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Determining the optimal duration of oral antibiotic cefalexin treatment for infants and young children with a clinical diagnosis of febrile urinary tract infection.

Submission date
19/07/2023

Recruitment status
Recruiting

Registration date
08/09/2023

Overall study status
Ongoing

Last Edited
28/08/2025

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Urine infections are very common in children. They can cause fever, abdominal pain and vomiting, and are usually treated with antibiotics. In adults, just a few days of antibiotics is usually enough to stop the infection. However, it is unclear if this is the same for children. Shorter treatment with antibiotics has benefits over longer treatments, including less side effects (e.g. diarrhoea, vomiting and rash) and a lower chance of developing bugs resistant to antibiotics (i.e. bacteria that antibiotics can't kill).

The CURLY trial aims to improve the treatment of children who have urine infections by finding out the shortest course of antibiotics which is effective to successfully cure the infection. The antibiotic used will be cefalexin, which is the most commonly used antibiotic used to treat this type of infection.

Who can participate?
Children (aged between 3 months and 11 years) with a urine infection.

What does the study involve?
The study will be conducted in at least 8 UK emergency departments and will last for a total of 30 months. Around 705 children will take part. The amount of antibiotics that children get will be either a 3, 5, 6, 8, or 10 day course. The amount of antibiotics that each child receives will be chosen fairly, using a study process called 'randomisation', where each child has an equal chance of getting one of the different courses.

After being discharged home from the emergency department, parents will use a smartphone or computer app to log antibiotic doses and report their child's symptoms. A follow-up appointment after 16-days will assess the child's symptoms and check that the infection has

cleared from the urine. A further urine sample will be tested after 30 days to check that the infection hasn't come back. More antibiotics will be prescribed if the treatment is not working well.

What are the possible benefits and risks of participating?
Benefits:
Children who take shorter treatments of cefalexin in the study may have fewer antibiotic side effects, such as diarrhoea, allergic reactions and thrush. Shorter treatments of antibiotics also stop 'bad bacteria' from forming. 'Bad bacteria' can be difficult to treat as some antibiotics can't kill them.

Children who participate in the trial will be monitored more closely than normal, using the information that families provide on an app and with an extra hospital appointment. This means we can make sure that participants are doing well, spot very early if further help is needed, and can provide more medicine if needed. An extra urine test will also make sure the infection has completely gone.
Taking part in the study will help children in the future as we will know the best number of days of cefalexin to give.

Risks:
Cefalexin used in the trial will be a standard proprietary oral liquid suspension. After reconstitution, each bottle contains 100ml of suspension at a concentration of 250mg/5ml. CURLY will apply the British National Formulary for Children weight-based cefalexin dosing schedule, following the target dose of 12.5 mg/kg twice daily. To reduce the risk of dose calculation errors and ensure that the desired volume is easy to draw-up, all sites will prescribe using a prespecified weight-dose volume table.

Cefalexin has a well-established safety profile, and it will be used within its current marketing authorisation. Clinicians will see patients face-to-face prior to prescribing the medication and will describe common side-effects of cefalexin, and what should be done if they occur. This information is also included within the CURLY website (and PIS). The CURLY app will explicitly prompt for known clinical adverse effects of cefalexin, primarily diarrhoea, rashes, and candida infections and these will be recorded on the eCRF. Any side-effects will be dealt with as per standard clinical practice. Expedited events will be reported to BCTU by the site as defined in the trial protocol.

For CURLY, there are no drug interactions or contraindications of note for cefalexin, other than those mentioned in the licensing label. As stated in the exclusion criteria, any child with a known allergy to cefalexin or previous severe allergic reaction to any beta-lactam antibiotic will be excluded from participation in the trial.

Procedures to support participants and maintain patient safety
In CURLY, normal pathways of care will be encouraged. However, there is a responsibility to balance this approach with the need to ensure the safety of all patients, particularly those treated for shorter durations than the current recommended practice.

Compared with standard clinical practice, additional measures for trial participants will be:

• The medicine tracker feature within the CURLY app will help parents/guardians to track medicine administration.

