PEER REVIEW HISTORY

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ARTICLE DETAILS

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<td>AUTHORS</td>
<td>Ibrahim, Laila; Babl, Franz; Orsini, Francesca; Hopper, Sandy; Bryant, Penelope</td>
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VERSION 1 - REVIEW

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GENERAL COMMENTS

<table>
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<th>ABSTRACT</th>
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| **Introduction**: Page 3 Lines 19-25: I think bringing the title and definition of HITH forward may be clearer. Suggest: “The study is a single-centre, open label, non-inferiority RCT. It is set in the Emergency Department (ED) at the Royal Children's Hospital (RCH) in Melbourne, Australia and the Hospital-in-the-Home (HITH) program; a home-care program, which provides outreach from RCH. Participants will be recruited from ED from January 2015 to December 2016.


**Ethics and Dissemination**: Page 3 Line 40: Will conference presentation (poster or verbal) be undertaken as well. If so, please add.

**Strengths and Limitations**: Page 4 Another limitation is that this is a single site, single city study. Antibiotic resistance is geographically influenced, and the availability/skills of home based care programs for children may not be available to many centres. These factors may limit applicability to other areas. If patients from non-English speaking backgrounds are excluded (see later), then generalizability may be affected as well.

**Body**

**Introduction**

Page 5 Line 13: Delete “Based on a small amount of literature” as
this is self-evident with only one reference.

Page 5 Line 24: Long sentence, suggest dividing. Suggestion, “However, they are not suitable for outpatient parenteral antibiotic therapy (OPAT) due to their frequent dosing. The majority of Paediatric OPAT services can only deliver once daily interventions.”

Page 6 Line 12: need to add to the last sentence for clarity. The main outcome is treatment failure; defined as a change in treatment due to lack of clinical improvement, or the occurrence of adverse events.”

Methods

Exclusion criteria

Are non-English speakers to be excluded? If not, how will the consent process and follow up phone calls and clinic visits be undertaken. Please consider.

Page 6 Line 49: Rather than defining toxicity by the limits on the “RCH Resuscitation card” can the authors use a referenced local guideline such as the following - http://www.rch.org.au/clinicalguide/guideline_index/Normal_Ranges_for_Phyiological_Variables/

Page 6 Line 52: Was the presence of underlying co-morbidities broader than immunosuppression and liver disease? Were children with renal disease, chronic lung disease, a CVC in situ excluded or included?

Page 7 Line 20 and 23: What is the smallest “fractions of days”? How precise can that be?

Page 8 Line 18-20: Revise this sentence. I think it should be two sentences. E.G. “A blood culture, nasal swab and, where relevant, a skin swab will be collected at presentation. A stool specimen will be collected within 48 hours of the first dose of antibiotics”.


Page 8 Line 30-32: Most day-to-day decisions in hospital practice are made by a delegate of the treating consultant. Those delegates are usually trainees in paediatrics (Registrars, Residents, Fellows depending on local terminology). Sometimes a consultant will be called upon to make a decision. I wonder if this could, or should be made more overt in your description. I am not sure if only a consultant makes the decisions in HITH. I think that if there are differences between the two services (inpatient vs HITH) it would be important to know, as trainee staff and consultant staff may make different decisions.
There is a bracket that opens “(risk difference and 95%...” The bracket is then not closed. Please revise.

How long will data and photos be stored? Are there predetermined reasons why access to the data and photos would be required? (relates to SPIRIT Item 27).

Richard Brindle
Public Health England
University of Bristol
University Hospitals Bristol
United Kingdom

Lead author on updated Cochrane review of interventions for cellulitis, author on present published review (2010).
Chief investigator of a trial on an intervention in cellulitis.

There are not many problems with the study design or manuscript. The problem is that this study is unnecessary. Firstly, very few patients need intravenous (IV) antibiotics and there is no evidence of superiority of IV so why set this as the standard? As long as the child can take oral antibiotics (i.e. not vomiting or aspirating) then they should receive them. If they wanted to do a useful trial in children it should be oral versus IV, though there is good evidence already that the two routes are equal in efficacy. The evidence does not suggest any one antibiotic is superior to another so any reasonable antibiotic that a child will swallow is fine. Secondly, a group from Christchurch in 2004 did a similar trial, in adults, to look at efficacy and patient satisfaction. They found the treatments were comparable and patients preferred home care. They also found patients treated at home received longer courses on IV antibiotics (Corwin 2004).

