

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	PAnTher Cub: Procalcitonin-guided Antibiotic Therapy for febrile neutropenia in children and young people with cancer. A single-arm pilot study
AUTHORS	Morgan, Jessica Phillips, Bob

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Oscar Gonzalez-Ramella Institution and Country: Hospital Civil de Guadalajara Dr. Juanl. Menchaca, Salvador QuHospital Civil de Guadalajara Dr. Juanl. Menchaca, Salvador Quevedo y Zubieta 750. Colonia Independencia, Departamento de Hematología y Oncología Pediátrica, Guadalajara, Jalisco, México CP 44340. Competing interests: None
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	<p>The treatment of paediatric cancer patients with events of fever and neutropenia still represents a challenge for clinicians today.</p> <p>Procalcitonin and C-reactive protein levels are used by many hospitals to regulate therapeutic behaviours on the use of antibiotics and the duration of treatment, however, there is no conclusive evidence that confers a prognostic value for CRP and Procalcitonin. Randomized, properly designed studies with a large number of patients are necessary to achieve this goal.</p> <p>In this article, the authors use a single-arm pilot study aimed to evaluate the feasibility of a study using a procalcitonin-guided stopping- rule for antibiotics in paediatric FN. The article perfectly describes that the final intention of the researchers is to carry out a prospective and final randomized study with more than 1000 patients.</p> <p>I believe that this article has a clear exploratory objective, to be able to safely reach a randomized study with a greater number of patients.</p> <p>It is sometimes difficult to describe results in this type of study. The comments added in the results section seem adequate to me, but I think they could be interpreted by the readers with a certain statistical bias. I believe that the authors of this article should increase the number of participants in the study, that although it is marked that its goal was 10 to 20 patients, I consider that a greater number of patients is necessary. In the same way, if the study is aimed at being the pilot for a larger study, it could also add patients from other hospital units. This would enrich the study and could yield even better guidelines if the study is inter-institutional feasible.</p> <p>On the other hand, I think that the discussion is still poor and could be enriched if the authors add extra medical literature and some of the larger studies that are in favour or against using these markers as a dynamic guide in the treatment of paediatric oncology patients</p>
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	with FN. Therefore, I recommend that the authors make these changes before the publication of this work. I sincerely believe that with these changes the article could be published and would be relevant to the medical community.
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REVIEWER	Reviewer name: Dr. Olga Cantú-Rodríguez Institution and Country: Universidad Autónoma de Nuevo León, Hospital Universitario "Dr. José Eleuterio González", Hematology Service, Monterrey, N.L., Mexico. Competing interests: None
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	<p>Evaluation for minor writing mistakes is necessary.</p> <ul style="list-style-type: none"> - Line 15, page 2: Supportive care trials in this population have - proven to be- difficult to undertake. - Line 15, page 2: This single-arm pilot study -aims- to evaluate... - Line 37, page 2: -There were a total of 16 episodes included in the study- (It's best not to start a sentence with a number). - Line 7, page 3: ... being treated for -cancer- are... - Line 25, page 3: ... genuinely -requires- antibiotics... - Line 18, page 6: (Again, it's best not to start a sentence with a number) - Line 34, page 7: (Double quotation in the beginning) <p>In the third page, line 18, it is better to specify the improvement of the patient's condition instead of referring to it only as "the patient is well", since it is subjective.</p> <p>On the other hand, it is necessary to rethink what the objective of the study is, if it is to justify the use of procalcitonin as a biomarker to make an informed therapeutic decision or on the feasibility and acceptance of this kind of protocol by the medical staff and the center. hospitable. The number of patients is extremely small, there is no control group, nor medium-term follow-up, for any conclusion on the validity of the quantitative research part, and the number of subjects interviewed for the qualitative part is also very limited. As it is a pilot study, they should determine and focus on one of the objectives such as the one they pursue and improve the N of the objective they decide for their work.</p>
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REVIEWER	Reviewer name: Dr. Haiko Jahn Institution and Country: Gold Coast University Hospital, Emergency Department, Royal Belfast Hospital for Sick Children, 80 Falls Road, Belfast, BT12 6BE, UK Competing interests: None
REVIEW RETURNED	23-Nov-2021

GENERAL COMMENTS	<p>Thank you for sharing this interesting pilot study regarding the use of PCT to risk stratify paediatric febrile neutropenia.</p> <ol style="list-style-type: none"> 1) Could you add the ethical approval you had for your study as part of the methods. 2) Could you revise figure 2, it appears to have data missing, I assume the Y axis is PCT level and X axis is time (what unit of time? hours, days?)
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REVIEWER	Reviewer name: Dr. Aditya Gupta
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	Institution and Country: All India Institute of Medical Sciences, Division of Pediatric Oncology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, 110029, India. Competing interests: None
REVIEW RETURNED	28-Nov-2021

GENERAL COMMENTS	<p>I congratulate the authors on undertaking the trial to address this important issue . However I would like to recommend few changes before the manuscript can be accepted for publication</p> <ol style="list-style-type: none"> 1. What was the median length of antibiotic usage in the patients in which the antibiotics couldn't be stopped. 2. Can a comparison be done between the two groups : early stoppage vs prolonged antibiotic usage 3. For the patients who could be successfully taken off antibiotics based on the procalcitonin levels , what was the underlying malignancy and what chemotherapy had they received 4. How many patients had high risk febrile neutropenia, presence of central lines, use of GCSF , this should be mentioned 5. There is a rampant use of short forms and abbreviations which are not standard. Please address to these/ explain on first usage eg abs, D2, D3 6. The personal opinions in the discussion are too lengthy . I would recommend to shorten these and concentrate on the scientific aspect more. 7. Please explain Figure 2 better. 8. The manuscript overall can be written better
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VERSION 1 – AUTHOR RESPONSE

Dear Reviewers,

Thank you very much for your thoughtful and constructive feedback to our manuscript entitled 'PAnTher Cub: Procalcitonin-guided Antibiotic Therapy for febrile neutropenia in children and young people with cancer. A single-arm pilot study'. We have carefully considered each of your comments and provide our responses below, in the order of your report.

Editor in Chief Comments to Author :

Confirm ethical approval in the text. It is only mentioned in Data sharing

We have added a sentence to the methods.

What this study adds delete "PAnTherCub demonstrated that"

We have amended as requested.

Methods add the semi-structured questionnaire as an appendix

There was no questionnaire within this study. However, we have added the interview topic guide to the appendices.

Figure 2 needs information re the axis (see comments of reviewer 1)

We have updated this figure in response to reviewer 1's comments.

Associate Editor

A nice and interesting article that I think that should take into account the reviewers comments. I consider that the limitations of "single-arm pilot study" should be emphasised in the text.

We have made some amendments, particularly to the discussion section of the manuscript, which we hope have clarified this sufficiently.

*Reviewer 1: Dr. Haiko Jahn, Gold Coast University Hospital, Friedrich-Schiller-Universität Jena
Thank you for sharing this interesting pilot study regarding the use of PCT to risk stratify
paediatric febrile neutropenia.*

1) Could you add the ethical approval you had for your study as part of the methods.

Thank you. We have added a sentence to the methods.

*2) Could you revise figure 2, it appears to have data missing, I assume the Y axis is PCT level
and X axis is time (what unit of time? hours, days?)*

We have updated this figure as requested.

Reviewer 2: Dr. Oscar Gonzalez-Ramella

*The treatment of paediatric cancer patients with events of fever and neutropenia still
represents a challenge for clinicians today.*

*Procalcitonin and C-reactive protein levels are used by many hospitals to regulate
therapeutic behaviours on the use of antibiotics and the duration of treatment, however,
there is no conclusive evidence that confers a prognostic value for CRP and Procalcitonin.
Randomized, properly designed studies with a large number of patients are necessary to
achieve this goal.*

*In this article, the authors use a single-arm pilot study aimed to evaluate the feasibility of a
study using a procalcitonin-guided stopping- rule for antibiotics in paediatric FN. The
article perfectly describes that the final intention of the researchers is to carry out a
prospective and final randomized study with more than 1000 patients.*

*I believe that this article has a clear exploratory objective, to be able to safely reach a
randomized study with a greater number of patients.*

*It is sometimes difficult to describe results in this type of study. The comments added in the
results section seem adequate to me, but I think they could be interpreted by the readers
with a certain statistical bias. I believe that the authors of this article should increase the
number of participants in the study, that although it is marked that its goal was 10 to 20
patients, I consider that a greater number of patients is necessary. In the same way, if the
study is aimed at being the pilot for a larger study, it could also add patients from other
hospital units. This would enrich the study and could yield even better guidelines if the study
is inter-institutional feasible.*

Thank you for your kind comment. In developing research studies for the assessment of new interventions, traditionally three steps are followed: pilot, feasibility and finally the definitive randomised controlled trial (we acknowledge this may then be followed by systematic reviews and meta-analyses). We believe the changes that the reviewer suggests (for a larger number of patients and the addition of other institutions) actually reflects the aims of a feasibility study – the next step along this path, following the sharing of these pilot results. We have attempted to make this clearer within the discussion section of the manuscript.

*On the other hand, I think that the discussion is still poor and could be enriched if the authors
add extra medical literature and some of the larger studies that are in favour or against
using these markers as a dynamic guide in the treatment of paediatric oncology patients
with FN.*

We hope that these concerns are now adequately addressed by our revisions.

*Therefore, I recommend that the authors make these changes before the publication of this
work. I sincerely believe that with these changes the article could be published and would be
relevant to the medical community.*

Reviewer 3: Dr. Aditya Gupta, All India Institute of Medical Sciences

I congratulate the authors on undertaking the trial to address this important issue. However I would like to recommend few changes before the manuscript can be accepted for publication

- 1. What was the median length of antibiotic usage in the patients in which the antibiotics couldn't be stopped.*
- 2. Can a comparison be done between the two groups : early stoppage vs prolonged antibiotic usage*
- 3. For the patients who could be successfully taken off antibiotics based on the procalcitonin levels , what was the underlying malignancy and what chemotherapy had they received*

We thank the reviewer for their careful reading of the paper. These first three points are certainly items which it will be essential to explore to assess the true value of a procalcitonin led approach to managing FN. The small numbers of episodes within this pilot mean that describing the data in such detail risks creating identifiability of individual patients, and the study is too small to make comparisons and was deliberately omitted from our statistical analysis plan. Accordingly, we would respectfully decline the request to adjust the manuscript this way.

- 4. How many patients had high risk febrile neutropenia, presence of central lines, use of GCSF, this should be mentioned*

We apologise for omitting the risk stratification data. All our patients had central lines, GCSF is not routinely used for prevention or treatment. These items of information, and the AUS (risk stratification) score are now added to this report.

- 5. There is a rampant use of short forms and abbreviations which are not standard. Please address to these/ explain on first usage eg abs, D2, D3*

We have amended these as requested.

- 6. The personal opinions in the discussion are too lengthy . I would recommend to shorten these and concentrate on the scientific aspect more.*

We are unclear which personal opinions the reviewer is referring to, given that our discussion follows a standard, relatively brief, format. As requested by reviewer 1, we have added a little to this section.

- 7. Please explain Figure 2 better.*

We trust that the amendments to Figure 2 requested by reviewer 1 have now resolved this issue.

- 8. The manuscript overall can be written better*

We hope the amendments overall will improve the reader's experience.

Reviewer 4: Dr. Olga Cantú-Rodríguez

Evaluation for minor writing mistakes is necessary.

- Line 15, page 2: Supportive care trials in this population have -proven to be- difficult to undertake.*
- Line 15, page 2: This single-arm pilot study -aims- to evaluate...*
- Line 37, page 2: -There were a total of 16 episodes included in the study- (It's best not to start a sentence with a number).*
- Line 7, page 3: ... being treated for -cancer- are...*
- Line 25, page 3: ... genuinely -requires- antibiotics...*
- Line 18, page 6: (Again, it's best not to start a sentence with a number)*

- Line 34, page 7: (Double quotation in the beginning)

Thank you. We have amended most of these minor errors, except the second, where we believe that as the study is complete, the past tense is appropriate.

In the third page, line 18, it is better to specify the improvement of the patient's condition instead of referring to it only as "the patient is well", since it is subjective.

We feel that specifying that a patient's condition must have improved is inaccurate, given that some children with FN have no symptoms or signs beyond a single fever – thus clinical improvement may not be described, yet still cessation of antibiotics is appropriate. A clinical assessment that the child is well (alongside the other criteria described in this sentence) is, we feel, the better descriptor of appropriate timing of discontinuation of antibiotics and is the phrasing used in educating the treating team about the use of the discontinuation rule.

On the other hand, it is necessary to rethink what the objective of the study is, if it is to justify the use of procalcitonin as a biomarker to make an informed therapeutic decision or on the feasibility and acceptance of this kind of protocol by the medical staff and the center. hospitable. The number of patients is extremely small, there is no control group, nor medium-term follow-up, for any conclusion on the validity of the quantitative research part, and the number of subjects interviewed for the qualitative part is also very limited.

As it is a pilot study, they should determine and focus on one of the objectives such as the one they pursue and improve the N of the objective they decide for their work.

As the reviewer states, this is indeed a non-randomised pilot study which aims to assess the acceptability of PCT guided approaches to paediatric FN. As per the standard stages discussed in response to reviewer 2, we agree that further work is needed in the following order:

- A feasibility study exploring issues relating to multiple study sites, patient randomisation (to control group) and confirming required sample sizes in preparation for the RCT. This may be nested within the larger RCT.
- A larger RCT to assess the use of procalcitonin guided approaches.

We trust our amendments to the discussion make this clearer.

We hope that these comments provide a comprehensive response to your concerns. We would be happy to provide details on any further issues that you wish us to clarify.

Yours sincerely,

The Authors

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Oscar Gonzalez-Ramella Institution and Country: Hospital Civil de Guadalajara Dr. Juanl. Menchaca, Salvador QuHospital Civil de Guadalajara Dr. Juanl. Menchaca, Salvador Quevedo y Zubieta 750. Colonia Independencia, Departamento de Hematología y Oncología Pediátrica, Guadalajara, Jalisco, México CP 44340. Competing interests: None
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	I have already reviewed this article before and I am pleased that the authors made the suggested changes. I think the article can be accepted for publication
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REVIEWER	Reviewer name: Dr. Olga Cantú-Rodríguez Institution and Country: Universidad Autónoma de Nuevo León, Hospital Universitario "Dr. José Eleuterio González", Hematology Service, Monterrey, N.L., Mexico. Competing interests: None
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	The quotes regarding the interview have grammatical errors, and some of the ideas are difficult to understand. They should be corrected according to the context of the interview. For example: "there was a lot of changes all happening all at once" (Prof 4) should be "there were (...)"
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REVIEWER	Reviewer name: Dr. Aditya Gupta Institution and Country: All India Institute of Medical Sciences, Division of Pediatric Oncology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, 110029, India. Competing interests: None
REVIEW RETURNED	28-Nov-2021

GENERAL COMMENTS	The queries have been appropriately addressed in the revised version.
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