• Parents/guardians will be provided with a telephone contact number at their local site for any questions or concerns.

• A text/email alert will be sent to the parent/guardian on the final day of treatment, reminding them that the cefalexin is due to finish, but recommending medical review if their child's symptoms are not resolving.

• A text/email "fit and well" check will be performed 48-72 hours after the end of treatment, asking the parent/guardian to report if their child has ongoing fever or other symptoms of concern and advising them to consider seeking medical advice for any ongoing issues. These concerns will be automatically flagged to the local trial team.

• Parents/guardians will have access to the CURLY trial website throughout the duration of the trial.

• If at any point the parent/guardian fails to respond to the text/email questionnaires, or if they do not attend the primary outcome visit, the local study team will attempt to telephone the parent/guardian to ensure that all is well with their child and, if necessary, to provide support and advice.

During PPI workshop discussions, parents and children/young people all felt that families would accept the (day 16) face-to-face follow-up as a positive opportunity for reassessment by a doctor. This would help reassure parents and children. The benefits of this reassurance were felt to outweigh any inconvenience of the appointment. Children and young people agreed that the final (day 30) follow-up assessment should not be done at the hospital. This was because most of the older participants would have recovered and returned to nursery or school.

Trial monitoring
A Trial Steering Committee (TSC), Trial Management Group (TMG) and Data Monitoring Committee (DMC) are in place for this trial. Regular meetings will occur as follows and email correspondence will be used for ad-hoc meetings/discussion and issues that require urgent advice or resolution:

(i) The DMC will meet before the start of patient recruitment, then at the end of the pilot phase to review the study data and advise on the continuation of the trial. The DMC will particularly consider safety, treatment side effects, presence of symptoms and report recommendations (if any) to the TSC.

(ii) The TSC will meet before the start of patient recruitment, then at least annually to provide advice to the TMG taking into consideration the DMC recommendation.

(iii) The TMG will meet every 4 weeks; this frequency will be adjusted according to need as the trial progresses.

No formal futility rules have been set to close the trial prematurely, however an internal pilot will be conducted over the first 6 months of recruitment to assess the feasibility of identifying eligible patients, to assess the acceptability of randomisation, and to determine if the pilot phase should continue to a full trial.

Where is the study run from?
Birmingham Clinical Trials Unit, University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
July 2023 to August 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
curly@trials.bham.ac.uk
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007455

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RG_23-011, IRAS 1007455

Study information

Scientific Title
Cefalexin for UTIs – Right treatment Length in Young children (the CURLY trial). A multi-centre, randomised trial to determine the optimal duration of cefalexin therapy for the treatment of febrile urinary tract infections in children.

Acronym
CURLY

Study objectives
Primary objective:
To determine the optimal (shortest effective) cefalexin duration for the treatment of febrile UTIs in children, to achieve clinical cure

Secondary objectives:
1. To assess the impact of cefalexin treatment duration on UTI recurrence (relapse or reinfection) up to 30 days post-randomisation.
2. To assess the impact of cefalexin treatment duration on microbiological cure and antimicrobial resistance.
3. To assess the impact of cefalexin treatment duration on antibiotic-associated adverse events, including diarrhoea, rashes, and candida infections.
4. To assess patient adherence to the trial drug across the treatment duration arms.
5. To quantify and draw inferences from any differences in quality of life (CHU9D) between the different treatment duration arms.
6. The health economics analysis will assess the cost-effectiveness of different antibiotic treatment durations, to include the effect of treatment duration on the cost of antibiotic resistance.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 31/08/2023, South Central - Hampshire A Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048210; hampshirea.rec@hra.nhs.uk), ref: 23/SC/0275