A few other points:
Many patients will have an increase in erythema within the first few days even if they are on an antibiotic as a result of the inflammatory response associated with toxin production. This is a major reason for ‘treatment failure’. Other measures the team could have used are limb circumference (diameter used in the Leman study and circumference by Johnson) and skin surface temperature (developed by Michael Montalto (michael.montalto@epworth.org.au) at the Royal Melbourne Hospital). The most useful measures of response are probably routine observations (temperature and pulse) rather than local signs.
Do you really want to subject over 100 children to unnecessary IV treatment?

Refs:
Montalto M et al. Skin surface temperature: a possible new outcome
measure for skin and soft tissue infection Australian Family Physician Vol. 42, No. 9, September 2013 653

REVIEWER
Sanjay Patel
Southampton Children's Hospital
UK
REVIEW RETURNED
03-Sep-2015

GENERAL COMMENTS
A well designed study that addresses an important question. Paediatric OPAT is a rapidly expanding field and this study addresses the issue of safety. It also addresses the issue of antimicrobial resistance, which is of concern to OPAT services in terms of their reliance on broad spectrum antibiotics such as ceftriaxone. The results could have a huge potential impact on how care is delivered to children in the future.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 - David Krieser

1. ABSTRACT  Introduction: Page 3 Lines 19-25: I think bringing the title and definition of HITH forward may be clearer. Suggest: “The study is a single-centre, open label, non-inferiority RCT. It is set in the Emergency Department (ED) at the Royal Children's Hospital (RCH) in Melbourne, Australia and the Hospital-in-the-Home (HITH) program; a home-care program, which provides outreach from RCH. Participants will be recruited from ED from January 2015 to December 2016.

Amended as per reviewer’s suggestion.


Amended as per reviewer’s suggestion.

3. Ethics and Dissemination: Page 3 Line 40: Will conference presentation (poster or verbal) be undertaken as well. If so, please add.

Amended as per reviewer’s suggestion under the heading ‘Ethical issues and dissemination’. Results of this study will be presented at international conferences as oral and poster presentations.

4. Strengths and Limitations: Page 4 Another limitation is that this is a single site, single city study. Antibiotic resistance is geographically influenced, and the availability/skills of home based care programs for children may not be available to many centres. These factors may limit applicability to other areas. If patients from non-English speaking backgrounds are excluded (see later), then generalizability may be affected as well.

Amended as per reviewer’s suggestion.
5. INTRODUCTION Page 5 Line 13: Delete “Based on a small amount of literature” as this is self-evident with only one reference. Page 5 Line 24: Long sentence, suggest dividing. Suggestion, “However, they are not suitable for outpatient parenteral antibiotic therapy (OPAT) due to their frequent dosing. The majority of Paediatric OPAT services can only deliver once daily interventions.”

Amended as per reviewer’s suggestion.

6. Page 6 Line 12: need to add to the last sentence for clarity. The main outcome is treatment failure; defined as a change in treatment due to lack of clinical improvement, or the occurrence of adverse events.”

Amended as per reviewer’s suggestion.

7. METHODS Exclusion criteria - Are non-English speakers to be excluded? If not, how will the consent process and follow up phone calls and clinic visits be undertaken. Please consider.

Non-English speakers will be included so long as at the time of consent, an interpreter is available. At our centre, an interpreter is available in person during normal working hours Monday to Friday and through telephone 24 hours a day. An interpreter service will also be used for subsequent phone calls and clinic visits similar to routine clinical practice involving non-English speakers. Amended to reflect this information.

8. Page 6 Line 49: Rather than defining toxicity by the limits on the “RCH Resuscitation card” can the authors use a referenced local guideline such as the following - http://www.rch.org.au/clinicalguide/guideline_index/Normal_Ranges_for_Physiological_Variables/

Amended as per reviewer’s suggestion.

9. Page 6 Line 52: Was the presence of underlying co-morbidities broader than immunosuppression and liver disease? Were children with renal disease, chronic lung disease, a CVC in situ excluded or included?

