PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ORAL-ONLY ANTIBIOTICS FOR BONE AND JOINT INFECTIONS IN CHILDREN - Study protocol for a nationwide randomized open-label non-inferiority trial.
AUTHORS	Bybeck Nielsen, Allan; Borch, Luise; Damkjaer, Mads; Glenthøj, Jonathan Peter; Hartling, Ulla; Hoffmann, Thomas Ulrik; Holm, Mette; Helleskov Rasmussen, Annett; Schmidt, Lisbeth; Schmiegelow, Kjeld; Stensballe, Lone Graff; Nygaard, Ulrikka

VERSION 1 – REVIEW

REVIEWER	Brad Spellberg Los Angeles County + University of Southern California
REVIEW RETURNED	04-Mar-2023

GENERAL COMMENTS	This is a protocol for a promising, welcomed study comparing oral only antibiotic therapy to IV therapy for osteomyelitis in children. 1) As a non pediatrician, I wonder about the age of inclusion. Do 15-18 year olds develop osteo the same as younger children (presumably growth plates closed for the former?), and are the challenges of administering the oral regimen the same (the latter can take pills daily, the former presumably need liquid medication administered by parents to a screaming baby?). Should the focus be on younger kids? Or would it be helpful to stratify randomization to at least ensure a balance of the younger vs. older kids in both arms, enabling secondary analyses to rule out differences based on age? 2) It would be helpful if in the Introduction the authors provided citations around the correct first statement, that new papers have been published challenging the traditional requirement for IV only therapy for osteomyelitis. Would at a minimum cite the recent WikiGuidelines published on osteomyelitis in JAMA Network Open that formally recommended oral therapy based on a review of data (PMID 35536578). Others to consider citing include PMID 34715060 and 36694838. 3) The citations in line 18 are wrong. You have cited the protocol for POET as reference #4 and the publication of the POET study as reference #5. You should delete reference 4, and use the current reference #5 for the citation of a large randomized controlled trial of oral therapy for endocarditis. As far as randomized controlled trial of oral therapy for osteomyelitis in adults, you should cite the above mentioned meta-analysis of 8 such trials (including OVIVA), PMID 34715060, and you should cite WikiGuidelines because it discusses a 9th such trial, PMID 35536578. Of note, the same meta-analyis also meta-analyzes 3 RCTs of oral therapy for endocarditis, and so should accompany the POET reference for the oral therapy for

	endocarditis. 4) Of note, you should also consider mentioning that one of the endocarditis RCTs in adults randomized patients to oral therapy up front, with no IV lead in, just as you propose to do for osteomyelitis. POET did not do that. However, in PMID 8686718, they did do this, and found oral as effective as IV, but safer. 5) I understand the complexity of giving a blinded placebo to young kids. However, I wonder how it can be unethical to do so when you are already giving IV as standard of care for the first few days. Seems like giving IV saline for a few days would not be unethical. So I don't find this argument compelling. I wonder instead if the argument could be that giving the IV placebo would require stay in the hospital, whereas not giving it allows the patients to never be hospitalized, and as such, giving the placebo has the potential to mask some of the real benefit of an oral only approach? 6) The antibiotic options are limited, i suspect due to the specific antibiograms of participating hospitals in Denmark. However, the authors should keep in mind this could limit generalizability to other settings where resistance rates are higher, and empiric regimens may need to cover additional pathogens pending identification of the etiologic bacteria. 7) Consider parent and (for older kids) child surveys of satisfaction. OVIVA found much higher satisfaction scores (depression, mobility, anxiety, etc) among adults given oral therapy. One would think this would be even more dramatic for parents of kids who could keep those kids out of the hospital and without an IV in them.

REVIEWER	Abrar Thabit King Abdulaziz University, Pharmacy Practice Department, Faculty of Pharmacy
REVIEW RETURNED	13-Mar-2023

GENERAL COMMENTS	This is an excellent protocol for a randomized open-label non-inferiority trial of oral-only vs. IV to PO treatment of bone and joint infections in pediatrics. A few comments need to be addressed. 1. Introduction: It might be worth mentioning that several oral antibiotics have demonstrated good bone and joint penetration profiles compared to their respective concentrations in the plasma to further justify the objective of this study (https://pubmed.ncbi.nlm.nih.gov/30772469/). 2. With regards to the inclusion and exclusion criteria, did the investigators also consider the gastrointestinal status of their patients to ensure that those recruited, particularly those who would be randomized to the oral-only group, do not have intestinal absorption issues (e.g., ileus, malabsorption, ...) or have conditions that may trigger nausea/vomiting (i.e., unable to tolerate oral medications)? It is mentioned under "Discontinuation/withdrawal of participants from study treatment" in point #3 that such patients will be allowed a max of 24h IV therapy. So, does that mean that if some patients presented with such conditions at baseline will be excluded from participation? If so, this should have been one of the exclusion criteria. 3. Also, what about patients with known/documented severe (IgE-mediated) allergies to B-lactam antibiotics? Were they excluded, too, since both IV and PO regimens consist of B-lactams only?