Study design
Interventional randomized parallel group controlled trial

Primary study design

Interventional

Study type(s)
Treatment, Efficacy

Health condition(s) or problem(s) studied
Urinary tract infections

Interventions
This trial aims to determine the optimal duration of oral cefalexin treatment for infants and young children with a clinical diagnosis of febrile urinary tract infection (UTI). The trial design is a multi-centre, open label, multi-arm randomised controlled trial with internal pilot, using a "DURATIONS design," which will produce a "cefalexin duration vs cure rate" curve to determine the optimal number of treatment days. The study will be conducted in at least 8 UK emergency departments and will last for a total of 30 months. The population includes infants and children (aged 3 months to 11 years) with a clinical diagnosis of febrile UTI in whom the decision has been made to treat with oral cefalexin. Around 705 children will take part, however, for this "DURATIONS" trial design, a total of 500 participants with a microbiological-confirmed UTI are required. All participants in CURLY will receive oral cefalexin administered as an oral liquid suspension. The trial will apply the British National Formulary for Children (BNFC) weight-based cefalexin dosing schedule, following the target dose of 12.5 mg/kg twice daily. Body weight should be obtained on the day of presentation to the ED by weighing children on an appropriate scale.

Trial participants will be randomised electronically at the level of the individual in a 1:1:1:1:1 ratio to one of five cefalexin course durations (3 days (6 doses), 5 days (10 doses), 6 days (12 doses), 8 days (16 doses) or 10 days (20 doses)) following confirmation of eligibility and informed consent provided. Randomisation will be provided by BCTU using a secure online system (available at https://bctu-redcap.bham.ac.uk), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who have been delegated the role of randomising participants into the trial as detailed on the CURLY Delegation Log.
After reconstitution, each bottle contains 100ml of suspension at a concentration of 250mg/5ml. Each patient will receive between 1 and 3 bottles, sufficient to cover their weight-based dose volume and assigned number of treatment days/doses.

For participants on all trial arms; urine samples will be collected at the baseline ED visit as part of standard clinical assessment, following consent. After being discharged home from the emergency department, parents will use a smartphone or computer app to log antibiotic doses and report their child's symptoms. Participants will provide another urine sample during the primary outcome assessment visit (follow-up appointment after 16-days to assess the child's symptoms and check that the infection has cleared from the urine). A further urine sample will be tested after 30 days to check that the infection hasn't come back. More antibiotics will be prescribed if the treatment is not working well.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)

Cefalexin

Primary outcome(s)
Clinical UTI cure rate, which will be assessed at a face-to-face follow-up assessment at 16 days post-randomisation. Clinical UTI cure is defined as those patients in whom there is (i) fever resolution and (ii) no additional systemic antibiotic prescription by 16 days post-randomisation. This primary outcome is informed by a systematic review that identified wide variation in the outcomes reported within paediatric febrile UTI trials, and proposed criteria to harmonise study design, which were endorsed by the European Medicines Agency.

Key secondary outcome(s))
Clinical:
1. UTI recurrence
1.1. Relapse (recurrent infection with the original bacterial strain) up to final follow-up, 30 days post-randomisation.
1.2. Reinfection (recurrent infection with a different bacterial strain) up to final follow-up, 30 days post-randomisation.
2. Individual components of the primary outcome
2.1. Fever resolution at the primary outcome assessment visit.
2.2. No additional systemic antibiotic prescription by the primary outcome assessment visit.
3. Microbiological cure
3.1. Urine sterilisation at the primary outcome assessment visit.
4. Antibiotic-associated adverse events
4.1. Antibiotic-associated adverse events, including diarrhoea, rash, and candida infections.
5. Adherence to trial drug
5.1. No more than one missed dose from the allocated full course, as logged on the medicine tracker page of the CURLY app and no additional dose(s) beyond the assigned treatment duration.
6. Antimicrobial resistance & ESBL rates
6.1. Overall rates of antibiotic resistance of urinary pathogens within pre- and post-treatment urine samples.
6.2. Regional rates of antibiotic resistance.
6.3. Identification of ESBL-producing organisms within post-treatment urine samples.
7. Quality of life – CHU9D
7.1. Differences in quality of life (using the Child Health Utility instrument CHU9D) between the different treatment duration arms.

