.

A 2012 Cochrane review including 13 studies (2032 patients) reports that Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis. It does not appear to work in patients with neuropathic bladder or in patients who have renal tract abnormalities. The rate of adverse events was low, but poorly described. The review indicates a need for further large well-conducted randomised controlled trials (RCTs) to clarify this question, particularly for longer term use for people without neuropathic bladder. (11)

**Hypothesis:**

Hiprex is as effective as nitrofurantoin in preventing rUTI

**Methods and Materials:**

We plan to recruit patients with known rUTI to a multi-centre open-label non-inferiority randomised control trial of Hiprex versus oral antibiotics to assess the efficacy of each arm in the recurrence of UTI.

We will seek ethical approval from the Ethics committees of the involved centres including Mercy Hospital for Women, Austin Health and Monash Medical Centre.

Inclusion criteria:

* 18 years old and above
* Have the capacity to give voluntary and informed consent
* Recurrent UTI with documented 2 or more infections in the last 6 months or 3 or more in the last 12 months.

Exclusion criteria:

* Contraindication to Hiprex: Severe renal or hepatic insufficiency, know allergy. Current use of sulphonamides e.g. sulfamethizole or sulfathiazole
* Contraindication to nitrofurantoin: Known allergy to Nitrofurantoin, G6PD enzyme deficiency, active hepatitis, Jaundice, interstitial pneumonitis, pulmonary fibrosis, severe renal insufficiency
* Previously tried and failed Hiprex prophylaxis
* Pregnancy/Breastfeeding
* Underlying renal disease e.g. renal transplant, vesicoureteric reflux
* Urethral disorders e.g. stricture, diverticulum
* Bladder outlet obstruction e.g. stage 3 or 4 cystocele
* Presence of fistula e.g. vesicovaginal or rectovaginal
* Urolithiasis
* Currently on prophylaxis or recent history of prophylaxis in last 3 months
* Permanent urinary indwelling catheter
* Poorly controlled diabetes mellitus
* Immunosuppressive treatments

Outcomes:

* Primary outcome:
	+ Recurrence of UTI in the 6 months duration of trial
* Secondary outcomes:
	+ Number of UTIs in 6 months of trial
	+ Time to first UTI
	+ Adverse events and side effects
	+ Cost of treatment

**Recruitment and quality control:**

Patients at time of recruitment will have a midstream urine sample to assess for current UTI or bacteriuria. If there was evidence of a current infection they will be treated based on the culture and sensitivity results with appropriate antibiotics. A repeat urine sample will be collected at the end of the treatment course to confirm resolution of the UTI. Furthermore, a renal tract ultrasound will be arranged for these patients (if already not performed) to exclude underlying renal tract abnormalities and assessment of bladder emptying. On this ultrasound, a pre- and post-void bladder volume will be measured. Abdominal and pelvic examination including a vaginal speculum examination will be performed to rule out any fistula, urethral abnormalities and pelvic organ prolapse. All patients will have a blood test to assess liver function and renal function and a urine cytology to investigate atypical/malignant urothelial cells. In those with positive findings of abnormal cells or haematuria in the urine specimen a cystoscopic examination will be performed as well as a bladder biopsy if indicated. Abnormal results will be managed in accordance with the unit’s policy. All pre-menopausal participants will need a negative urine pregnancy test at the time of recruitment.

Once inclusion and exclusion criteria are applied, patients will be randomly assigned to either Hiprex and Vitamin C or oral antibiotic groups. All patients will complete a questionnaire of socio-demographic status and background medical and surgical profile.

Allocation will be in order of block randomisation using a block random sequence generator. We will use randomisation in permuted blocks to achieve balance in each arm. The blocks will be in varying sizes of 6,8 and 10.

Patients in the oral antibiotic arm (antibiotic group) will receive Nitrofurantoin 100 mg capsules daily (50mg daily if renal impairment) for 6 months and the Hiprex arm (Hiprex group) will receive Hiprex 1g tablets twice a day and vitamin C for 6 months.

If a participant reported symptoms suggesting UTI (See below for Diagnosis of UTI), a clean mid-stream urine sample for culture and sensitivity will be collected. If UTI was diagnosed based on the criteria described below, then the appropriate antibiotic therapy will be commenced with a follow up sample urine to confirm complete treatment of the UTI. A UTI during the trial phase will not lead to exclusion from the study. Patients will continue the treatment to which they were assigned in the beginning of the trial.

Occurrence of UTI is the primary outcome of the trial (binary data). The secondary outcomes include number of UTIs (count) and time to first UTI (surveillance data). We will collect and report on all adverse outcomes during the trial phase as part of the secondary outcomes.

Efforts will be made to minimise missing values. We will use the multiple imputation approach to handle missing values.

It is important to mention that either of these treatments are standard treatments used in day to day clinical practice in the units involved. Either of these medications can be used at the discretion of the responsible medical practitioner. Also, the investigations detailed above will be performed on all patients who present with rUTI. It is only in the setting of this trial that participants will be randomised to either of the 2 groups. The researchers involved in this trial by no means have any intention to modify or discriminate the standard of care currently being applied in the relevant units.

