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A clinical trial of extended (high) treatment dose antibiotics in combination with methenamine hippurate compared to the standard of care (either prophylactic (low) dose antibiotic treatment or methenamine hippurate) in people with chronic urinary tract infection

Submission date
16/09/2025

Recruitment status
Not yet recruiting

Registration date
06/11/2025

Overall study status
Ongoing

Last Edited
10/12/2025

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic urinary tract infection (UTI) is a condition where patients experience persistent urinary tract infections with daily symptoms. It is a recently recognised type of UTI. Currently, treatment for chronic UTI follows NICE guidelines for recurrent UTIs (characterised by frequent infections with symptom-free periods in between). This includes short courses of treatment-dose antibiotics, extended courses of low-dose prophylactic antibiotics or methenamine hippurate monotherapy. These treatments are often ineffective for chronic cases.
The purpose of this trial is to assess whether extended courses of treatment (higher) dose antibiotics, combined with the urinary antiseptic methenamine hippurate, is more effective at treating chronic UTI than standard treatment of either low-dose prophylactic antibiotics or methenamine hippurate monotherapy over 12 weeks. It will also assess whether this approach is safe and feasible. The trial will also use fresh urine microscopy to detect white blood cells as an indicator of infection, as standard tests used in the NHS, such as urine cultures and dipstick analysis, often fail to identify chronic infections.

Who can participate?
Patients aged 18 years and over who have experienced chronic UTI symptoms for at least 3 months

What does the study involve?
Participants will be randomly assigned into one of two groups:
Group 1 will receive a treatment dose antibiotic in combination with the urinary antiseptic,

methenamine hippurate (1 g twice daily). The treating clinician will select one of the following antibiotics based on the individual needs of the participant, such as their medical history, concomitant medications and any known allergies:
1. Cefalexin (500 mg four times daily), or
2. Nitrofurantoin (100 mg twice daily), or
3. Trimethoprim (200 mg twice daily)

Group 2 will receive a low-dose prophylactic antibiotic or the urinary antiseptic, methenamine hippurate. The treating clinician will select one of the following treatments based on the individual needs of the participant, such as their medical history, concomitant medications and any known allergies:
1. Amoxicillin (250 mg once daily), or
2. Cefalexin (125 mg once daily), or
3. Nitrofurantoin (50 mg once daily), or
4. Trimethoprim (100 mg once daily), or
5. Methenamine hippurate (1 g twice daily)

Participants will be taking trial medication for 12 weeks and will be required to attend clinic for assessments every 4 weeks. Participant will complete questionnaires and provide blood, urine, and perineal (the area between the vagina and anus) swabs samples.

What are the possible benefits and risks of participating?

The goal of the trial is to find a more effective way to manage chronic UTI, reducing symptoms and improving quality of life for patients with this condition. If successful, this study may support changes to treatment guidelines and lead to better outcomes for those living with chronic UTI.

Although all antibiotics used in the trial (amoxicillin, cefalexin, nitrofurantoin, and trimethoprim), and methenamine hippurate, are widely used and generally well tolerated, there remains a potential risk of side effects for participants.

Common side effects associated with the trial antibiotics include diarrhoea, nausea, indigestion, vomiting, skin rashes, urticaria (a skin reaction causing raised, red, and itchy welts or patches on the skin), headache, and fungal infections. In addition, Trimethoprim commonly causes hyperkalaemia (high potassium levels in the bloods), while nitrofurantoin has been very rarely linked to acute pulmonary damage. The frequency of anaphylactic reactions varies and is not always well documented; however, available data suggests they are very rare with amoxicillin and trimethoprim, and unknown for nitrofurantoin and cefalexin.

Methenamine Hippurate may cause nausea, vomiting, and bladder irritation; haematuria (blood in the urine) is a rare side effect.

Participants will be informed of all potential adverse events during the informed consent process and they will be advised to monitor and report any side effects to their research team. All participants will be provided with a patient safety card which contains the contact details of the research team in and out of office hours and they will be advised to carry with them at all times. In addition to minimise the risks associated with laboratory abnormalities; blood tests will be conducted every 4 weeks to detect any abnormal results. The trial protocol includes specific guidance on managing abnormal blood findings and outlines how and when IMP adjustments should be made.

Some of the IMPs carry potential risks during pregnancy, as outlined in the Summary of Product Characteristics for each drug. Trimethoprim is contraindicated during pregnancy, particularly in the first 12 weeks, due to its impact on folic acid levels. Nitrofurantoin is contraindicated during labour and delivery because of the risk of haemolysis in the infant’s immature red blood cells. Additionally, all IMPs are excreted in breast milk.

