BMJ Open

7-day compared with 10-day antibiotic treatment for febrile urinary tract infections in children: protocol of a randomised controlled trial

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To cite: Daniel M, Szajewska H, Pańczyk-Tomaszewska M. 7-day compared with 10-day antibiotic treatment for febrile urinary tract infections in children: protocol of a randomised controlled trial. *BMJ Open* 2018;**8**:e019479. doi:10.1136/bmjopen-2017-019479

► Prepublication history for this paper is available online. To view these files, please visit the journal online http://dx.doi.org/10.1136/bmjopen-2017-019479).

Received 5 September 2017
Revised 1 December 2017
Accepted 25 January 2018

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ABSTRACT

Introduction The optimal duration of antibiotic therapy in children with febrile urinary tract infections (UTIs) is still a matter of debate. Current guidelines recommend treating children with febrile UTIs with antimicrobials for 7 to 14 days. We aim to compare the efficacy and safety of 7-day versus 10-day course of oral or sequence therapy (intravenous with a switch to oral) with cefuroxime/cefuroxime axetil for febrile UTIs in children.

Methods and analysis A non-inferiority, double-blind, randomised, controlled trial will be conducted. Two hundred twenty-one patients aged 3 months to 7 years with febrile UTIs (defined as a combination of fever and leucocyturia in urine sediment) will be randomly assigned to a 7-day treatment arm (7 days of cefuroxime/cefuroxime axetil followed by 3 days of blinded placebo) or a 10-day treatment arm (7 days of cefuroxime/cefuroxime axetil followed by 3 days of blinded cefuroxime axetil). The primary outcome measure will be frequencies of recurrence and reinfection of UTI during the 6 months after the intervention.

Ethics and dissemination The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed paediatric journal. Abstracts will be submitted to relevant national and international conferences.

Date and protocol version identifier 04/09/2017

Trial registration number NCT03221504.

Strengths and limitations of this study

- The study design (randomised controlled trial; RCT) is the most robust methodology to assess the effectiveness of therapeutic interventions.
- The findings of this RCT, whether positive or negative, will contribute to the formulation of further recommendations on the duration of treatment of febrile UTIs with antimicrobials (7 or 10 days) in children.
- The findings may not be generalisable to settings with different UTI aetiologies and antibiotic susceptibilities.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections in children. UTIs comprise a range of conditions caused by the presence of microorganisms in the urinary tract.[1 2] These include asymptomatic UTI (significant bacteriuria with pyuria and without clinical symptoms); symptomatic lower UTI or cystitis (significant bacteriuria with pyuria and symptoms such as dysuria, new-onset urinary incontinence, lack of proper stream, frequency, urgency); upper UTI or acute pyelonephritis (significant bacteriuria with pyuria, increased levels of markers of inflammation such as white blood cells (WBCs), C reactive protein and procalcitonin and clinical symptoms: fever, back pain, abdominal pain, vomiting and diarrhoea). In young children (<2 years), non-specific symptoms make it difficult to distinguish pyelonephritis from cystitis; therefore, a UTI with fever in small children should be treated as pyelonephritis.[3 4]

The prevalence rates of UTIs depend on age and sex. In neonates and infants <6 months, the UTI prevalence is higher among boys and is caused by congenital anomalies of the kidney and urinary tract. In children <7 years of age, the prevalence of one episode of symptomatic UTI amounts to 3%–7% in girls and 1%–2% in boys, whereas 8%–30% have one or more recurrence of a UTI.[5–8] Most (85%–90%) UTIs in children are caused by the Gram-negative bacillus *Escherichia coli*.[5 9] Other Gram-negative bacterial pathogens, more common among boys, include *Proteus mirabilis* and *P. vulgaris*.[10 11]

Clinical symptoms of a UTI depend on the age of the child. In infants and children <2 years, they may include fever, decreased appetite, abdominal pain, intestinal colic, vomiting and diarrhoea. More specific symptoms of a UTI observed by parents include anxiety, crying during urination, unpleasant smell of urine and purulent secretions in

diapers. In older children, symptoms include dysuria, frequency, urgency, new-onset urinary incontinence (daily and nocturnal) and back pain.[11 12] Children with symptoms suggestive of a UTI or with unexplained fever (no abnormalities in the physical examination) should be suspected of having a UTI, and a urine sample test and urine culture should be performed.[3] An increased number of leucocytes in the centrifuged urinary sediment (>10 in the field of view) is indicative of a UTI.[3 5 11]

Empirical antibiotic therapy should be given as soon as a UTI has been diagnosed (clinical signs and pyuria) and urine for culture has been collected.[1–4 13–16] In previously published European and global guidelines, there has been no consensus among experts regarding the duration of therapy for a febrile UTI. Depending on the recommendation, the duration of treatment should be between 7 and 14 days. The American Academy of Paediatrics and the Canadian Paediatric Society recommend administering antibiotics for 7–14 days.[4 14] The National Institute for Health and Care Excellence, the European Society for Paediatric Urology, Clinical Practice Guidelines in Spain, the Kidney Health Australia—Caring for Australasians with Renal Impairment Guideline (Australia) and the Polish Society of Paediatric Nephrology recommend administering antibiotics for 7–10 days.[1–3 15 16] If the clinical condition of the patient allows for oral therapy, there is no reason to give the antibiotic intravenously. Many studies have shown no differences in the efficacy of intravenous, oral or sequential therapy. This is confirmed by available recommendations for UTI treatment[2–4 13–16] and previously published research results.[17–19]

Trial objectives and hypothesis

We aim to assess the effectiveness of a 7-day compared with a 10-day course of antibiotic treatment for febrile UTIs in children. We hypothesise that a 7-day course of antibiotic therapy is equally effective as a 10-day course of therapy and would entail a lower risk of adverse events and better compliance.

METHODS AND ANALYSIS

The trial is registered at ClinicalTrials.gov (NCT03221504) and any important changes to the protocol will be implemented there.

Trial design

This study is designed as a randomised, placebo-controlled, double-blind, non-inferiority trial.

Settings and participants

The study will be performed in paediatric units of the paediatric hospital of the Medical University of Warsaw and in the paediatric department of The Holy Family Specialist Hospital in Warsaw. Additionally, patients treated at the Nephrology Outpatient Clinic of the Medical University of Warsaw will be recruited. The start of the recruitment is planned in August 2017 and should be completed within the following 2 years.

Eligibility criteria

Recruited children for the trial must fulfil all of the following inclusion criteria: aged from 3 months to 7 years; clinical diagnosis of a febrile UTI at presentation according to a urinalysis (WBCs in the sediment >10 in the field of view); fever ≥38°C; positive urine collection with sensitivity for cefuroxime, treatment with cefuroxime or cefuroxime axetil.

Exclusion criteria will include the following: history of a UTI in the last 3 months, prophylaxis for a UTI, severe obstructive uropathy (defined as ≥III grade according to Society for Fetal Urology Classification), antibiotic therapy in the last month, allergy to the study drugs, immunosuppression therapy, disease with immune deficiency and children with other coexisting infections, for example, meningitis, sepsis, pneumonia, otitis.

Interventions

The intervention under investigation will be the administration of cefuroxime axetil or placebo (after 7 days of antibiotic treatment). The placebo suspension consists of a mixture of talc, sucrose and water together with gum arabic to give the product the correct rheological properties as well as a tutti frutti aroma to give the suspension a smell similar to that of the antibiotic. The treatment will involve the supply of oral cefuroxime axetil (30 mg/kg/day) in two divided doses; the dosage of the placebo will be like that of antibiotic syrup. The appearance of the placebo syrup will be comparable to the suspension containing the antibiotic. The study products (cefuroxime axetil and components of placebo) will be funded by the Medical University of Warsaw. The placebo will be prepared in the hospital pharmacy.

Study procedure

The parents of each participating child will receive oral and written information regarding the study. Participants with a febrile UTI will be randomised, as soon as we receive the results of urine culture and antibiotic sensitivity tests and after the 7-day treatment with cefuroxime (intravenous, orally or sequentially—the choice of an antibiotic regime will depend on clinical status such as toxic appearance, vomiting, diarrhoea); first arm will be receiving antibiotic (cefuroxime axetil, orally) from day 8 to day 10 or the second arm will be receiving placebo.

The placebo will be administered orally, in syrup. Blinded suspensions will be prepared by the hospital pharmacy. At any time, caregivers will have the right to withdraw the participating child from the study; they will be not obliged to give reasons for this decision, and there will be no effect on subsequent physician and/or institutional medical care.

Follow-up

All study participants will be followed up 10 days, 3 months and 6 months after the intervention.

Compliance

Compliance with the study protocol will be assessed by direct interview with the patient and/or caregiver and by measuring the amount of the fluid left in the bottle. Based on previously published trials, it seems appropriate to consider those participants receiving <75% of the recommended doses as being non-compliant.

Concomitant medications

If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

Outcome measures

The primary outcome measure will be the frequency of recurrence of the UTI during the 3 months after the intervention. The recurrence of a UTI is diagnosed when the next infection is caused by the same microorganism with the same sensitivity to antibiotics, during the 3 months following the treatment of the initial UTI.[20]

The secondary outcome measures will be reinfections of UTI, new onset of a UTI between 3 and 6 months after the interventions, antibiotic-associated diarrhoea (AAD) and compliance. Reinfection of UTI is diagnosed when the next infection is caused by a different bacteria. AAD is defined as at least three loose or watery stools for at least 48 hours during antibiotic treatment and 7 days after administration of the antibiotic.

Participant timeline

The study plan for recruitment, interventions, assessment and visits for the participants are summarised in table 1.

Sample size

Based on data from previous studies, we assumed the frequency of recurrence of UTIs to be 14% in the group of patients of similar age. To detect no difference between the groups, then 184 patients are required to be 90% certain that the upper limit of a one-sided 95% CI will exclude a difference of more than 15% in favour of the standard group. Taking into account that 20% of the patients will be lost to follow-up, we have calculated that a total of 221 children will be needed.

Recruitment

The recruitment rates will be monitored every month. In the case of poor or slow recruitment, the reasons at various levels, such as the patient, the recruiting clinician, the centre and the trial design, will be evaluated.

Sequence generation

An independent researcher from the Medical University of Warsaw will generate the randomisation scheme. Block randomisation will be used, with a block size of 10. Randomisation codes will not be disclosed until all data have been gathered and the final analysis has been

Table 1 Timetable of activities planned during the study

	Study period				
	Enrolment and allocation	Postallocation			Close-out (after the end of follow-up period)
Time point	Day 1	Day 10	Month 3	Month 6	
Enrolment					
Eligibility screen	X				
Informed consent	X				
Randomisation of the participant	X				
Study product distribution	X				
Interventions					
Cefuroxime axetil					
Placebo					
Assessments					
Recurrence of UTI			X		X
Reinfection of UTI			X		X
New onset of UTI				X	X
Adverse events		X			X
AAD		X			X
Telephone contact*			X	X	X
Return of non-used study products		X			

*In case of suspicion of congenital anomalies of the kidney and the urinary tract—hospitalisation in Nephrology Clinic or visit at Nephrology Outpatient Clinic of the Medical University of Warsaw.
AAD, antibiotic-associated diarrhoea; UTI, urinary tract infection.

conducted. During the study, researchers and participants will not be aware of the affiliation with the patient group.

Allocation concealment

Allocation concealment will be ensured using opaque, sealed, numbered envelopes and will be performed after getting informed consent and registering the basic demographic data to the case report form (CRF). An independent person will dispense the numbered study products according to a computer-generated randomisation list.

Blinding

The antibiotic and placebo will be packaged in identical bottles. Suspensions will look and taste similar. The bottles will be delivered by the pharmacy in sealed and sequentially numbered opaque envelopes. All participants and investigators will be blinded to the intervention until the completion of the study.

Data collection and management

Confidentiality of participants will be ensured during the workshop process. All study participants will be assigned a study identification number. Data will be entered and stored in a password-protected electronic database. Records for all participants, CRFs, all source documents, laboratory data and so on will be accessible to the involved researchers only.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all participants in the groups to which they were randomised for whom outcomes will be available (including dropouts and withdrawals). We will also carry out a per protocol analysis on the primary and secondary outcomes. This analysis will include children who have completed the entire treatment protocol as originally planned, with availability 6 months after intervention. χ^2 tests (Pearson's or Fisher's test) will be used for binary outcome measures. We will calculate the differences between treatments with 95% CIs and analyse skewed distributions on log scales with results transformed on linear scales.

Auditing

The Bioethics Committee did not require auditing for this study.

ETHICS AND DISSEMINATION

The study protocol and template consent forms have been reviewed and approved by the Bioethics Committee of the Medical University of Warsaw. Any modifications to the protocol that may affect the conduct of the study will be presented to the Committee. Verbal and written information regarding informal consent will be presented to the caregivers. A parent or a legal guardian will have to sign the informed consent forms prior to the randomisation. Patients may withdraw from the study at any time without prejudice, as is documented and explained at the time of providing consent. The full protocol will be available freely due to open access publication. Abstracts will be submitted to relevant national and international conferences.

Contributors MD and MP-T conceptualised the study. MD developed the first draft of the manuscript. MD, MP-T and HS contributed to the development of the study protocol and approved the final draft of the manuscript.

Funding This study will be funded by the Medical University of Warsaw.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Bioethics Committee of the Medical University of Warsaw.

Provenance and peer review Not commissioned; externally peer reviewed.

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