	4. Under "Choice of antibiotic treatment", change "ceftriaxon" to "ceftriaxone" 5. Under "Choice of antibiotic treatment", it is better to report the frequency of dosing as "divided every 8 hours" or "divided every 6 hours" instead of "in 3 doses" and "in 4 doses", respectively. 6. Under "Risks and safety monitoring", what about potential allergic reactions if those children have never been exposed to a B-lactam antibiotic and this is their first exposure? Also, aren't severe IgE-mediated reactions (i.e., anaphylaxis, angioedema, or urticaria) considered SAE? These questions were raised because allergy testing isn't routinely done and it is not part of the trial's procedures, but it remains a potential safety issue. 7. Table 2: Please change "Clostridium" to "Clostridioides"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Brad Spellberg, Los Angeles County + University of Southern California

Comments to the Author:

This is a protocol for a promising, welcomed study comparing oral only antibiotic therapy to IV therapy for osteomyelitis in children.

Thank you for all your relevant comments. Please see our answers below.

1) As a non pediatrician, I wonder about the age of inclusion. Do 15-18 year olds develop osteo the same as younger children (presumably growth plates closed for the former?), and are the challenges of administering the oral regimen the same (the latter can take pills daily, the former presumably need liquid medication administered by parents to a screaming baby?). Should the focus be on younger kids? Or would it be helpful to stratify randomization to at least ensure a balance of the younger vs. older kids in both arms, enabling secondary analyses to rule out differences based on age?

We acknowledge the heterogenic population and the age-dependent challenges in the administration of oral (as well as iv) medicine and we agree on the importance of an equal distribution between younger and older children. The main difference between younger and older children is the distribution of pathogens. *K. kingae* is the dominating pathogen in younger children and *S. aureus* is the dominating pathogen in older children. Compared to *S. aureus* infections, *K. kingae* infections tend to present with a milder clinical picture including mildly elevated inflammatory markers, which is why we chose to stratify by CRP aiming at an equal distribution between severity as well as age.

2) It would be helpful if in the Introduction the authors provided citations around the correct first statement, that new papers have been published challenging the traditional requirement for IV only therapy for osteomyelitis. Would at a minimum cite the recent WikiGuidelines published on osteomyelitis in JAMA Network Open that formally recommended oral therapy based on a review of data (PMID 35536578). Others to consider citing include PMID 34715060 and 36694838.

Thank you for the reference. The WikiGuidelines are now cited.

3) The citations in line 18 are wrong. You have cited the protocol for POET as reference #4 and the publication of the POET study as reference #5. You should delete reference 4, and use the current reference #5 for the citation of a large randomized controlled trial of oral therapy for endocarditis. As far as randomized controlled trial of oral therapy for osteomyelitis in adults, you should cite the above mentioned meta-analysis of 8 such trials (including OVIVA), PMID 34715060, and you should cite WikiGuidelines because it discusses a 9th such trial, PMID 35536578. Of note, the same meta-analyis also meta-analyzes 3 RCTs of oral therapy for endocarditis, and so should accompany the POET reference for the oral therapy for endocarditis.

Thank you for pointing that out. The citations are corrected and the meta-analysis as well as the WikiGuidelines are now cited.

4) Of note, you should also consider mentioning that one of the endocarditis RCTs in adults randomized patients to oral therapy up front, with no IV lead in, just as you propose to do for osteomyelitis. POET did not do that. However, in PMID 8686718, they did do this, and found oral as effective as IV, but safer.

That is interesting, thank you. We added that information to the introduction including reference to PMID 8686718.

5) I understand the complexity of giving a blinded placebo to young kids. However, I wonder how it can be unethical to do so when you are already giving IV as standard of care for the first few days. Seems like giving IV saline for a few days would not be unethical. So I don't find this argument compelling. I wonder instead if the argument could be that giving the IV placebo would require stay in the hospital, whereas not giving it allows the patients to never be hospitalized, and as such, giving the placebo has the potential to mask some of the real benefit of an oral only approach?

That is an interesting point. We never tried that approach with the ethical committee, maybe we should have. We are not that concerned about the administration of IV saline for a few days, but more about establishing (and often re-establishing) the IV line. This is often quite complicated in small children and may include several painful attempts, the use of sedation and even general anesthesia in some cases. A double blinded study would of course have generated more reliable data than our current study with a blinded evaluation of the primary outcome, but we do not believe that the difference in data quality justifies exposing all the children to the often complicated procedure of establishing an IV line (and also give all the children oral treatment which in some age groups is very challenging as well). We have removed the argument in the text.

We agree that placebo IV treatment would have the potential to mask some of the real benefits of an oral-only approach, but we believe these considerations to be of minor importance in our setup, where no outcomes are focused on these benefits.