Based on this information, the trial excludes participants who are pregnant (or planning pregnancy during trial participation) or breastfeeding. Additionally, individuals of childbearing potential who are unwilling or unable to use an acceptable method of contraception for the

duration of the trial and for one week after the final dose will also be excluded. All participants of childbearing potential will be required to complete a urine pregnancy testing at the screening visit and at all other scheduled trial visits.
The collection of blood samples can be uncomfortable but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort around the needle site. Every effort will be made to minimise this. Blood samples will be taken at every visit.

Where is the study run from?
University College London Comprehensive Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
February 2025 to April 2028

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
The EAT-UP Trial Team, cctu.eat-up@ucl.ac.uk

Contact information

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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1011957

ClinicalTrials.gov (NCT)
NCT07202949

Protocol serial number
CTU/2019-342

Study information

Scientific Title
EAT-UP - Extended Antibiotic Treatment in chronic UTI Patients; a Phase II safety and efficacy trial

Acronym
EAT-UP

Study objectives
The primary objective is to assess the safety, feasibility and efficacy of using an extended treatment (high) dose of one of the following antibiotics: cefalexin, trimethoprim or nitrofurantoin, in combination with the urinary antiseptic methenamine hippurate compared to standard prophylactic (low) dose treatment with cefalexin, trimethoprim, nitrofurantoin, amoxicillin, or methenamine hippurate alone in the treatment of chronic urinary tract infection (UTI) in women.

Efficacy will be determined using the primary outcome: the reduction of urinary white blood cell (WBC) counts, an indicator of infection, at the 12-week timepoint.

Safety will be measured by how many side effects, also called adverse events, are reported by the participants.

Feasibility will be determined by comparing compliance rates (how well participants follow the treatment plan) between treatment arms.

Secondary objectives of the trial are assessing the following between the treatment arms:
1. How many times people needed rescue treatment (medications given when a participant experiences a flare in their UTI symptoms) throughout the trial
2. Changes in bacteria within the gut over the course of treatment by using perineal swab samples to check for antibiotic-resistant bacteria, particularly E. coli
3. Changes in bacteria within the urinary tract over the course of treatment by using urine samples to identify which bacteria are present, how many are found, and how sensitive or resistant they are to different antibiotics
4. Side effects reported
5. Health-related quality of life and disease symptoms as reported by the participant

6. Treatment satisfaction as reported by the participants
7. Impression of improvement in symptoms as reported by the participant
8. How well participants took the medication as prescribed

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 05/11/2025, Wales Research Ethics Committee 3 (Health and Care Research Wales, Floor 4, Crown Building, Cardiff, CF10 3NQ, United Kingdom; -; Wales.REC3@wales.nhs.uk), ref: 25/WA/0300

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Chronic urinary tract infection

Interventions
Participants will be recruited and randomly allocated (via an online web-based randomisation service called Sealed Envelope) to one of two treatment arms in a 1:1 ratio:

Arm A (Experimental): Treatment dose antibiotic in combination with methenamine hippurate
Arm A includes treatment with one of three treatment dose antibiotic options, selected by the treating clinician, in combination with methenamine hippurate. Participants allocated to this arm will receive combination therapy, consisting of one of the following antibiotics:
1. Cefalexin (500 mg four times daily), or
2. Nitrofurantoin (100 mg twice daily), or
3. Trimethoprim (200 mg twice daily)
in combination with Methenamine Hippurate (1 g twice daily) for 12 weeks.

Arm B (Active Comparator): Prophylactic dose antibiotic or methenamine Hippurate monotherapy
Arm B includes treatment with one of four prophylactic dose antibiotics or methenamine hippurate, but not both, selected by the treating clinician. Participants in this arm will receive monotherapy of one of the following:
1. Amoxicillin (250 mg once daily), or
2. Cefalexin (125 mg once daily), or
3. Nitrofurantoin (50 mg once daily), or
4. Trimethoprim (100 mg once daily), or
5. Methenamine hippurate (1 g twice daily) for 12 weeks.

All treatment will be taken orally. Participants will be followed up every 4 weeks while taking trial medication.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Amoxicillin, nitrofurantoin, cefalexin, trimethoprim, methenamine hippurate

Primary outcome(s)
Urinary white blood cell (WBC) count measured using fresh urine microscopy at baseline, week 4, week 8 and week 12, used as the principal biomarker to indicate urinary tract inflammation.