Children with cellulitis related to a central line (although not simply presence of a CVC) will be excluded due to the potential for different organisms and therefore potential need for different antibiotics. Children with renal disease and chronic lung disease will not be excluded as the use of ceftriaxone or flucloxacillin is not contraindicated. However, if these children required another form of intervention eg oxygen or IV fluids then they would be excluded under the criteria ‘Other medical diagnoses necessitating admission to hospital for observation or treatment relating to the known medical condition’.

10. Page 7 Line 20 and 23: What is the smallest “fractions of days”? How precise can that be?

This has now been amended to ‘fractions of days to one decimal point’.

11. Page 8 Line 18-20: Revise this sentence. I think it should be two sentences. E.G. “A blood culture, nasal swab and, where relevant, a skin swab will be collected at presentation. A stool specimen will be collected within 48 hours of the first dose of antibiotics”.

Amended as per reviewer’s suggestion.

12. Page 8 Line 18-20: How is the relevance of the skin swab determined? Clinician preference?
Presence of discharge? Please elaborate.

A skin swab is performed by ED clinicians only in the presence of discharge from the site of cellulitis. Amended as per reviewer’s suggestion.

13. Page 8 Line 30-32: Most day-to-day decisions in hospital practice are made by a delegate of the treating consultant. Those delegates are usually trainees in paediatrics (Registrars, Residents, Fellows depending on local terminology). Sometimes a consultant will be called upon to make a decision. I wonder if this could, or should be made more overt in your description. I am not sure if only a consultant makes the decisions in HITH. I think that if there are differences between the two services (inpatient vs HITH) it would be important to know, as trainee staff and consultant staff may make different decisions.

In both inpatient ward and HITH services, the management decisions for cellulitis are usually made by senior trainees/registrar in paediatrics. Sometimes a consultant will be called upon to make a decision; this is more likely to occur on the ward than in HITH. Amended as per reviewer’s suggestion.

14. Statistical analysis Page 10 Lines 22-24: There is a bracket that opens “(risk difference and 95%...” The bracket is then not closed. Please revise.

Amended as per reviewer’s suggestion.

15. Ethical Issues and consent Page 10 How long will data and photos be stored? Are there predetermined reasons why access to the data and photos would be required? (relates to SPIRIT Item 27).

All data will be retained until 7 years after last contact with patients or once all patients involved in the study have reached 25 years of age (whichever is longer) as per the ethics requirements for our institution. There are no pre-determined reasons why access to the data or photos would be required after the end of the study. Regarding confidentiality (SPIRIT item 27), electronic data will be kept in a password-protected database as per the protocol. The case report forms will be kept in a locked filing cabinet, accessible only by the researchers. Amended as per reviewer’s suggestion.

Reviewer: 2 - Richard Brindle

1. There are not many problems with the study design or manuscript. The problem is that this study is unnecessary. Firstly, very few patients need intravenous (IV) antibiotics and there is no evidence of superiority of IV so why set this as the standard? As long as the child can take oral antibiotics (i.e. not vomiting or aspirating) then they should receive them. If they wanted to do a useful trial in children it should be oral versus IV, though there is good evidence already that the two routes are equal in efficacy. The evidence does not suggest any one antibiotic is superior to another so any reasonable antibiotic that a child will swallow is fine.

The authors agree with the reviewer that children should not be subjected to unnecessary invasive IV therapy. Unfortunately there is no evidence in children that any oral antibiotic is as efficacious as IV treatment for moderate/severe cellulitis, and some evidence that a proportion of children clearly fail oral therapy when tried. Based on our prospective observational study (accepted for publication in the
Pediatric Infectious Disease Journal)[1], of 700 children presenting with cellulitis to ED, 57% were discharged on oral antibiotics and 43% were treated with IV antibiotics. Of those with moderate/severe uncomplicated cellulitis, 45% had been started on oral therapy and cellulitis had progressed despite this. We also have unpublished data showing that of those discharged on oral antibiotics 10% re-presented due to worsening cellulitis: these were then started on IV therapy with successful outcomes. This high re-presentation rate suggests in most cases, our clinicians would not unnecessarily resort to IV therapy as first line. There may be patients started on IV therapy who could have had oral therapy instead, but our experience tells us this number is likely to be small and these children will exist in both groups. We have added a comment to this effect in the Introduction: 'In a recent study at our institution of children presenting with cellulitis to the Emergency Department, 57% were discharged on oral antibiotics and 43% were treated with IV antibiotics due to extensive, rapidly spreading or complicated cellulitis or worsening features despite oral antibiotics. 45% of those with uncomplicated moderate/severe cellulitis had been started on oral therapy and cellulitis had progressed despite this. Of those discharged on oral antibiotics, 10% re-presented with worsening cellulitis, suggesting there is a culture of trying oral antibiotics first and not starting IV antibiotics unnecessarily (unpublished data).

2. Secondly, a group from Christchurch in 2004 did a similar trial, in adults, to look at efficacy and patient satisfaction. They found the treatments were comparable and patients preferred home care. They also found patients treated at home received longer courses on IV antibiotics (Corwin 2004). Corwin P, Toop L, McGeoch G, Than M, Wynn-Thomas S, Wells JE, et al. Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital. BMJ 2005;330(7483):129-32. doi:10.1136/bmj.38309.447975.EB

The fact a study of IV in hospital versus IV at home (and not oral antibiotics) for cellulitis was published by the BMJ nicely highlights the importance of this treatment paradigm. Although the study cited sets the scene for home IV treatment of cellulitis in adults, it shows the dichotomy with children who are routinely treated in hospital with no alternative to go home, despite it being preferable for patients and families. As the reviewer would be aware, an adult study cannot inform about safety or efficacy in children.

3. A few other points:
Many patients will have an increase in erythema within the first few days even if they are on an antibiotic as a result of the inflammatory response associated with toxin production. This is a major reason for ‘treatment failure’. Other measures the team could have used are limb circumference (diameter used in the Leman study and circumference by Johnson) and skin surface temperature (developed by Michael.Montalto (michael.montalto@epworth.org.au) at the Royal Melbourne Hospital). The most useful measures of response are probably routine observations (temperature and pulse) rather than local signs.
Montalto M et al. Skin surface temperature: a possible new outcome measure for skin and soft tissue infection Australian Family Physician Vol. 42, No. 9, September 2013 653

The studies cited are all in adults with lower limb cellulitis which is likely a rather different pathological process (eg involvement of venous stasis, lymphatic congestion) than the cellulitis we observe all over the body in children. It is clear from our unpublished data that paediatric clinicians do not use a single measure to determine either the decision to use IV antibiotics, or failure of treatment; rather they use several parameters which include presence of fever, degree of erythema, swelling, tenderness and functional impairment of the affected area. Lack of improvement of these signs and symptoms
ultimately lead to a ‘change in treatment’ which is why we have chosen this as our primary outcome. In addition, for the home arm, a change in treatment also means a necessity for admission to hospital, hence an indicator for failure of home treatment.

4. Do you really want to subject over 100 children to unnecessary IV treatment?

As delineated above with data to support it, (and highlighted by the reviewer’s cited studies of IV treatment in adults), IV treatment is not unnecessary in the vast majority of children in whom it is prescribed by experienced paediatric ED clinicians. To suggest that their experience and decisions are routinely incorrect is somewhat inflammatory towards them. We refer the reviewer to the other two reviews. Our study is investigating whether children who have already had a decision to be treated with IV, can have this treatment at home.

We wish the reviewer well in his RCT of additional oral antibiotics for adults with cellulitis.

Reviewer: 3 - Sanjay Patel

1. A well designed study that addresses an important question. Paediatric OPAT is a rapidly expanding field and this study addresses the issue of safety. It also addresses the issue of antimicrobial resistance, which is of concern to OPAT services in terms of their reliance on broad spectrum antibiotics such as ceftriaxone. The results could have a huge potential impact on how care is delivered to children in the future.

Thank you for your encouraging review.

References

1. Ibrahim LF HS, Babl FE, Bryant PA. Who can safely have antibiotics at home? A prospective observational study in children with moderate/severe cellulitis. The Pediatric Infectious Disease Journal 2015
Cellulitis: Home Or Inpatient in Children from the Emergency Department (CHOICE): protocol for a randomised controlled trial

Laila F Ibrahim, Franz E Babl, Francesca Orsini, Sandy M Hopper and Penelope A Bryant


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