All patients will be provided contact information of the research team involved in the trial to report any side effects or discuss any concerns or if they wished to withdraw from the trial. Patients will be followed up after randomisation at 3 months and 6 months. Patient satisfaction will be evaluated at the 2 visits of the study drug with a visual analogue score (VAS) chart. All adverse events will be recorded and dealt with to the patient’s satisfaction. Patients will have the option of withdrawal at any point during the study if significant side effects are experienced.

At the end of 6 months the prophylaxis (antibiotic and Hiprex) will be discontinued and all patients will be followed up either by an appointment in person or by telephone. We will follow up patients for 3 months after the termination of the trial drugs in regard to any episode of UTI.

*Diagnosis of UTI:*

We will collect midstream urine samples with patients not voiding for at least 3 hours earlier and after washing the genital area with a sterile water wipe. We define diagnosis of UTI based on 103 or more colony- forming units (CFU) in 1 ml of clean voided midstream urine, and at least two of the following lower urinary tract symptoms (LUTS): dysuria, frequency, urgency, suprapubic pain, nocturia and hematuria. *(M. Grabe, R. Bartoletti, T.E. Bjerklund Johansen, T. Cai, M. Çek, B. Köves, K.G. Naber, R.S. Pickard, P. Tenke, F. Wagenlehner, B. Wullt. Guidelines on urological infections. European Association of Urology 2015)*

*Diagnosis of Bacteriuria:*

Presence of 105 colony- forming units (CFU) of a single bacterial species in 2 consecutive samples of clean voided midstream urine in the absence of any urinary symptoms. *(Rubin RH, Shapiro ED, Andriole VT et al. Evaluation of new anti- infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 1992;15 Suppl 1:S216-27. Epub 1992/11/01)*

Diagnosis of pyuria:

Presence of 10 or more white blood cells per high power field (x400) in the resuspended sediment of centrifuged aliquot of urine or per cubic millimeter of unspun urine. *(M. Grabe, R. Bartoletti, T.E. Bjerklund Johansen, T. Cai, M. Çek, B. Köves, K.G. Naber, R.S. Pickard, P. Tenke, F. Wagenlehner, B. Wullt. Guidelines on urological infections. European Association of Urology 2015)*

*Adverse reaction and side effects:*

An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (*Adverse drug reactions: definitions, diagnosis, and management.*

 *Lancet. 2000 Oct 7;356(9237):1255-9*)

**Sample size and power calculation:**

There is a paucity of evidence in regards to the efficacy of nitrofurantoin versus Hiprex in preventing rUTIs. Most studies comparing these two medications date from the 1980s. Three RCTs were used (15-17) to calculate the sample size and power for this study, Sample size and power calculation was performed using an online software from Sealed Envelope Ltd. 2012 and Power calculator for a binary outcome non-inferiority trial. (17)

We calculated the sample size for this non-inferiority study using an estimate of 60% success for the nitrofurantoin group and a 15% non-inferiority limit. With 5% alpha and 80% power, we therefore require 264 patients (132 in each group).

The intention-to-treat (ITT) analysis approach, supported by the per-protocol approach, will be adopted to make inference on the possible non-inferiority of the Hiprex arm, compared to the nitrofurantoin arm, in terms of 6-month freedom from UTI recurrence. The proportions of patients with at least one UTI recurrence (with 95% CIs) in the 2 study arms will be calculated. Logistic regression with ‘treatment group’ as the only covariate will be employed to draw inference on the possible non-inferiority of Hiprex treatment compared to the nitrofurantoin treatment. The odds ratio (with 95% CIs) will be calculated with the nitrofurantoin arm as the reference group. Appropriate parametric or non-parametric statistical techniques will be employed to analyse the data for secondary aims of the study.

**Plain language summary:**

Bladder infections (urinary tract infections or UTI) are amongst the most common infections in women. It is estimated that almost 50% of women will experience at least one episode of UTI in their life time and almost 44% will experience a recurrence within 6 months. These infections can be very troublesome and cause issues like burning sensation when urinating or going very frequently to pass urine, lower abdominal pain, nausea and vomiting, tiredness, days lost from work and sometimes admission to hospitals.

While treatments are available to treat these infections, some women will experience several UTI during a year. These women may benefit from preventive treatments. In this study, we are planning to use Methenamine Hippurate or Hiprex which breaks down to a specific chemical in the bladder which can stop the bacteria growing in the bladder; it is not an antibiotic.

The rationale in using this medication is that to date there has been no bacterial resistance reported to Hiprex and generally it is a well-tolerated medication with a low side effect profile. In this study, we will compare Hiprex to nitrofurantoin, an antibiotic used for many years to treat and prevent UTI. While effective, nitrofurantoin has the same implications as other antibiotics when used long-term which are resistance and side effects.

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