6) The antibiotic options are limited, i suspect due to the specific antibiograms of participating hospitals in Denmark. However, the authors should keep in mind this could limit generalizability to other settings where resistance rates are higher, and empiric regimens may need to cover additional pathogens pending identification of the etiologic bacteria.

We will keep that in mind when analyzing and interpreting the results of the trial.

7) Consider parent and (for older kids) child surveys of satisfaction. OVIVA found much higher satisfaction scores (depression, mobility, anxiety, etc) among adults given oral therapy. One would think this would be even more dramatic for parents of kids who could keep those kids out of the hospital and without an IV in them.

Yes, we do believe that this would be even more pronounced for parents and kids. Several studies have documented a higher satisfaction among patients treated at-home, e.g. PMID PMID: 31420292, and we decided not to investigate that further.

Reviewer: 2

Dr. Abrar Thabit, King Abdulaziz University

Comments to the Author:

This is an excellent protocol for a randomized open-label non-inferiority trial of oral-only vs. IV to PO treatment of bone and joint infections in pediatrics. A few comments need to be addressed.

Thank you for all your relevant comments. Please see our answers below.

1. Introduction: It might be worth mentioning that several oral antibiotics have demonstrated good bone and joint penetration profiles compared to their respective concentrations in the plasma to further justify the objective of this study (https://pubmed.ncbi.nlm.nih.gov/30772469/).

We added that to the introduction including the reference.

2. With regards to the inclusion and exclusion criteria, did the investigators also consider the gastrointestinal status of their patients to ensure that those recruited, particularly those who would be randomized to the oral-only group, do not have intestinal absorption issues (e.g., ileus, malabsorption, ...) or have conditions that may trigger nausea/vomiting (i.e., unable to tolerate oral medications)? It is mentioned under "Discontinuation/withdrawal of participants from study treatment" in point #3 that such patients will be allowed a max of 24h IV therapy. So, does that mean that if some patients presented with such conditions at baseline will be excluded from participation? If so, this should have been one of the exclusion criteria.

We aim to exclude children with intestinal absorption issues (e.g. ileus, malabsorption) by exclusion criteria #4 (Significant co-morbidities that might influence the choice of treatment…). If the child after randomization is unable to tolerate oral (or IV) medication, a maximum of 24 hours in the opposite arm is accepted without changing the treatment strategy. If the treatment in the other arm exceeds 24 hours, it is considered a change in treatment strategy, and we will report the number of children with a change in treatment strategy in both groups. For the main analyses of the primary, secondary and safety outcomes, children with a change in treatment strategy will be analysed according to their allocated treatment (intention to treat).

3. Also, what about patients with known/documented severe (IgE-mediated) allergies to B-lactam antibiotics? Were they excluded, too, since both IV and PO regimens consist of B-lactams only?

IgE-mediated B-lactam allergy is rare in our setting. However, inclusion of children with allergy is possible, since the empiric treatment regimens according to the protocol can be changed due to allergic reactions (*"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."*)

4. Under "Choice of antibiotic treatment", change "ceftriaxon" to "ceftriaxone"

Changed, thank you.

5. Under "Choice of antibiotic treatment", it is better to report the frequency of dosing as "divided every 8 hours" or "divided every 6 hours" instead of "in 3 doses" and "in 4 doses", respectively.

Changed, thank you.

6. Under "Risks and safety monitoring", what about potential allergic reactions if those children have never been exposed to a B-lactam antibiotic and this is their first exposure? Also, aren't severe IgE-mediated reactions (i.e., anaphylaxis, angioedema, or urticaria) considered SAE? These questions were raised because allergy testing isn't routinely done and it is not part of the trial's procedures, but it remains a potential safety issue.

Yes, it is a potential safety issue and severe IgE-mediated reactions would be considered an SAE. We are using the standard FDA SAE-definition, but due to the word limit, we did not specify this definition in the published protocol. We therefore consider the following to be SAEs (which will include severe IgE-mediated reactions): Results in death or is life-threatening or requires inpatient hospitalization or causes prolongation of existing hospitalization or results in persistent or significant disability/incapacity or may have caused a congenital anomaly/birth defect or requires intervention to prevent permanent impairment or damage.

7. Table 2: Please change "Clostridium" to "Clostridioides"

Changed, thank you.

VERSION 2 – REVIEW

REVIEWER	Brad Spellberg Los Angeles County + University of Southern California
REVIEW RETURNED	25-Apr-2023

GENERAL COMMENTS	All comments addressed

REVIEWER	Abrar Thabit King Abdulaziz University, Pharmacy Practice Department, Faculty of Pharmacy
REVIEW RETURNED	26-Apr-2023

GENERAL COMMENTS	I appreciate the work done by the authors. All the suggested edits were incorporated and the comments were responded to with good clarifications. I have no further comments.