Key secondary outcome(s))
1. The impact of lower urinary tract symptoms (LUTS) on a participant's quality of life is measured using Lower Urinary Tract Symptoms quality of life (ICIQ-LUTSqol) scores at baseline, Week 4, Week 8 and Week 12
2. Participant's experience of urinary tract symptoms is measured using Whittington 39-point Lower Urinary Tract Symptoms (W-39 LUTS) scores at baseline, Week 4, Week 8 and Week 12
3. Participant's generic quality of life is measured using EuroQol EQ-5D 5-Level Health Related Quality of Life Questionnaire (EQ-5D-5L) scores at baseline and Week 12
4. Participant's perception of change in their condition following treatment is measured using Patient Global Impression of Improvement (PGI-I) scores at Week 4, Week 8 and Week 12
5. Participant's satisfaction with treatment will be measured using Lübeck Medication Satisfaction (LMS) Questionnaire scores at Week 12 only
6. Frequency of rescue therapy use for participants requiring further treatment escalation for an acute flare of symptoms will be collected at Week 4, Week 8 and Week 12
7. Treatment adherence is measured by The Medication Adherence Report Scale (MARS-5) scores at Week 4, Week 8 and Week 12
8. Safety and tolerability as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events will be measured at Baseline, Week 4, Week 8 and Week 12
9. Participant's urine will be tested to evaluate the changes in the type of bacteria found in the urine, the amount of bacteria and how the bacteria is responding to antibiotics (urine culture species, cfu/ml count, sensitivities and resistance profiles) at baseline and Week 12
10. Changes in perineal swab analyses will be used to measure any changes in how bacteria in the gut responds to antibiotics (including the E. coli identified, sensitivities and resistance profiles) at baseline and Week 12

Completion date
30/04/2028

Eligibility

Key inclusion criteria
1. A diagnosis of chronic UTI, without structural or functional urinary tract abnormality*, as defined as daily persistent symptoms affecting storage (urinary frequency, urgency or urge incontinence) and urinary tract pain symptoms (including bladder pain, urethral pain, or dysuria), for at least 3 months, with previously associated transient symptomatic improvement to antibiotic treatment for UTI, which in the opinion of the delegated clinician is secondary to chronic urinary tract infection

2. A fresh urine microscopy examination showing ≥20 white blood cells/µl of urine at the screening visit
3. Female** patients
4. Aged ≥18 years
5. Screening blood result of eGFR ≥45ml/min/1.72 m2
6. Able and willing to attend trial visits and comply with all study procedures for the duration of the trial
7. Able and willing to provide informed consent prior to any study related assessments and/or procedures

* A structural or functional abnormality may include kidney reflux, current or long-term catheter use, renal transplant, diversion surgery, renal stones, grade 2 or above utero-vaginal prolapse or incomplete bladder emptying.
** For the purposes of this trial, a female will be defined as an individual assigned female at birth who has a female urinary tract.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
Female

Total final enrolment
0

Key exclusion criteria
1. Inability to take at least one of the following antibiotics: cefalexin, nitrofurantoin, or trimethoprim, at prophylactic and treatment dose according to NICE guidelines, and/or the Summary of Product Characteristics (such as hepatic or renal dysfunction), or any other medical contraindications (such as allergies, intolerances or concomitant medications).
2. Inability to take methenamine hippurate due to medical contraindications.
3. Current use of immune-modulating drugs for the treatment of chronic illnesses such as rheumatoid arthritis, chronic lung disease, any other autoimmune conditions or cancer.
4. Current use of Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors*.
5. A current diagnosis of bladder cancer.
6. A diagnosis of an active sexually transmitted infection or recently diagnosed with a sexually transmitted infection within the last 3 months.
7. Previous use of an antibiotic at treatment dose as per NICE guidelines for more than 14 consecutive days for treatment of UTI in the last 3 months.

8. Pregnancy (or planned pregnancy during trial participation) and/or breastfeeding.
9. Women of childbearing potential that are unable/unwilling to use an acceptable method of contraception (as described in section 3.4.1) to avoid pregnancy for the duration of the trial and for 1 week after the last dose of trial medication.
10. Current participation in another clinical trial of a device, interventional medicinal product, advanced therapy, or surgical procedure; or previous participation within 6 months of the screening visit.
11. Any medical condition or previous treatment which in the investigator's opinion compromises the potential participant's ability to participate.
*Patient's must not have taken a Sodium-Glucose Transport Protein 2 (SGLT2) inhibitor within 24 hours before the screening visits to be eligible for the trial.

Date of first enrolment
19/01/2026

Date of final enrolment
31/05/2027

Locations

Countries of recruitment
United Kingdom

Study participating centre
The Whittington Hospital
Highgate Hill
London
England
N19 5NF

Sponsor information

Organisation
University College London Comprehensive Clinical Trials Unit

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date