Economic:
8. Health economics
8.1. An incremental cost-utility analysis will determine the Cost per Quality Adjusted Life Years of the different treatment durations over the follow-up period.

Completion date
31/08/2027

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 07/02/2025:
1. Age 3 months to 11 years inclusive
2. Clinical diagnosis of febrile UTI at presentation to ED as defined by both:

2.1. Temperature (≥38°C measured by any method OR likely fever in last 24 hours)
2.2. AND Clinical feature(s) suggestive of UTI at presentation (i.e. one or more of the following):
2.2.1. If <2 years of age:
• Poor feeding
• Vomiting
• Irritability
2.2.2. If ≥2 years of age:
• Vomiting
• Dysuria
• Urinary frequency
• Urinary urgency
• Abdominal or flank pain
• Suprapubic or flank tenderness
3. Early urine test suggesting likely UTI as defined by any one of the following:
3.1. Dipstick: nitrite positive AND leucocyte esterase positive.
3.2. Dipstick: nitrite positive AND leucocyte esterase negative (on a fresh urine sample).
3.3. Dipstick: leucocyte esterase positive AND nitrite negative AND the treating clinician assesses there to be good clinical evidence of a UTI (e.g. obvious urinary symptoms).
3.4. Abnormal urine microscopy (bacteriuria by microscopy with Gram stain
4. Decision to treat with oral cefalexin on discharge from the ED.

Previous participant inclusion criteria:
1. Age 3 months to 11 years inclusive
2. Clinical diagnosis of febrile UTI at presentation to ED as defined by both:
2.1. Temperature (≥38°C measured by any method OR likely fever in last 24 hours)
2.2. AND Clinical feature(s) suggestive of UTI at presentation (i.e. one or more of the following):
2.2.1. If <2 years of age:
• Poor feeding
• Vomiting
• Irritability
2.2.2. If ≥2 years of age:
• Vomiting
• Dysuria
• Urinary frequency
• Urinary urgency
• Abdominal or flank pain
• Suprapubic or flank tenderness
3. Early urine test suggesting likely UTI as defined by either:
3.1. Abnormal urine dipstick (both nitrite and leucocyte esterase positive)
3.2. OR Abnormal urine microscopy (bacteriuria by microscopy with Gram stain)
4. Decision to treat with oral cefalexin on discharge from the ED.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 months

Upper age limit
11 years

Sex
All

Key exclusion criteria
1. Known congenital anomalies of the kidney and urinary tract (CAKUT), reflux nephropathy or indwelling catheter.
2. Known immune deficiency (e.g. HIV, malignancy, solid-organ transplant recipients) or currently recieving immunosuppression therapy.
3. Systemic antibiotics for any reason (treatment or prophylaxis) in the previous 14 days.
4. Weight > 50kg.
5. Known allergy to cefalexin or previous severe allergic reaction to any beta-lactam antibiotic*
* e.g. ampicillin, amoxicillin, cephalosporins, co-amoxiclav, penicillin.

Date of first enrolment
01/10/2023

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Ireland

Study participating centre
Birmingham Childrens Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Royal Liverpool Childrens Hospital
Alder Hey Hospital
Eaton Road

West Derby
Liverpool
United Kingdom
L12 2AP

Study participating centre
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
St Michael's Hill
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
The Royal Belfast Hospital for Sick Children
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
St Georges Hospital
Blackshaw Road
Tooting

London
United Kingdom
SW17 0QT

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
Chelsea and Westminster Hospital
Chelsea and Westminster Hospital NHS Foundation Trust
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Children's Health Ireland at Crumlin
Cooley Rd
Crumlin
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D12 N512

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study are/will be available upon request as we operate a controlled access approach.

Requests for data generated during this study will be considered by BCTU (via bctudatashare@contacts.bham.ac.uk). Data will typically be available within six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the Chief Investigator and, where appropriate (or in absence of the Chief Investigator) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent Trial Steering Committee (TSC).

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes

Protocol file	version 2.0	21/06/2023	03/10/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes