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ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN - A nationwide randomized open-label non-inferiority trial.

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ABSTRACT:

Introduction: Children with bone and joint infections are traditionally treated with intravenous antibiotics for three to ten days followed by oral antibiotics. Oral-only treatment has not been tested in randomized trials.

Methods and analysis: Children (three months to 18 years) will be randomized 1:1 with the experimental group receiving high dose oral antibiotics and the control group receiving intravenous antibiotics with a shift in both groups to standard oral antibiotics after clinical and paraclinical improvement. Children in need of acute surgery or systemic features requiring intravenous therapy, including septic shock, are excluded. The primary outcome is defined as a normal blinded standardized clinical assessment 6 months after end of treatment. Secondary outcomes are non-acute treatment failure and recurrent infection. Outcomes will be compared by a non-inferiority assumption with an inferiority margin of 5%.

Ethics and dissemination: The trial has the potential to reduce unnecessary hospitalization and use of IV antibiotics in children with bone or joint infections. Due to the close follow up, exclusion of severely ill children and predefined criteria for discontinuation of the allocated therapy, we expect the risk of treatment failure to be minimal.

Trial registration number: NCT04563325 (clinicaltrials.gov).

ARTICLE SUMMARY:

Strengths and limitations of this study:

- The prospective randomized design with blinded evaluation of the primary outcome will reduce potential bias.
- The primary outcome, sequelae at 6 months, is of clear clinical relevance.
- The pragmatic design with full integration into daily clinical practice ensures a high transferability of the generated data.
- The 12 months follow-up reduces the risk of missing long-term sequelae.
- The pragmatic criteria of inclusion involve a risk of including children with non-bacterial bone or joint disease.

INTRODUCTION

In recent years the necessity of intravenous (IV) antibiotic treatment of children and adults with severe bacterial infections has been questioned as the evidence hereof is lacking. Oral-only treatment has been demonstrated to be safe and non-inferior to IV treatment for children with e.g., severe pneumonia [1] and febrile urinary tract infections [2] including urinary tract infections with bacteraemia [3]. In large prospective randomized trials, early shift from IV to oral antibiotic treatment has been demonstrated to be safe and non-inferior to longer courses of IV treatment for adults with infectious diseases such as endocarditis [4] and bone and joint infection (BJI) [5].

Prospective studies on children with BJI have demonstrated that individualized antibiotic therapy with significantly reduced treatment duration is non-inferior to the previous long-term treatment [6-9] and that only 2-4 days of IV therapy followed by 1-3 weeks of oral therapy is sufficient in most cases. The recommendations of individualized and shorter treatment have been adopted in Denmark with good results [10]. These significant changes in treatment strategies raise the question of whether most children with BJI could be treated with oral antibiotics only. One small case series [11] and one retrospective case-control study [12] found oral-only therapy as a valid alternative to the current standard treatment, but the issue has not been investigated in randomized controlled trials.

METHODS AND ANALYSIS:

Study hypothesis and design:

We hypothesize that oral-only antibiotic therapy is non-inferior (non-inferior margin 5%) to initial IV therapy followed by oral therapy in children and adolescents with BJI and test that hypothesis in a nationwide, multicentre, randomized, controlled, open-label, non-inferiority trial.

Included children will be randomized 1:1 with the experimental group receiving high dose oral antibiotic therapy and the control group receiving IV antibiotic therapy with a shift in both groups to standard oral therapy after clinical and paraclinical improvement.

Trial participants:

Children and adolescents are considered for inclusion when they present with suspicion of BJI. Recruitment will be nationwide from all 18 paediatric departments in Denmark. Request a complete list of study sites and primary investigators at allan.bybeck.nielsen@regionh.dk.

Criteria of inclusion is listed in table 1.

Delayed inclusion:

Most patients will be included in the study before the start of treatment. If inclusion is not performed before administration of antibiotic therapy (e.g., the treating physician is not aware of the project), up to 24 hours of antibiotic treatment will be accepted before inclusion in the study to achieve adequate participant enrolment.

Early termination of falsely included patients:

To reflect the daily clinical setting and facilitate timely entry to the study, the patients are eligible for entry based on the available clinical information, often before the final diagnosis is made. In most cases, the clinical suspicion of infection is sustained (e.g., by positive microbiology or imaging), and the study treatment is completed with or without further evidence of infection. If the suspicion of infection is abandoned during the study period, it will lead to early termination from the study according to the following criteria:

1. The suspicion of infection is abandoned, and antibiotic therapy is stopped prematurely.
2. The course of the disease is explained by another diagnosis (not BJI) that is made during treatment or follow up. Examples:
    a. Imaging reveals another diagnosis e.g., bone tumour, Legg-Calve-Perthes disease, or soft tissue infection with no involvement of bone or joint structures.
    b. Recurrent symptoms with no confirmation of infection leads to another final diagnosis, such as juvenile idiopathic arthritis (JIA), chronic recurrent multifocal osteomyelitis (CRMO), or other non-infectious diseases.

c. Lyme arthritis is suspected, and the antibiotic treatment is changed targeting *Borrelia burgdorferi*.

Early terminated patients without BJI, will not continue follow-up in the trial. They will be included in the analysis of the safety outcomes, but not in the analysis of any other outcomes. For transparency, details on all early terminated patients will be reported.

Minimizing bias:

Staff and participants are not blinded to the treatment allocation, since we consider intravenous placebo treatment to be unethical in this group of children and adolescents. To minimize bias, the evaluation of the primary outcome is blinded.

Diagnostic procedures and procedures during antibiotic treatment:

According to randomization the child will receive 1) oral-only antibiotic therapy or 2) IV antibiotic therapy with shift to oral therapy after clinical and paraclinical improvement. All other aspects of diagnosing and treating the infection will follow current guidelines on paediatric BJI. This includes recommendations for mobilization, physiotherapy, analgesic drugs etc. which are all permitted during the trial. A throat swab for *Kingella kingae* will be added to the routine diagnostic procedures. All children will be evaluated with routine blood samples and clinical examination including grading of symptoms and pain score. See Appendix 1 for collection of extra material. The parents and/or the child will complete a daily registration of temperature and pain score, which will be reported weekly in an electronic questionnaire directly linked to the eCRF (electronic case report form). In these questionnaires, the parents and/or the child will also report adherence (number of missed doses) and drug side effects. The participant timeline is illustrated in figure 1.

Choice of antibiotic treatment and predefined treatment strategies:

The antibiotic treatment is administered as “initial treatment” (IV vs. high dose oral) with a shift to “follow up treatment” (oral) after clinical and paraclinical improvement.

Initial treatment (randomized):

Empiric IV treatment (standard group):

- Ceftriaxon 100 mg/kg/day in 1 dose (max. 4000 mg/day)

Empiric oral treatment (experimental group):

- Age < 5 years:
    - Amoxicillin+Clavulanate 1:8, 100 mg/kg/day in 3 doses (max. 3000 mg amoxicillin/day)
- Age > 5 years:
    - Dicloxacillin 200 mg/kg/day in 4 doses (max. 8000 mg dicloxacillin/day)

Follow up treatment (not randomized):

Empiric oral treatment (both groups):

- Age < 5 years:
    - Amoxicillin+Clavulanate 1:4, 50 mg/kg/day in 3 doses (max. 1500 mg amoxicillin/day)
- Age > 5 years:
    - Dicloxacillin, 100 mg/kg/day in 4 doses (max. 4000 mg dicloxacillin/day)

If infection with *Staphylococcus aureus* is suspected or confirmed, oral rifampicin 20 mg/kg/day in 3 doses (max. 900 mg/day) can be added to the empiric therapy in both groups for optimal penetration and staphylococcal coverage.

According to daily clinical practice, the empiric antibiotic can be adjusted within the same route of administration (oral to oral or IV to IV) due to susceptibility testing, allergic reactions, adverse events, or patient preferences to increase adherence (e.g., taste) in both groups.

Treatment duration:

In both groups, the treatment duration is individualized according to the rate of improvement. The minimum duration of the “initial treatment” is 3 days with a shift to “follow-up treatment” after clinical improvement (pain and mobility) and paraclinical improvement (decreasing C-reactive protein (CRP)). The follow-up treatment is given for four weeks (spondylodiscitis), three weeks (other bone infections), or one

week (joint infection only). The follow-up treatment will only be terminated if the child has no symptoms and a normal clinical exam, otherwise, the antibiotic therapy can be prolonged until these criteria are fulfilled.

Follow up:

All children will receive a clinical follow-up after 6 and 12 months. Any complaints or positive findings during follow-up will be evaluated and treated according to local guidelines. All patients and parents will be instructed to contact the department in the case of any symptoms indicating BJI during follow-up.

Registration of information from patient records:

During treatment and follow-up, the local primary investigator will maintain contact with the clinical team to identify potential outcomes. The primary investigator will register information in the patient's eCRF in a predesigned database (software version: REDCap® 9.1.0). Registered data will include age, sex, medical history, symptoms, clinical findings, blood samples, microbiological findings, imaging, treatment details and absence/presence of predefined outcomes. Missing data will be retrieved by a telephone interview if possible.

Primary outcome:

1. Proportion of children with sequelae 6 months after initiation of treatment defined as abnormal mobility or function of the affected joint/bone. Evaluated by blinded clinical examination by a qualified paediatrician and/or paediatric orthopaedic surgeon [6 months].

Blinding: The assessor (qualified paediatrician or paediatric surgeon) of the primary outcome will be blinded for the intervention as well as any other details on the course of disease. The assessor will be informed about the age of the child as well as the approximate location of the infection and will perform a predefined systematic clinical examination of the relevant area (categories: 1) lower extremities, 2) upper extremities incl. claviculae and scapulae, and 3) columna, costae, and sternum). The exact anatomical location including side (left or right) will not be revealed. The child and parents will be followed by a study

nurse who will secure that the blinding is respected. The primary outcome is met if there are any positive findings related to the previously infected bone or joint.

If indicated, any clinical findings will be further evaluated according to standard clinical practice and if this evaluation fails in confirming the sequelae (e.g., suspicion of clinical scoliosis followed by normal scoliosis imaging), the primary outcome is not met.

Secondary outcomes:

1. Non-acute treatment failure. Proportion of children with change of antibiotic therapy due to non-acute treatment failure [28 days]

   This will be evaluated by two paediatric specialists and is suggested by the following parameters:

   a. Temp. above 38,5 ^{0}C after more than 72 hours of antibiotic therapy

   b. Increasing CRP after more than 96 hours of antibiotic therapy

   c. No improvement in mobility or pain after 120 hours of antibiotic therapy.

2. Recurrent infection. Proportion of children with recurrence of symptoms and signs (same anatomical location) after completion of antibiotic treatment requiring further antibiotic administration [6 months]

Other predefined outcome measures:

Safety outcomes and other predefined outcome measures are listed in table 2.

Discontinuation/withdrawal of participants from study treatment:

If the allocated treatment is no longer compatible with good clinical care, the randomized strategy will be discontinued. The participant will continue follow-up in the trial and will be included in the primary analyses (intention-to-treat) but not in secondary analyses (per-protocol). Routine clinical care consistent with the new information will be recommended. Reasons for discontinuation/withdrawal of the randomized strategy includes:

1. Development of severe disease or complications (safety outcome no. 1).

2. Non-acute treatment failure (secondary outcome no. 1). Non-acute treatment failure will be evaluated by two paediatric specialists, the local paediatrician responsible for the treatment, and one of the chief investigators. The decision to change therapy will be based on a complete evaluation of the clinical condition and the treating paediatrician will make the final decision.
3. Unable to receive oral treatment, e.g., vomiting with no improvement on anti-nausea medications. If the patient is only temporarily unable to receive oral treatment, e.g., intercurrent gastroenteritis or vomiting primarily due to pain or fever, IV treatment for max. 24 hours will be accepted without discontinuation of the allocated oral strategy.
4. Unable to maintain IV access. If the participant is temporarily without IV access, e.g., waiting for anaesthetic assistance, oral treatment for max. 24 hours will be accepted without discontinuation of the allocated IV strategy.
5. No suitable medication exists within the allocated strategy (IV vs. oral) due to susceptibility testing, contraindications, or adverse reactions.
6. Non-adherence to the allocated therapy.
7. Withdrawal of consent from participant/parents.

Statistical methods and analyses:

The plan for statistical analyses is based on the estimand framework [15,16].

Sample size and power calculation:

Outcomes will be compared by a non-inferiority assumption with an inferiority margin of 5% and an expected treatment success of 99% in both groups. With a one-sided significance level (alpha) of 2.5% and accounting for a 10% rate of drop-out, a sample size of 180 children in the principal stratum, 92 children in each group, will provide a power of 90% to detect non-inferiority.

Randomization:

Web-based computer randomization (TrialPartner by DEFACTUM) will be used to allocate patients to the treatment groups at a 1:1 ratio stratified by CRP (<35 vs. ≥35). The randomization will be in randomly permuted blocks with varying block sizes of 4 and 6.

Target population / the principal stratum:

The principal stratum will include all randomized children but exclude children with the intercurrent event of early termination i.e., children with no BJI. All randomized children will be included in the analysis of the three safety outcomes. For the remaining outcomes, including the primary and secondary outcomes, only data from children in the principal stratum will be analysed.

Statistical analyses for the primary outcome:

Based on the principal stratum, the population level summary measure will be the risk difference (RD), calculated as the proportion with sequelae after 6 months in the experimental group (oral only) minus the proportion with sequelae after 6 months in the control group (IV+oral), with one-sided 97.5% confidence limits. If the absolute upper one-sided 97.5% confidence interval is less than 5%, then the criteria of non-inferiority will be met.

Based on intention-to-treat (ITT) principle, the primary analysis of the primary outcome will include all participants in the principal stratum.

A secondary per-protocol analysis (PPP) will also be performed excluding all participants experiencing one or more of the predefined intercurrent events leading to a discontinuation of the allocated treatment strategy.

Missing data: The primary outcome will be evaluated in all participants who attend the follow up after 6 months. We only expect missing data if the participant is lost to follow up or withdraw their consent. Due to the close follow-up at each local department, we expect missing data to be less than 5% and equal in both groups. If the missing data are more than 5%, we will impute data based on available knowledge for the patient and the observations of the other patients in the same randomized group. Sensitivity analyses will include tipping point analyses for the imputation.

Statistical analyses for the secondary outcomes:

Based on the principal stratum, the primary analysis (ITT) described in 6.4.2 will be repeated for the secondary outcomes: “Non-acute treatment failure” and “Recurrent infection”. The secondary analysis (PPP) described above will be repeated for “Recurrent infection” but not for “Non-acute treatment failure” while this outcome is one of the intercurrent events excluding the participant from the secondary analysis (PPP).

Missing data: If a participant experiences one of the secondary outcomes, it will be registered in the medical record. Due to the close follow-up and the national design including complete surveillance of all paediatric departments in Denmark with access to all electronic medical records, only cases where participants withdraw from all follow-up or relocate to another country are at risk for missing data on secondary outcomes. We expect this to be less than 5% and no imputation is planned for the secondary outcomes.

Statistical analyses for the safety outcomes:

For safety outcomes 1 and 2, we will report the total number of participants in each treatment group meeting these outcomes.

For safety outcome 3, the outcome will be the fraction of days the child is affected by one or more of these non-serious adverse events. The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. The population-level summary measure will be the difference between the means of the fractions with two-sided 95% CLs based on the normal approximation for the estimated mean difference. The mean of the individual fractions in each randomized group will also be presented with two-sided 95% CLs based on the normal approximation for the estimated mean.

In addition, we will also for each randomized group present the total number of non-serious adverse events, the number of children who had one or more non-serious adverse events, the number of non-serious adverse events per person-year at risk, and the total number of days with one or more non-serious adverse event.

Risks and safety monitoring:

All antibiotics used in the trial are licensed agents with well described safety profiles approved for treating BJIs in children. The trial is not a clinical trial of an investigational medical product. The following therefore describes our own procedures for safety reporting.

Since our hypothesis is founded on the existing literature [11,12] as well as the general development in antibiotic treatment for children in recent years [1-3] and since we are excluding children with severe disease, we consider the risk of insufficient treatment to be minimal. Due to the close follow-up, we expect to promptly recognize insufficient treatment and evaluate whether a change in treatment is needed. In our recent retrospective study on Danish paediatric BJI infections [10], approximately 5% of children receiving the current standard treatment needed a change in antibiotic therapy due to insufficient effect (data not published). In the current study, we expect a similar need for change in therapy in both groups. The infection and the antibiotic treatment may result in discomfort (pain, fever), side effects (loose stool, abdominal pain, rash), or rarely other complications, but the risk of these events is not increased due to participation in the study. Unexpected adverse effects may occur, but the close follow-up including a 24/7 hotline to the hospital staff, enables us to react promptly to any unexpected incidents. Children and adolescents in the experimental group can avoid the establishment of intravenous access which in most children is a painful procedure. On the other hand, children in the experimental group need to take oral antibiotics for a longer period.

Serious adverse events (SAEs) are not expected in this study due to the exclusion of patients with septic appearance and the fact that paediatric BJI is a condition not associated with mortality or severe morbidity. Only one of 82 children in our recent retrospective study of paediatric BJI developed sepsis or any other SAE [10].

Safety and data monitoring committee:

For monitoring the study, an independent safety and data monitoring committee will be established. The committee will consist of two independent paediatricians and a biostatistician with experience in paediatric

infectious diseases and in the monitoring of RCTs will be consulted if needed. The committee will function independently of all other individuals conducting the study and all potential and serious adverse events (SAEs) will be reported to the committee. The committee will review all safety data by treatment arm every 6-12 months. The committee will be empowered to advise suspending the trial.

Roles, funding, and patient compensation:

The project is initiated by chief investigators Allan Bybeck Nielsen and Ulrikka Nygaard (sponsor). Each site has a primary investigator. The protocol is finalized by the listed authors which includes the chief investigators, main collaborators (Professor Lone Graff Stensballe and Professor Kjeld Schmiegelow) as well as primary investigators from sites with an expected inclusion of more than 10 participants. Funding is received from The Research Foundation of Copenhagen University Hospital, Copenhagen Health Science Partners, and Innovation Fund Denmark. None of the investigators or main collaborators are financially attached to private enterprises, foundations, etc. that have interests in the research project. Neither the patients enrolled in the project, nor their families will receive any kind of payment for participating in the project.

Ethics and dissemination:

The treating paediatrician will obtain informed consent according to the ethical approval, see Information for Parents in Appendix 2. As described in “Risks and safety monitoring”, we consider the risk of harm to the participants to be minimal. The hypothesis has never been tested before and the radical change in treatment cannot be made in a scientific ethical sense without being based on a study at the current level of evidence. The hypothesis has not been tested in adults and it is not possible to perform the study on adults and transmit the data directly to children, as there are large differences in the course of BJIs between children and adults. If the experimental therapy is non-inferior to the standard therapy, the study is expected to lead to a radical change in the treatment of BJI in children and adolescents. The results of the project (whether positive, negative, or inconclusive) will be submitted for publication in scientific peer-reviewed international journals. All investigators and main collaborators will be given the opportunity of authorship of the main publication(s) according to the ICJME criteria.

The study will be performed under the approval of The Ethics Committee of the Capital Region of Denmark (Ref.: H-20009117) and conducted according to the guidelines and recommendations of Good Clinical Practice and the Declaration of Helsinki.

Patient and public involvement

Parents of children in different age groups were involved in designing the participant information. No patient, parent, or the public was involved in designing, writing, or editing the protocol.

Trial registration, trial status and protocol amendments:

The study is registered at www.clinicaltrials.gov (NCT04563325), Trial registration dataset in Appendix 3. Recruitment was started September 15th, 2020. All sites are active, and 148 patients have been recruited in the principal stratum by February 1st, 2023.

In version 1.0 of the protocol and at the initial registration on www.clinicaltrials.gov, all outcomes, except the primary outcome, were categorized as secondary outcomes. After finishing the statistical analysis plan, the categories of the outcomes were changed so that only two secondary outcomes are now registered. The remaining nine are now registered as “Other Outcome Measures” including three safety outcomes corresponding to the current protocol version 2.0. In this revision of the outcome categories after the initiation of the study, four exploratory outcomes were dismissed:

a. Level of CRP. Comment: Will be reported but not considered as an outcome.

b. Disability days. Comment: This registration was missed in the electronic questionnaire and data are not registered.

c. Duration of IV antibiotics. Comment: Will be reported but not considered as an outcome.

d. Adherence (parental report of missed doses). Comment: Will be reported but not considered as an outcome.

DISCUSSION:

With the current protocol, we aim to investigate if oral-only antibiotic treatment is non-inferior to the current standard therapy of initially intravenous antibiotic treatment followed by oral treatment in children and adolescents with BJI.

The strengths of our study are the randomized controlled design with a blinded primary outcome evaluation and the national inclusion of all 18 paediatric departments in Denmark. The trial is fully embedded into daily clinical practice and reflects standard practice in all aspects other than randomization and collection of data. The main limitation is the pragmatic criteria of inclusion without strict diagnostic criteria introducing a potential risk of including children with non-bacterial arthritis or osteomyelitis. We aim to reduce this risk by early termination of children if a non-infectious condition is established during treatment or follow-up. The pragmatic design ensures timely inclusion of patients and reflects daily clinical practice where antibiotic therapy is often initiated before strict diagnostic confirmation of bacterial infection.

The choice of a non-inferiority design was based on the combination of 1) the high treatment success of the current IV treatment and the overall favourable outcomes of these types of infection, 2) the practical aspects of realistic recruitment, and 3) the potential large benefits of the experimental oral treatment. This choice is in accordance with current recommendations on non-inferiority clinical trials [13]. We initially decided to use 10% non-inferiority margin, which was based on consensus among a wide range of infectious disease specialists, paediatric infectious disease specialists and paediatric orthopaedic surgeons balancing the potential risks and benefits of oral treatment. This margin was further supported by published guidelines suggesting similar non-inferiority margins when evaluating treatment of other bacterial infections [14]. After 6-month follow-up of the first 100 children, no sequelae were registered in the trial, equalling a treatment success of 100% in both groups. Due to this very high overall treatment success, we reduced the non-inferiority margin to 5% and adjusted the sample size estimation to 184 (initially 180) with expected treatment success of 99%.

Based on extrapolated Danish data from 2012-2017[10], more than 100 children are diagnosed with BJI in Denmark each year. If the experimental therapy is successful, these children will benefit significantly from

the new treatment in terms of shorter admissions, avoidance of intravenous access, earlier return to everyday activities, and better quality of life during the treatment. The results are expected to influence the treatment strategies of children with BJIs worldwide. Especially in countries with similar resistance spectrum where the results can be directly applied, but also in countries with a more challenging resistance spectrum, where the general demand (often non-evidence based) of IV antibiotics for severe infections will be challenged.

NOTES

Author Contributions

Allan Bybeck Nielsen and Ulrikka Nygaard equally contributed to the conception and design of the protocol. Allan Bybeck Nielsen drafted the first and subsequent versions of the protocol. All other authors commented on and constructively criticized the design of the protocol. All authors read and approved the final manuscript.

Competing interests:

None of the authors are financially attached to private enterprises, foundations, etc. that have interests in the research project.

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Data sharing statement

The study protocol and statistical analysis plan will be provided in this publication. The statistical code and individual participant data will be shared upon reasonable request to facilitate the conduction of systematic reviews with meta-analysis of individual participant data.

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Insurance

All children enrolled in the project are covered by the Danish Patient Insurance Association (Patienterstatningen).

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FIGURE LEGENDS

Figure 1: Participant timeline.

Table 1: Criteria of inclusion and exclusion.

Table 2: Safety outcomes and other predefined outcome measures.

Table 1. Criteria of inclusion and exclusion.

Inclusion criteria: The participant must meet both of the following criteria: 1. Age: Three months to 18 years at study entry. 2. Antibiotic treatment of uncomplicated bone or joint infection.
Exclusion criteria: Any of the following criteria exclude the participant from the study: 1. Severe disease at admission, e.g., septic shock, or any concomitant invasive infection, e.g., necrotizing fasciitis, requiring intravenous antibiotics in the opinion of the treating clinician. 2. Complicated bone or joint infection, e.g., prosthetic material, infection secondary to or complicated by trauma, severe pyomyositis or other substantial soft tissue infections. 3. Expected need of major surgery within the first 24 hours of treatment, e.g., drilling, debridement, fenestration, surgical drainage, synovectomy. Minor surgery as diagnostic surgical bone biopsy or diagnostic joint fluid aspiration including lavage is not a criterion for exclusion. 4. Significant co-morbidities that might influence the choice of treatment or the course of the infection, e.g., immunodeficiency or sickle cell anaemia. 5. Previous bone or joint infection. 6. Antibiotic therapy for more than 24 hours before inclusion. 7. Documented pathogen with limited treatment options that do not permit randomization, e.g., the pathogen is only sensitive to intravenous antibiotics. 8. Prior enrolment in the trial.

Table 2. Safety outcomes and other predefined outcome measures.

No.	Category	Specification	Time frame
1	Safety	Proportion of children with severe complications during antibiotic treatment, e.g. need for intensive care, septic shock, organ failure, pyomyositis, endocarditis, deep venous thrombosis.	28 days
2	Safety	Proportion of children with need for surgical intervention during antibiotic treatment. Diagnostic surgical intervention (diagnostic joint aspiration or diagnostic bone biopsy) excluded	28 days
3	Safety	Proportion of children with treatment-related adverse events e.g. complications of IV access (infection, need for replacement, extravasation) and drug side effects reported by medical staff or by parents (electronic questionnaire)	3 months
4	Exploratory	Time to apyrexia from initiation of antibiotic treatment	28 days
5	Exploratory	Level of mobility and pain assessed by daily grading of symptoms by medical staff and daily standardized pain scores from participants and/or parents. Score systems: Visual Analog Scale (VAS) or Face Legs Activity Cry Consolability (FLACC) scale, both with scores from 0 (no pain) to 10 (worst pain).	14 days
6	Exploratory	Total duration of antibiotic therapy	3 months
7	Exploratory	Proportion of children with sequelae, e.g. abnormal mobility and growth abnormalities, assessed by clinical examination by a qualified paediatrician 12 month after the initiation of treatment, accepted range 11-14 months	14 months
8	Exploratory	Proportion of children with radiological abnormalities assessed by a qualified radiologist 12 months after initiation of treatment, accepted range 11-14 months	14 months
9	Exploratory	Secondary infection with antimicrobial-resistant organisms or *Clostridium difficile*	3 months

Figure 1. Participant timeline.

	STUDY PERIOD									
	Enrollment Allocation		Intervention (high dose IV vs. high dose Oral)				Standard follow-up treatment		Follow-up	
Timepoint:	**D_{-1}**	**D_0**	**D_1**	**D_2**	**D_3**	**…**	**D↑**	**D↑$_{+7/21/28}$**	**M_6**	**M_{12}**
Enrollment:										
Eligibility screen	(x)	x								
Informed consent		x								
Allocation		x								
Intervention:										
High dose IV (standard group)		x	x	x	x	x				
High dose oral (experimental group)		x	x	x	x	x				
Standard dose oral (both groups)							x			
End of therapy (both groups)								x		
Assessments:										
Clinical assessment	(x)	x	(x)	(x)	(x)	(x)	x	x		x
Blood samples / imaging	(x)	x	(x)	(x)	(x)	(x)	x	x	(x)	x
Parental registration (temperature, pain, side effects)		x	x	x	x	x	x	x		
Blinded clinical assessment (primary endpoint)									**X**	
Assessment of secondary endpoints			x	x	x	x	x	x	x	x
24/7 hotline to hospital staff		x	x	x	x	x	x	x	x	x

x = performed

(x) = performed if clinically relevant

D1 = Day 1, D2 = Day 2 etc.

D↑ = Day of clinical/paraclinical improvement

D↑$_{+7/21/28}$ = 7 days (septic arthritis), 21 days (osteomyelitis) or 28 days (spondylodiscitis) after D↑

M6 = Month 6, M12 = Month 12

Appendix 1: Biological specimens

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use:

When routine samples (blood, joint fluid, bone biopsy, throat swabs or any other material) are collected, extra material will be collected to test and improve diagnostic tools in children with infections. Samples will only be obtained in addition to routine samples, i.e. blood will be obtained at the same time as routine blood samples without extra cannulations and joint fluid or bone material will only be obtained if joint puncture or bone biopsy is performed according to the national guideline for pediatric bone and joint infections. The maximum volume of blood taken for analysis is 2 ml/kg/day, the maximum volume of joint fluid is 10 ml (in addition to routine analysis) and the maximum number of bone biopsies is 2 (in addition to routine biopsies). These samples will be stored and analyzed according to the "CHILD" protocol approved by the Danish National Ethics Committee (protocol no. H-18065635). According to the "CHILD" protocol, these samples will be analyzed for pathogen-targeted PCR, host transcriptomics and other -omics, inflammatory parameters (cytokines and their receptors, immunomodulatory agents), and antibiotic concentrations. No analysis on the human genome of the child or adolescent will be performed. The samples will be saved in a research biobank until 31.12.2029. The remaining material will be transferred to a biobank and might be used for future research projects, but only after additional approval from the Ethics Committee and the Danish data protection agency.

APPENDIX 2: Parent information and consent form

Information for parents

Bone and joint infections in children and adolescents - a research project

Original title: Oral antibiotika til børn og unge med led- og knogleinfektioner. Et nationalt, randomiseret, kontrolleret forsøg.

Summary:

- Children and young people with bone and joint infections are treated with intravenous antibiotics for about 3-5 days followed by oral antibiotics for 1-4 weeks.
- We want to investigate whether oral antibiotics from day one is as effective as the current treatment. If this is confirmed, children with bone and joint infections can be treated at home and avoid unnecessary needlesticks.

Dear parents

We hereby ask if you would allow your child to participate in a research project on the treatment of children and adolescents with bone or joint infections. Before you decide, please read this information carefully and we will then talk to you about the project. Participation is voluntary, and you can withdraw your consent at any time and without explanation. We expect 200 children and young people from all over Denmark to participate in the project.

Purpose:
We want to investigate whether oral antibiotics (tablets or oral solutions) from day one (new treatment) are as effective as the current treatment, where antibiotics are given intravenously for the first days followed by oral treatment.

Background:
Today, we treat many infections in children and adolescents with oral antibiotics. However, joint and bone infections are still treated with intravenous antibiotics for the first 3-5 days followed by oral antibiotics for 1-4 weeks. The duration of intravenous antibiotic has been greatly reduced in recent years and some studies have shown that oral antibiotics throughout the full treatment period may be sufficient. However, so far, no studies have compared the two treatments.

Project plan:
Your child will randomly be selected to receive one of two treatments:

1. New treatment: Oral antibiotics from day one. The first dose is taken at the hospital, but then the treatment can take place either at home or in hospital depending on your child's condition.
2. Current treatment: Intravenous antibiotics from day one until there is improvement in the condition (typically 3-5 days). Then switch to oral antibiotics. The intravenous treatment will be performed in the hospital.

All children and adolescents will be followed closely by doctors and nurses for the effect of treatment (development in pain, redness, swelling, temperature). During treatment at home, all families will be

contacted by telephone twice a week by a project nurse as an additional follow-up. In addition, the Children and Adolescents Department can be contacted 24 hours a day throughout the treatment period. The effect of the treatment will be assessed with blood tests, among other things. The total duration of treatment follows common guidelines in both groups (usually 2-4 weeks) depending on the condition of the child.

There will be a follow up appointment after 6 and 12 months, during which time your child will be examined by a doctor, and an X-ray may be taken.

If your child does not participate in the project, he/she will receive the current treatment.

Sampling and storage of samples:
Children involved in the project will have blood tests taken according to the standard practice of treating bone and joint infections. When these standard blood samples are drawn, a small amount of blood will also be drawn for additional analyses. If other samples are taken due to standard practice, such as fluid from a joint, extra material will be stored if possible. In some cases, you will be asked for an additional sample, such as saliva, urine, feces or throat swab. The collected material will be stored in a research biobank until December 31st, 2029. It will be used to measure antibiotic concentrations and to investigate new methods for diagnosing infectious conditions in children and adolescents. The material will be encoded for anonymity and will not be directly traceable back to your child. After 2029, excess material will be transferred to a biobank for future research and will only be applicable after new approval from the Scientific Ethics Committee. You can always have the material from your child destroyed.

Side effects, risks, complications and disadvantages:
We ask you and your child to participate in this project because your child is among the children where we do not know if the best treatment is oral or intravenous antibiotics. There is a small risk that the new treatment is insufficient, which is why we will follow your child closely. If the treatment is insufficient, it will immediately be reassessed and, if necessary, changed. A small number of children are insufficiently treated with the current treatment and need a change of treatment along the way. We expect this to be the case with the new treatment as well.

Antibiotics can cause side effects such as abdominal pain, diarrhea and skin rash. We expect the side effects to be the same in the two groups. Extra blood samples will be taken at the same time as the regular blood samples, and your child will not be subjected to more needlesticks than usual. The total amount of blood taken each time will be a maximum of 1-2% of the child's blood volume and this will have no effect on the health of the child.

There may be risks to the project that we do not yet know, but we do not expect increased side effects or complications either in the short or long term.

Managing personal data:
The research team will obtain relevant health information in the electronic patient record relating to the disease episode, including the condition of the child, blood tests, bacterial examinations and scans. If we need more information, we will contact you after hospitalization with questions about the course of the disease. Before the analysis, the samples collected and data from medical records data will be assigned a

code so that the child's civil registration number (CPR number) does not appear directly. Data will be stored in a database created for the research project. The Danish Data Protection Act and Data Protection Regulation will be respected.

Benefits of the project

The expected benefits of the project include that most children and adolescents with bone or joint infections in the future will be able to receive oral antibiotics from day one. Hereby time at the hospital as well as insertion of intravenous catheters are reduced. This reduces insecurity in the child and increases the quality of life. There is no direct benefit for your child, but children who are randomized to the new treatment will avoid the insertion of an intravenous catheter.

Exclusion from the project

Your child can be excluded from the project if he/she appears seriously ill, if an intravenous catheter cannot be inserted, oral treatment cannot be performed, major surgery is needed, or another diagnosis is made along the way.

Financial support

The project has received funding from the Danish National Hospital's Research Foundation (DKK 3.25 million) and Copenhagen Health Science Partners (DKK 0.5 million) for salaries for researchers, analyses, statisticians and dissemination. None of the associated researchers have economic or commercial interests in the results of the study or its beneficiaries. There are no financially affiliated companies.

The project has been approved by the Scientific Ethics Committee with protocol number (j.nr. H-20009117). On the next page you will find information about your rights as a participant in a research project.

We hope that this information has helped you decide whether your child can take part in the project. You are welcome to contact us if you would like to know more about the project. It is possible to obtain information about the results when these are published on the project's website: childathome.dk.

Sincerely,

National primary investigator:
Allan Bybeck Nielsen, MD
BørneUngeKlinikken
Rigshospitalet
Tlf +45 3545 3545

Local primary investigator:

Participants rights in a health science research project

Information from the Scientific Ethics Committee, translated from "Forsøgspersoners rettigheder I et sundhedsvidenskabeligt forskningsprojekt"

As a parent to a participant in a biomedical research project, please note that:

- Your child's participation in the research project is entirely voluntary and he/she may only participate after you have been informed verbally and in writing about the research project and signed the consent form
- You may withdraw your consent verbally, in writing or by any other clear indication at any time and leave the project. Withdrawing your consent does not affect your right to current or future treatment or any other rights you or your child may have
- You are entitled to bring a family member, friend or acquaintance to the introductory consultation
- You are entitled to take time to think things over before you sign the consent form
- Information about your child's health as well as other personal and confidential information about your child that comes to light in connection with the research project are covered by a duty of confidentiality
- Storage of personal information on your child, including information contained in your child's blood samples and tissue, will be in accordance with regulations in the Danish Data Protecting Act and the Danish Health Act
- In accordance with the Danish Act on Free Access to Public Records, you have legal right of access to experimental protocols. This means that you can both access all documents concerning your child's participation in the study, except for the sections that contain trade secrets or confidential information about other people.
- In accordance with the Danish Act Governing the Right to Complain and to Obtain Compensation in the Danish Healthcare System, you may lodge a complaint and seek compensation. If you are injured during the trial, please contact the Patient Compensation Association; for more information visit www.patienterstatningen.dk.

October 2018

APPENDIX 3: Trial registration data set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ClinicalTrials.gov: NCT04563325
Date of registration in primary registry	18th September 2020
Secondary identifying numbers	H-20009117 (The Ethics Committee of the Capital Region of Denmark)
Source(s) of monetary or material support	Copenhagen University Hospital Rigshospitalet
Primary sponsor	Copenhagen University Hospital Rigshospitalet, Ulrikka Nygaard
Secondary sponsor(s)	N/A
Contact for public queries	Allan Bybeck Nielsen allan.bybeck.nielsen@regionh.dk
Contact for scientific queries	Allan Bybeck Nielsen allan.bybeck.nielsen@regionh.dk
Public title	ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN
Scientific title	ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN - A nationwide randomized open-label non-inferiority trial.
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Antibiotic treatment of bone and joint infections in children and adolescents
Intervention(s)	Standard: IV + oral antibiotic treatment vs. Experimental: Oral only antibiotic treatment.
Key inclusion and exclusion criteria	Inclusion: - Age 3 months to 18 years - Antibiotic therapy for bone or joint infection. Exclusion: - Severe disease at admission - Complicated bone or joint infection - Expected need of major surgery within the first 24 hours of treatment - Significant co-morbidities - Previous bone or joint infection. - Antibiotic therapy for more than 24 hours before inclusion.
Study type	Open label, randomized 1:1, non-inferiority trial. Investigator of the primary endpoint is blinded to treatment allocation.
Date of first enrolment	Sep 2020
Target sample size	180
Recruitment status	Recruiting
Primary outcome	Proportion of children with sequelae 6 months after initiation of treatment defined as abnormal mobility or function of the affected joint/bone. Evaluated by blinded clinical examination by a qualified pediatrician and/or pediatric orthopedic surgeon.
Secondary outcomes	- Non acute treatment failure - Recurrent infection

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	app 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1+13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1+13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3+12
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7+8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5+7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4+7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	app2+3
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	app 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	app 3

BMJ Open

ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN - Study protocol for a nationwide randomized open-label non-inferiority trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-072622.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Apr-2023
Complete List of Authors:	Bybeck Nielsen, Allan; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Borch, Luise; Gødstrup Hospital, Paediatrics and Adolescent Medicine; Gødstrup Hospital, NIDO - Centre for Research and Education Damkjaer, Mads; Lillebaelt Hospital - University Hospital of Southern Denmark, Paediatrics and Adolescent Medicine; University of Southern Denmark, Regional Health Research Glenthøj, Jonathan Peter; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Hartling, Ulla; Odense University Hospital, Paediatrics and Adolescent Medicine Hoffmann, Thomas Ulrik; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Holm, Mette; Aarhus University Hospital, Paediatrics and Adolescent Medicine Helleskov Rasmussen, Annett; Lillebaelt Hospital - University Hospital of Southern Denmark, Paediatrics and Adolescent Medicine Schmidt, Lisbeth ; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Schmiegelow, Kjeld; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Stensballe, Lone Graff; Copenhagen University Hospital, Paediatrics and Adolescent Medicine Nygaard, Ulrikka; Copenhagen University Hospital, Paediatrics and Adolescent Medicine; Copenhagen University Hospital, Department of Paediatrics and Adolescent Medicine
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Infectious diseases
Keywords:	Paediatric infectious disease & immunisation < PAEDIATRICS, Clinical Trial, ORAL MEDICINE, Patient-Centered Care

TITLE PAGE

Title: ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN – Study protocol for a nationwide randomized open-label non-inferiority trial.

Date and Version No: 29-06-2022, version 2.0

Keywords: Bone and joint infection, osteomyelitis, septic arthritis, oral treatment, antibiotics

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Correspondence: Dr. Allan Bybeck Nielsen, allan.bybeck.nielsen@regionh.dk

Conflicts of interests: All authors have no conflicts of interest to declare.

Registrations:

Research Ethics Committee Ref: H-20009117

Trial registration number: NCT04563325 (clinicaltrials.gov)

Word count: Abstract: 192 words. Text: 3993 words. 2 tables. 1 Figure.

ABSTRACT:

Introduction: Children with bone and joint infections are traditionally treated with intravenous antibiotics for three to ten days followed by oral antibiotics. Oral-only treatment has not been tested in randomized trials.

Methods and analysis: Children (three months to 18 years) will be randomized 1:1 with the experimental group receiving high dose oral antibiotics and the control group receiving intravenous antibiotics with a shift in both groups to standard oral antibiotics after clinical and paraclinical improvement. Children in need of acute surgery or systemic features requiring intravenous therapy, including septic shock, are excluded. The primary outcome is defined as a normal blinded standardized clinical assessment 6 months after end of treatment. Secondary outcomes are non-acute treatment failure and recurrent infection. Outcomes will be compared by a non-inferiority assumption with an inferiority margin of 5%.

Ethics and dissemination: The trial has the potential to reduce unnecessary hospitalization and use of IV antibiotics in children with bone or joint infections. Due to the close follow up, exclusion of severely ill children and predefined criteria for discontinuation of the allocated therapy, we expect the risk of treatment failure to be minimal.

Trial registration number: NCT04563325 (clinicaltrials.gov).

ARTICLE SUMMARY:

Strengths and limitations of this study:

- The prospective randomized design with blinded evaluation of the primary outcome will reduce potential bias.
- The primary outcome, sequelae at 6 months, is of clear clinical relevance.
- The pragmatic design with full integration into daily clinical practice ensures a high transferability of the generated data.
- The 12 months follow-up reduces the risk of missing long-term sequelae.
- The pragmatic criteria of inclusion involve a risk of including children with non-bacterial bone or joint disease.

INTRODUCTION

In recent years the necessity of intravenous (IV) antibiotic treatment of children and adults with severe bacterial infections has been questioned as the evidence hereof is lacking[1]. Oral-only treatment has been demonstrated to be safe and non-inferior to IV treatment for children with e.g., severe pneumonia [2] and febrile urinary tract infections [3] including urinary tract infections with bacteraemia [4]. In large prospective randomized trials, early shift from IV to oral antibiotic treatment and even oral-only antibiotic treatment has been demonstrated to be safe and non-inferior to longer courses of IV treatment for adults with infectious diseases such as endocarditis [5,6] and bone and joint infection (BJI) [1,7]. Several oral antibiotics have demonstrated good bone and joint penetration profiles compared to their respective plasma concentrations [8].

Prospective studies on children with BJI have demonstrated that individualized antibiotic therapy with significantly reduced treatment duration is non-inferior to the previous long-term treatment [9-12] and that only 2-4 days of IV therapy followed by 1-3 weeks of oral therapy is sufficient in most cases. The recommendations of individualized and shorter treatment have been adopted in Denmark with good results [13]. These significant changes in treatment strategies raise the question of whether most children with BJI could be treated with oral antibiotics only. One small case series [14] and one retrospective case-control study [15] found oral-only therapy as a valid alternative to the current standard treatment, but the issue has not been investigated in randomized controlled trials.

METHODS AND ANALYSIS:

Study hypothesis and design:

We hypothesize that oral-only antibiotic therapy is non-inferior (non-inferior margin 5%) to initial IV therapy followed by oral therapy in children and adolescents with BJI and test that hypothesis in a nationwide, multicentre, randomized, controlled, open-label, non-inferiority trial.

Included children will be randomized 1:1 with the experimental group receiving high dose oral antibiotic therapy and the control group receiving IV antibiotic therapy with a shift in both groups to standard oral therapy after clinical and paraclinical improvement.

Trial participants:

Children and adolescents are considered for inclusion when they present with suspicion of BJI. Recruitment will be nationwide from all 18 paediatric departments in Denmark. Request a complete list of study sites and primary investigators at allan.bybeck.nielsen@regionh.dk.

Criteria of inclusion is listed in table 1.

Delayed inclusion:

Most patients will be included in the study before the start of treatment. If inclusion is not performed before administration of antibiotic therapy (e.g., the treating physician is not aware of the project), up to 24 hours of antibiotic treatment will be accepted before inclusion in the study to achieve adequate participant enrolment.

Early termination of falsely included patients:

To reflect the daily clinical setting and facilitate timely entry to the study, the patients are eligible for entry based on the available clinical information, often before the final diagnosis is made. In most cases, the clinical suspicion of infection is sustained (e.g., by positive microbiology or imaging), and the study treatment is completed with or without further evidence of infection. If the suspicion of infection is abandoned during the study period, it will lead to early termination from the study according to the following criteria:

1. The suspicion of infection is abandoned, and antibiotic therapy is stopped prematurely.
2. The course of the disease is explained by another diagnosis (not BJI) that is made during treatment or follow up. Examples:
    a. Imaging reveals another diagnosis e.g., bone tumour, Legg-Calve-Perthes disease, or soft tissue infection with no involvement of bone or joint structures.
    b. Recurrent symptoms with no confirmation of infection leads to another final diagnosis, such as juvenile idiopathic arthritis (JIA), chronic recurrent multifocal osteomyelitis (CRMO), or other non-infectious diseases.

c. Lyme arthritis is suspected, and the antibiotic treatment is changed targeting *Borrelia burgdorferi*.

Early terminated patients without BJI, will not continue follow-up in the trial. They will be included in the analysis of the safety outcomes, but not in the analysis of any other outcomes. For transparency, details on all early terminated patients will be reported.

Minimizing bias:

Staff and participants are not blinded to the treatment allocation, since we consider intravenous placebo treatment to be unethical in this group of children and adolescents. To minimize bias, the evaluation of the primary outcome is blinded.

Diagnostic procedures and procedures during antibiotic treatment:

According to randomization the child will receive 1) oral-only antibiotic therapy or 2) IV antibiotic therapy with shift to oral therapy after clinical and paraclinical improvement. All other aspects of diagnosing and treating the infection will follow current guidelines on paediatric BJI. This includes recommendations for mobilization, physiotherapy, analgesic drugs etc. which are all permitted during the trial. A throat swab for *Kingella kingae* will be added to the routine diagnostic procedures. All children will be evaluated with routine blood samples and clinical examination including grading of symptoms and pain score. See Appendix 1 for collection of extra material. The parents and/or the child will complete a daily registration of temperature and pain score, which will be reported weekly in an electronic questionnaire directly linked to the eCRF (electronic case report form). In these questionnaires, the parents and/or the child will also report adherence (number of missed doses) and drug side effects. The participant timeline is illustrated in figure 1.

Choice of antibiotic treatment and predefined treatment strategies:

The antibiotic treatment is administered as “initial treatment” (IV vs. high dose oral) with a shift to “follow up treatment” (oral) after clinical and paraclinical improvement.

Initial treatment (randomized):

Empiric IV treatment (standard group):

- Ceftriaxone 100 mg/kg/day (max. 4000 mg/day)

Empiric oral treatment (experimental group):

- Age < 5 years:
    - Amoxicillin+Clavulanate 1:8, 100 mg/kg/day divided every 8 hours (max. 3000 mg amoxicillin/day)
- Age > 5 years:
    - Dicloxacillin 200 mg/kg/day divided every 6 hours (max. 8000 mg dicloxacillin/day)

Follow up treatment (not randomized):

Empiric oral treatment (both groups):

- Age < 5 years:
    - Amoxicillin+Clavulanate 1:4, 50 mg/kg/day divided every 8 hours (max. 1500 mg amoxicillin/day)
- Age > 5 years:
    - Dicloxacillin, 100 mg/kg/day divided every 6 hours (max. 4000 mg dicloxacillin/day)

If infection with *Staphylococcus aureus* is suspected or confirmed, oral rifampicin 20 mg/kg/day divided every 8 hours (max. 900 mg/day) can be added to the empiric therapy in both groups for optimal penetration and staphylococcal coverage.

According to daily clinical practice, the empiric antibiotic can be adjusted within the same route of administration (oral to oral or IV to IV) due to susceptibility testing, allergic reactions, adverse events, or patient preferences to increase adherence (e.g., taste) in both groups.

Treatment duration:

In both groups, the treatment duration is individualized according to the rate of improvement. The minimum duration of the “initial treatment” is 3 days with a shift to “follow-up treatment” after clinical

improvement (pain and mobility) and paraclinical improvement (decreasing C-reactive protein (CRP)). The follow-up treatment is given for four weeks (spondylodiscitis), three weeks (other bone infections), or one week (joint infection only). The follow-up treatment will only be terminated if the child has no symptoms and a normal clinical exam, otherwise, the antibiotic therapy can be prolonged until these criteria are fulfilled.

Follow up:

All children will receive a clinical follow-up after 6 and 12 months. Any complaints or positive findings during follow-up will be evaluated and treated according to local guidelines. All patients and parents will be instructed to contact the department in the case of any symptoms indicating BJI during follow-up.

Registration of information from patient records:

During treatment and follow-up, the local primary investigator will maintain contact with the clinical team to identify potential outcomes. The primary investigator will register information in the patient's eCRF in a predesigned database (software version: REDCap® 9.1.0). Registered data will include age, sex, medical history, symptoms, clinical findings, blood samples, microbiological findings, imaging, treatment details and absence/presence of predefined outcomes. Missing data will be retrieved by a telephone interview if possible.

Primary outcome:

1. Proportion of children with sequelae 6 months after initiation of treatment defined as abnormal mobility or function of the affected joint/bone. Evaluated by blinded clinical examination by a qualified paediatrician and/or paediatric orthopaedic surgeon [6 months].

Blinding: The assessor (qualified paediatrician or paediatric surgeon) of the primary outcome will be blinded for the intervention as well as any other details on the course of disease. The assessor will be informed about the age of the child as well as the approximate location of the infection and will perform a predefined systematic clinical examination of the relevant area (categories: 1) lower extremities, 2) upper extremities incl. claviculae and scapulae, and 3) columna, costae, and sternum). The exact anatomical

location including side (left or right) will not be revealed. The child and parents will be followed by a study nurse who will secure that the blinding is respected. The primary outcome is met if there are any positive findings related to the previously infected bone or joint.

If indicated, any clinical findings will be further evaluated according to standard clinical practice and if this evaluation fails in confirming the sequelae (e.g., suspicion of clinical scoliosis followed by normal scoliosis imaging), the primary outcome is not met.

Secondary outcomes:

1. Non-acute treatment failure. Proportion of children with change of antibiotic therapy due to non-acute treatment failure [28 days]

   This will be evaluated by two paediatric specialists and is suggested by the following parameters:

   a. Temp. above 38,5 ^{0}C after more than 72 hours of antibiotic therapy

   b. Increasing CRP after more than 96 hours of antibiotic therapy

   c. No improvement in mobility or pain after 120 hours of antibiotic therapy.

2. Recurrent infection. Proportion of children with recurrence of symptoms and signs (same anatomical location) after completion of antibiotic treatment requiring further antibiotic administration [6 months]

Other predefined outcome measures:

Safety outcomes and other predefined outcome measures are listed in table 2.

Discontinuation/withdrawal of participants from study treatment:

If the allocated treatment is no longer compatible with good clinical care, the randomized strategy will be discontinued. The participant will continue follow-up in the trial and will be included in the primary analyses (intention-to-treat) but not in secondary analyses (per-protocol). Routine clinical care consistent with the new information will be recommended. Reasons for discontinuation/withdrawal of the randomized strategy includes:

1. Development of severe disease or complications (safety outcome no. 1).

2. Non-acute treatment failure (secondary outcome no. 1). Non-acute treatment failure will be evaluated by two paediatric specialists, the local paediatrician responsible for the treatment, and one of the chief investigators. The decision to change therapy will be based on a complete evaluation of the clinical condition and the treating paediatrician will make the final decision.
3. Unable to receive oral treatment, e.g., vomiting with no improvement on anti-nausea medications. If the patient is only temporarily unable to receive oral treatment, e.g., intercurrent gastroenteritis or vomiting primarily due to pain or fever, IV treatment for max. 24 hours will be accepted without discontinuation of the allocated oral strategy.
4. Unable to maintain IV access. If the participant is temporarily without IV access, e.g., waiting for anaesthetic assistance, oral treatment for max. 24 hours will be accepted without discontinuation of the allocated IV strategy.
5. No suitable medication exists within the allocated strategy (IV vs. oral) due to susceptibility testing, contraindications, or adverse reactions.
6. Non-adherence to the allocated therapy.
7. Withdrawal of consent from participant/parents.

Statistical methods and analyses:

The plan for statistical analyses is based on the estimand framework [16,17].

Sample size and power calculation:

Outcomes will be compared by a non-inferiority assumption with an inferiority margin of 5% and an expected treatment success of 99% in both groups. With a one-sided significance level (alpha) of 2.5% and accounting for a 10% rate of drop-out, a sample size of 180 children in the principal stratum, 92 children in each group, will provide a power of 90% to detect non-inferiority.

Randomization:

Web-based computer randomization (TrialPartner by DEFACTUM) will be used to allocate patients to the treatment groups at a 1:1 ratio stratified by CRP (<35 vs. ≥35). The randomization will be in randomly permuted blocks with varying block sizes of 4 and 6.

Target population / the principal stratum:

The principal stratum will include all randomized children but exclude children with the intercurrent event of early termination i.e., children with no BJI. All randomized children will be included in the analysis of the three safety outcomes. For the remaining outcomes, including the primary and secondary outcomes, only data from children in the principal stratum will be analysed.

Statistical analyses for the primary outcome:

Based on the principal stratum, the population level summary measure will be the risk difference (RD), calculated as the proportion with sequelae after 6 months in the experimental group (oral only) minus the proportion with sequelae after 6 months in the control group (IV+oral), with one-sided 97.5% confidence limits. If the absolute upper one-sided 97.5% confidence interval is less than 5%, then the criteria of non-inferiority will be met.

Based on intention-to-treat (ITT) principle, the primary analysis of the primary outcome will include all participants in the principal stratum.

A secondary per-protocol analysis (PPP) will also be performed excluding all participants experiencing one or more of the predefined intercurrent events leading to a discontinuation of the allocated treatment strategy.

Missing data: The primary outcome will be evaluated in all participants who attend the follow up after 6 months. We only expect missing data if the participant is lost to follow up or withdraw their consent. Due to the close follow-up at each local department, we expect missing data to be less than 5% and equal in both groups. If the missing data are more than 5%, we will impute data based on available knowledge for the patient and the observations of the other patients in the same randomized group. Sensitivity analyses will include tipping point analyses for the imputation.

Statistical analyses for the secondary outcomes:

Based on the principal stratum, the primary analysis (ITT) described in 6.4.2 will be repeated for the secondary outcomes: “Non-acute treatment failure” and “Recurrent infection”. The secondary analysis (PPP) described above will be repeated for “Recurrent infection” but not for “Non-acute treatment failure” while this outcome is one of the intercurrent events excluding the participant from the secondary analysis (PPP).

Missing data: If a participant experiences one of the secondary outcomes, it will be registered in the medical record. Due to the close follow-up and the national design including complete surveillance of all paediatric departments in Denmark with access to all electronic medical records, only cases where participants withdraw from all follow-up or relocate to another country are at risk for missing data on secondary outcomes. We expect this to be less than 5% and no imputation is planned for the secondary outcomes.

Statistical analyses for the safety outcomes:

For safety outcomes 1 and 2, we will report the total number of participants in each treatment group meeting these outcomes.

For safety outcome 3, the outcome will be the fraction of days the child is affected by one or more of these non-serious adverse events. The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. The population-level summary measure will be the difference between the means of the fractions with two-sided 95% CLs based on the normal approximation for the estimated mean difference. The mean of the individual fractions in each randomized group will also be presented with two-sided 95% CLs based on the normal approximation for the estimated mean.

In addition, we will also for each randomized group present the total number of non-serious adverse events, the number of children who had one or more non-serious adverse events, the number of non-serious adverse events per person-year at risk, and the total number of days with one or more non-serious adverse event.

Risks and safety monitoring:

All antibiotics used in the trial are licensed agents with well described safety profiles approved for treating BJIs in children. The trial is not a clinical trial of an investigational medical product. The following therefore describes our own procedures for safety reporting.

Since our hypothesis is founded on the existing literature [14,15] as well as the general development in antibiotic treatment for children in recent years [2-4] and since we are excluding children with severe disease, we consider the risk of insufficient treatment to be minimal. Due to the close follow-up, we expect to promptly recognize insufficient treatment and evaluate whether a change in treatment is needed. In our recent retrospective study on Danish paediatric BJI infections [13], approximately 5% of children receiving the current standard treatment needed a change in antibiotic therapy due to insufficient effect (data not published). In the current study, we expect a similar need for change in therapy in both groups. The infection and the antibiotic treatment may result in discomfort (pain, fever), side effects (loose stool, abdominal pain, rash), or rarely other complications, but the risk of these events is not increased due to participation in the study. Unexpected adverse effects may occur, but the close follow-up including a 24/7 hotline to the hospital staff, enables us to react promptly to any unexpected incidents. Children and adolescents in the experimental group can avoid the establishment of intravenous access which in most children is a painful procedure. On the other hand, children in the experimental group need to take oral antibiotics for a longer period.

Serious adverse events (SAEs) are not expected in this study due to the exclusion of patients with septic appearance and the fact that paediatric BJI is a condition not associated with mortality or severe morbidity. Only one of 82 children in our recent retrospective study of paediatric BJI developed sepsis or any other SAE [13].

Safety and data monitoring committee:

For monitoring the study, an independent safety and data monitoring committee will be established. The committee will consist of two independent paediatricians and a biostatistician with experience in paediatric

infectious diseases and in the monitoring of RCTs will be consulted if needed. The committee will function independently of all other individuals conducting the study and all potential and serious adverse events (SAEs) will be reported to the committee. The committee will review all safety data by treatment arm every 6-12 months. The committee will be empowered to advise suspending the trial.

Roles, funding, and patient compensation:

The project is initiated by chief investigators Allan Bybeck Nielsen and Ulrikka Nygaard (sponsor). Each site has a primary investigator. The protocol is finalized by the listed authors which includes the chief investigators, main collaborators (Professor Lone Graff Stensballe and Professor Kjeld Schmiegelow) as well as primary investigators from sites with an expected inclusion of more than 10 participants. Funding is received from The Research Foundation of Copenhagen University Hospital, Copenhagen Health Science Partners, and Innovation Fund Denmark. None of the investigators or main collaborators are financially attached to private enterprises, foundations, etc. that have interests in the research project. Neither the patients enrolled in the project, nor their families will receive any kind of payment for participating in the project.

Ethics and dissemination:

The treating paediatrician will obtain informed consent according to the ethical approval, see Information for Parents in Appendix 2. As described in “Risks and safety monitoring”, we consider the risk of harm to the participants to be minimal. The hypothesis has never been tested before and the radical change in treatment cannot be made in a scientific ethical sense without being based on a study at the current level of evidence. The hypothesis has not been tested in adults and it is not possible to perform the study on adults and transmit the data directly to children, as there are large differences in the course of BJIs between children and adults. If the experimental therapy is non-inferior to the standard therapy, the study is expected to lead to a radical change in the treatment of BJI in children and adolescents. The results of the project (whether positive, negative, or inconclusive) will be submitted for publication in scientific peer-reviewed international journals. All investigators and main collaborators will be given the opportunity of authorship of the main publication(s) according to the ICJME criteria.

The study will be performed under the approval of The Ethics Committee of the Capital Region of Denmark (Ref.: H-20009117) and conducted according to the guidelines and recommendations of Good Clinical Practice and the Declaration of Helsinki.

Patient and public involvement

Parents of children in different age groups were involved in designing the participant information. No patient, parent, or the public was involved in designing, writing, or editing the protocol.

Trial registration, trial status and protocol amendments:

The study is registered at www.clinicaltrials.gov (NCT04563325), Trial registration dataset in Appendix 3. Recruitment was started September 15th, 2020. All sites are active, and 148 patients have been recruited in the principal stratum by February 1st, 2023.

In version 1.0 of the protocol and at the initial registration on www.clinicaltrials.gov, all outcomes, except the primary outcome, were categorized as secondary outcomes. After finishing the statistical analysis plan, the categories of the outcomes were changed so that only two secondary outcomes are now registered. The remaining nine are now registered as “Other Outcome Measures” including three safety outcomes corresponding to the current protocol version 2.0. In this revision of the outcome categories after the initiation of the study, four exploratory outcomes were dismissed:

a. Level of CRP. Comment: Will be reported but not considered as an outcome.

b. Disability days. Comment: This registration was missed in the electronic questionnaire and data are not registered.

c. Duration of IV antibiotics. Comment: Will be reported but not considered as an outcome.

d. Adherence (parental report of missed doses). Comment: Will be reported but not considered as an outcome.

DISCUSSION:

With the current protocol, we aim to investigate if oral-only antibiotic treatment is non-inferior to the current standard therapy of initially intravenous antibiotic treatment followed by oral treatment in children and adolescents with BJI.

The strengths of our study are the randomized controlled design with a blinded primary outcome evaluation and the national inclusion of all 18 paediatric departments in Denmark. The trial is fully embedded into daily clinical practice and reflects standard practice in all aspects other than randomization and collection of data. The main limitation is the pragmatic criteria of inclusion without strict diagnostic criteria introducing a potential risk of including children with non-bacterial arthritis or osteomyelitis. We aim to reduce this risk by early termination of children if a non-infectious condition is established during treatment or follow-up. The pragmatic design ensures timely inclusion of patients and reflects daily clinical practice where antibiotic therapy is often initiated before strict diagnostic confirmation of bacterial infection.

The choice of a non-inferiority design was based on the combination of 1) the high treatment success of the current IV treatment and the overall favourable outcomes of these types of infection, 2) the practical aspects of realistic recruitment, and 3) the potential large benefits of the experimental oral treatment. This choice is in accordance with current recommendations on non-inferiority clinical trials [18]. We initially decided to use 10% non-inferiority margin, which was based on consensus among a wide range of infectious disease specialists, paediatric infectious disease specialists and paediatric orthopaedic surgeons balancing the potential risks and benefits of oral treatment. This margin was further supported by published guidelines suggesting similar non-inferiority margins when evaluating treatment of other bacterial infections [19]. After 6-month follow-up of the first 100 children, no sequelae were registered in the trial, equalling a treatment success of 100% in both groups. Due to this very high overall treatment success, we reduced the non-inferiority margin to 5% and adjusted the sample size estimation to 184 (initially 180) with expected treatment success of 99%.

Based on extrapolated Danish data from 2012-2017[13], more than 100 children are diagnosed with BJI in Denmark each year. If the experimental therapy is successful, these children will benefit significantly from

the new treatment in terms of shorter admissions, avoidance of intravenous access, earlier return to everyday activities, and better quality of life during the treatment. The results are expected to influence the treatment strategies of children with BJIs worldwide. Especially in countries with similar resistance spectrum where the results can be directly applied, but also in countries with a more challenging resistance spectrum, where the general demand (often non-evidence based) of IV antibiotics for severe infections will be challenged.

NOTES

Author Contributions

Allan Bybeck Nielsen and Ulrikka Nygaard initiated and planned the study, and they contributed equally to the initial conception and design of the study protocol. Allan Bybeck Nielsen drafted the first and subsequent versions of the study protocol. Luise Borch, Mads Damkjær, Jonathan Peter Glenthøj, Ulla Hartling, Thomas Ulrik Hoffmann, Mette Holm, Annett Helleskov Rasmussen, Lisbeth Samsø Schmidt, Kjeld Schmiegelow and Lone Graff Stensballe made substantial contributions to the design of the study, and they critically revised the study protocol. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Competing interests:

None of the authors are financially attached to private enterprises, foundations, etc. that have interests in the research project.

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Data sharing statement

The study protocol and statistical analysis plan will be provided in this publication. The statistical code and individual participant data will be shared upon reasonable request to facilitate the conduction of systematic reviews with meta-analysis of individual participant data.

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Insurance

All children enrolled in the project are covered by the Danish Patient Insurance Association (Patienterstatningen).

STUDY SITES

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FIGURE LEGENDS

Figure 1: Participant timeline.

Table 1: Criteria of inclusion and exclusion.

Table 2: Safety outcomes and other predefined outcome measures.

Table 1. Criteria of inclusion and exclusion.

Inclusion criteria: The participant must meet both of the following criteria: 1. Age: Three months to 18 years at study entry. 2. Antibiotic treatment of uncomplicated bone or joint infection.
Exclusion criteria: Any of the following criteria exclude the participant from the study: 1. Severe disease at admission, e.g., septic shock, or any concomitant invasive infection, e.g., necrotizing fasciitis, requiring intravenous antibiotics in the opinion of the treating clinician. 2. Complicated bone or joint infection, e.g., prosthetic material, infection secondary to or complicated by trauma, severe pyomyositis or other substantial soft tissue infections. 3. Expected need of major surgery within the first 24 hours of treatment, e.g., drilling, debridement, fenestration, surgical drainage, synovectomy. Minor surgery as diagnostic surgical bone biopsy or diagnostic joint fluid aspiration including lavage is not a criterion for exclusion. 4. Significant co-morbidities that might influence the choice of treatment or the course of the infection, e.g., immunodeficiency or sickle cell anaemia. 5. Previous bone or joint infection. 6. Antibiotic therapy for more than 24 hours before inclusion. 7. Documented pathogen with limited treatment options that do not permit randomization, e.g., the pathogen is only sensitive to intravenous antibiotics. 8. Prior enrolment in the trial.

Table 2. Safety outcomes and other predefined outcome measures.

No.	Category	Specification	Time frame
1	Safety	Proportion of children with severe complications during antibiotic treatment, e.g. need for intensive care, septic shock, organ failure, pyomyositis, endocarditis, deep venous thrombosis.	28 days
2	Safety	Proportion of children with need for surgical intervention during antibiotic treatment. Diagnostic surgical intervention (diagnostic joint aspiration or diagnostic bone biopsy) excluded	28 days
3	Safety	Proportion of children with treatment-related adverse events e.g. complications of IV access (infection, need for replacement, extravasation) and drug side effects reported by medical staff or by parents (electronic questionnaire)	3 months
4	Exploratory	Time to apyrexia from initiation of antibiotic treatment	28 days
5	Exploratory	Level of mobility and pain assessed by daily grading of symptoms by medical staff and daily standardized pain scores from participants and/or parents. Score systems: Visual Analog Scale (VAS) or Face Legs Activity Cry Consolability (FLACC) scale, both with scores from 0 (no pain) to 10 (worst pain).	14 days
6	Exploratory	Total duration of antibiotic therapy	3 months
7	Exploratory	Proportion of children with sequelae, e.g. abnormal mobility and growth abnormalities, assessed by clinical examination by a qualified paediatrician 12 month after the initiation of treatment, accepted range 11-14 months	14 months
8	Exploratory	Proportion of children with radiological abnormalities assessed by a qualified radiologist 12 months after initiation of treatment, accepted range 11-14 months	14 months
9	Exploratory	Secondary infection with antimicrobial-resistant organisms or *Clostridioides difficile*	3 months

Figure 1. Participant timeline.

	STUDY PERIOD									
	Enrollment Allocation		Intervention (high dose IV vs. high dose Oral)				Standard follow-up treatment		Follow-up	
Timepoint:	**D_{-1}**	**D_0**	**D_1**	**D_2**	**D_3**	**…**	**D↑**	**D↑$_{+7/21/28}$**	**M_6**	**M_{12}**
Enrollment:										
Eligibility screen	(x)	x								
Informed consent		x								
Allocation		x								
Intervention:										
High dose IV (standard group)		x	x	x	x	x				
High dose oral (experimental group)		x	x	x	x	x				
Standard dose oral (both groups)							x			
End of therapy (both groups)								x		
Assessments:										
Clinical assessment	(x)	x	(x)	(x)	(x)	(x)	x	x		x
Blood samples / imaging	(x)	x	(x)	(x)	(x)	(x)	x	x	(x)	x
Parental registration (temperature, pain, side effects)		x	x	x	x	x	x	x		
Blinded clinical assessment (primary endpoint)									**X**	
Assessment of secondary endpoints			x	x	x	x	x	x	x	x
24/7 hotline to hospital staff		x	x	x	x	x	x	x	x	x

x = performed

(x) = performed if clinically relevant

D1 = Day 1, D2 = Day 2 etc.

D↑ = Day of clinical/paraclinical improvement

D↑$_{+7/21/28}$ = 7 days (septic arthritis), 21 days (osteomyelitis) or 28 days (spondylodiscitis) after D↑

M6 = Month 6, M12 = Month 12

Appendix 1: Biological specimens

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use:

When routine samples (blood, joint fluid, bone biopsy, throat swabs or any other material) are collected, extra material will be collected to test and improve diagnostic tools in children with infections. Samples will only be obtained in addition to routine samples, i.e. blood will be obtained at the same time as routine blood samples without extra cannulations and joint fluid or bone material will only be obtained if joint puncture or bone biopsy is performed according to the national guideline for pediatric bone and joint infections. The maximum volume of blood taken for analysis is 2 ml/kg/day, the maximum volume of joint fluid is 10 ml (in addition to routine analysis) and the maximum number of bone biopsies is 2 (in addition to routine biopsies). These samples will be stored and analyzed according to the "CHILD" protocol approved by the Danish National Ethics Committee (protocol no. H-18065635). According to the "CHILD" protocol, these samples will be analyzed for pathogen-targeted PCR, host transcriptomics and other -omics, inflammatory parameters (cytokines and their receptors, immunomodulatory agents), and antibiotic concentrations. No analysis on the human genome of the child or adolescent will be performed. The samples will be saved in a research biobank until 31.12.2029. The remaining material will be transferred to a biobank and might be used for future research projects, but only after additional approval from the Ethics Committee and the Danish data protection agency.

APPENDIX 2: Parent information and consent form

Information for parents

Bone and joint infections in children and adolescents - a research project

Original title: Oral antibiotika til børn og unge med led- og knogleinfektioner. Et nationalt, randomiseret, kontrolleret forsøg.

Summary:

- Children and young people with bone and joint infections are treated with intravenous antibiotics for about 3-5 days followed by oral antibiotics for 1-4 weeks.
- We want to investigate whether oral antibiotics from day one is as effective as the current treatment. If this is confirmed, children with bone and joint infections can be treated at home and avoid unnecessary needlesticks.

Dear parents

We hereby ask if you would allow your child to participate in a research project on the treatment of children and adolescents with bone or joint infections. Before you decide, please read this information carefully and we will then talk to you about the project. Participation is voluntary, and you can withdraw your consent at any time and without explanation. We expect 200 children and young people from all over Denmark to participate in the project.

Purpose:
We want to investigate whether oral antibiotics (tablets or oral solutions) from day one (new treatment) are as effective as the current treatment, where antibiotics are given intravenously for the first days followed by oral treatment.

Background:
Today, we treat many infections in children and adolescents with oral antibiotics. However, joint and bone infections are still treated with intravenous antibiotics for the first 3-5 days followed by oral antibiotics for 1-4 weeks. The duration of intravenous antibiotic has been greatly reduced in recent years and some studies have shown that oral antibiotics throughout the full treatment period may be sufficient. However, so far, no studies have compared the two treatments.

Project plan:
Your child will randomly be selected to receive one of two treatments:

1. New treatment: Oral antibiotics from day one. The first dose is taken at the hospital, but then the treatment can take place either at home or in hospital depending on your child's condition.
2. Current treatment: Intravenous antibiotics from day one until there is improvement in the condition (typically 3-5 days). Then switch to oral antibiotics. The intravenous treatment will be performed in the hospital.

All children and adolescents will be followed closely by doctors and nurses for the effect of treatment (development in pain, redness, swelling, temperature). During treatment at home, all families will be

contacted by telephone twice a week by a project nurse as an additional follow-up. In addition, the Children and Adolescents Department can be contacted 24 hours a day throughout the treatment period. The effect of the treatment will be assessed with blood tests, among other things. The total duration of treatment follows common guidelines in both groups (usually 2-4 weeks) depending on the condition of the child.

There will be a follow up appointment after 6 and 12 months, during which time your child will be examined by a doctor, and an X-ray may be taken.

If your child does not participate in the project, he/she will receive the current treatment.

Sampling and storage of samples:
Children involved in the project will have blood tests taken according to the standard practice of treating bone and joint infections. When these standard blood samples are drawn, a small amount of blood will also be drawn for additional analyses. If other samples are taken due to standard practice, such as fluid from a joint, extra material will be stored if possible. In some cases, you will be asked for an additional sample, such as saliva, urine, feces or throat swab. The collected material will be stored in a research biobank until December 31st, 2029. It will be used to measure antibiotic concentrations and to investigate new methods for diagnosing infectious conditions in children and adolescents. The material will be encoded for anonymity and will not be directly traceable back to your child. After 2029, excess material will be transferred to a biobank for future research and will only be applicable after new approval from the Scientific Ethics Committee. You can always have the material from your child destroyed.

Side effects, risks, complications and disadvantages:
We ask you and your child to participate in this project because your child is among the children where we do not know if the best treatment is oral or intravenous antibiotics. There is a small risk that the new treatment is insufficient, which is why we will follow your child closely. If the treatment is insufficient, it will immediately be reassessed and, if necessary, changed. A small number of children are insufficiently treated with the current treatment and need a change of treatment along the way. We expect this to be the case with the new treatment as well.

Antibiotics can cause side effects such as abdominal pain, diarrhea and skin rash. We expect the side effects to be the same in the two groups. Extra blood samples will be taken at the same time as the regular blood samples, and your child will not be subjected to more needlesticks than usual. The total amount of blood taken each time will be a maximum of 1-2% of the child's blood volume and this will have no effect on the health of the child.

There may be risks to the project that we do not yet know, but we do not expect increased side effects or complications either in the short or long term.

Managing personal data:
The research team will obtain relevant health information in the electronic patient record relating to the disease episode, including the condition of the child, blood tests, bacterial examinations and scans. If we need more information, we will contact you after hospitalization with questions about the course of the disease. Before the analysis, the samples collected and data from medical records data will be assigned a

code so that the child's civil registration number (CPR number) does not appear directly. Data will be stored in a database created for the research project. The Danish Data Protection Act and Data Protection Regulation will be respected.

Benefits of the project

The expected benefits of the project include that most children and adolescents with bone or joint infections in the future will be able to receive oral antibiotics from day one. Hereby time at the hospital as well as insertion of intravenous catheters are reduced. This reduces insecurity in the child and increases the quality of life. There is no direct benefit for your child, but children who are randomized to the new treatment will avoid the insertion of an intravenous catheter.

Exclusion from the project

Your child can be excluded from the project if he/she appears seriously ill, if an intravenous catheter cannot be inserted, oral treatment cannot be performed, major surgery is needed, or another diagnosis is made along the way.

Financial support

The project has received funding from the Danish National Hospital's Research Foundation (DKK 3.25 million) and Copenhagen Health Science Partners (DKK 0.5 million) for salaries for researchers, analyses, statisticians and dissemination. None of the associated researchers have economic or commercial interests in the results of the study or its beneficiaries. There are no financially affiliated companies.

The project has been approved by the Scientific Ethics Committee with protocol number (j.nr. H-20009117). On the next page you will find information about your rights as a participant in a research project.

We hope that this information has helped you decide whether your child can take part in the project. You are welcome to contact us if you would like to know more about the project. It is possible to obtain information about the results when these are published on the project's website: childathome.dk.

Sincerely,

National primary investigator:
Allan Bybeck Nielsen, MD
BørneUngeKlinikken
Rigshospitalet
Tlf +45 3545 3545

Local primary investigator:

Participants rights in a health science research project

Information from the Scientific Ethics Committee, translated from "Forsøgspersoners rettigheder I et sundhedsvidenskabeligt forskningsprojekt"

As a parent to a participant in a biomedical research project, please note that:

- Your child's participation in the research project is entirely voluntary and he/she may only participate after you have been informed verbally and in writing about the research project and signed the consent form
- You may withdraw your consent verbally, in writing or by any other clear indication at any time and leave the project. Withdrawing your consent does not affect your right to current or future treatment or any other rights you or your child may have
- You are entitled to bring a family member, friend or acquaintance to the introductory consultation
- You are entitled to take time to think things over before you sign the consent form
- Information about your child's health as well as other personal and confidential information about your child that comes to light in connection with the research project are covered by a duty of confidentiality
- Storage of personal information on your child, including information contained in your child's blood samples and tissue, will be in accordance with regulations in the Danish Data Protecting Act and the Danish Health Act
- In accordance with the Danish Act on Free Access to Public Records, you have legal right of access to experimental protocols. This means that you can both access all documents concerning your child's participation in the study, except for the sections that contain trade secrets or confidential information about other people.
- In accordance with the Danish Act Governing the Right to Complain and to Obtain Compensation in the Danish Healthcare System, you may lodge a complaint and seek compensation. If you are injured during the trial, please contact the Patient Compensation Association; for more information visit www.patienterstatningen.dk.

October 2018

APPENDIX 3: Trial registration data set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ClinicalTrials.gov: NCT04563325
Date of registration in primary registry	18th September 2020
Secondary identifying numbers	H-20009117 (The Ethics Committee of the Capital Region of Denmark)
Source(s) of monetary or material support	Copenhagen University Hospital Rigshospitalet
Primary sponsor	Copenhagen University Hospital Rigshospitalet, Ulrikka Nygaard
Secondary sponsor(s)	N/A
Contact for public queries	Allan Bybeck Nielsen allan.bybeck.nielsen@regionh.dk
Contact for scientific queries	Allan Bybeck Nielsen allan.bybeck.nielsen@regionh.dk
Public title	ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN
Scientific title	ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN - A nationwide randomized open-label non-inferiority trial.
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Antibiotic treatment of bone and joint infections in children and adolescents
Intervention(s)	Standard: IV + oral antibiotic treatment vs. Experimental: Oral only antibiotic treatment.
Key inclusion and exclusion criteria	Inclusion: - Age 3 months to 18 years - Antibiotic therapy for bone or joint infection. Exclusion: - Severe disease at admission - Complicated bone or joint infection - Expected need of major surgery within the first 24 hours of treatment - Significant co-morbidities - Previous bone or joint infection. - Antibiotic therapy for more than 24 hours before inclusion.
Study type	Open label, randomized 1:1, non-inferiority trial. Investigator of the primary endpoint is blinded to treatment allocation.
Date of first enrolment	Sep 2020
Target sample size	180
Recruitment status	Recruiting
Primary outcome	Proportion of children with sequelae 6 months after initiation of treatment defined as abnormal mobility or function of the affected joint/bone. Evaluated by blinded clinical examination by a qualified pediatrician and/or pediatric orthopedic surgeon.
Secondary outcomes	- Non acute treatment failure - Recurrent infection

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	app 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1+13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1+13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3+12
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7+8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5+7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4+7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	app2+3
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	app 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	app 3