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**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | Antibiotic Treatment following surgical drainage of perianal abscess (ATLAS): protocol for a multicenter, double-blind, placebo-controlled, randomized trial |
|---------------------|-------------------------------------------------------------------------------------------------|
| AUTHORS             | van Oostendorp, Justin; Dekker, Lisette; van Dieren, Susan; Bemelman, Willem; Han-Geurts, Ingrid |

**VERSION 1 – REVIEW**

| REVIEWER            | Sorensen, Karam Matlub Odense University Hospital |
| REVIEW RETURNED     | 09-Sep-2022 |

| GENERAL COMMENTS    | I want to congratulate the authors for this long-waited protocol. The study has a solid design with clear primary and secondary objectives and a proper method to answer the research question. I would like to ask the authors to elaborate on the following minor comments:
1. RCTs end up in many cases creating an environment, which can be far from the daily clinical practice. This study will not include (due to exclusions) a group of patients, with comorbidities, who are previously shown as the only group to have a benefit of postoperative antibiotics after abscess drainage. I am concerned about what ever results the study will show, it might be difficult to apply in the daily practice.
2. How is it possible to be sure if the patient have a fistula by a phone call? If not, I would recommend rephrasing the sentence.
3. Is there a time limit for non-responders for the follow-up questionnaire?
4. If the patient develops a recurrence of the abscess, and it reveals an underlying/missed fistula, how is it going to be reported? A recurrence or a fistula or both? I would like to suggest to clarify this in the protocol.
5. Sample calculation is based on assumptions, derived from a rather questionable quality literature (as we all know in the case of perianal sepsis) that the fistula formation between 30-50%. I am concerned about the risk of underpowered study, as the study is including first time anal abscess. A recently published RCT on the subject (aspiration+antibiotics vs surgical drainage) showed no significant difference and the formation of the fistula was 15%. Can you elaborate more on the sample calculation?
6. “The abscess is adequately drained”. I would recommend a more detailed description of the incision-drainage procedure, as there might be risk of lacking homogeneity in a multicenter study with some differences in daily surgical practice, especially in the absence of a standardized procedure, which might have an impact on the study results. |
7. In case of un-blinding due to suspected side effects to study medications and the participant does not fully receive the prescribed study medications, is he/she going to be included in the analysis of the primary end point?

REVIEWER
El Boghdady, Michael
Guy's and St Thomas' Hospitals NHS Trust

REVIEW RETURNED
30-Sep-2022

GENERAL COMMENTS
I would like to congratulate the authors for this protocol. Authors mentioned they will study Antibiotics (Abx) vs no Abx, while in the Abx group: Ciprofloxacin and Metronidazole will be used. We agree this is one of the most common regimes, however, microbiology guidance varies from one country to another and from one hospital to another. In the UK, the ACPGBI recommends the use of antibiotics only if the perianal abscess is complicated, while there was no recommendation in uncomplicated perianal abscesses. A previous study looked at a local variation in clinical practice based on microguidance: El Boghdady, M., Zhao, S., Najdawi, A. et al. Post-Operative Antibiotics Prescription for Perianal Abscesses: International Microguidelines Required. Indian J Surg (2022). https://doi.org/10.1007/s12262-022-03504-2 Cirpo + Metronidazole are not always the guidance, however, the use of Metronidazole has been widely used, as there are reports to decrease postop pain.

Can authors explain if their local or national guidance recommend this combination of antibiotics for treatment of perianal abscesses postop. Any national or local guidelines recommending these or is it department/surgeons' preference?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Karam Matlub Sorensen, Odense University Hospital

Comments to the Author:
I want to congratulate the authors for this long-waited protocol. The study has a solid design with clear primary and secondary objectives and a proper method to answer the research question. I would like to ask the authors to elaborate on the following minor comments:
1. RCTs end up in many cases creating an environment, which can be far from the daily clinical practice. This study will not include (due to exclusions) a group of patients, with comorbidities, who are previously shown as the only group to have a benefit of postoperative antibiotics after abscess drainage. I am concerned about what ever results the study will show, it might be difficult to apply in the daily practice.

Response:
- First, one of the reasons of excluding this group of patients was the placebo-controlled design of the trial. Because the group of patients with comorbidities benefit from the administration of antibiotics ethical concerns are raised when they were included in our study.
- Second, with excluding this group of patients we are studying the most prominent and homogeneous group of patients for which we hypothesize that the administration of
postoperative antibiotics will also have a substantial benefit, namely the reduction of fistula formation.

2. How is it possible to be sure if the patient have a fistula by a phone call? If not, I would recommend rephrasing the sentence.

Response:

- We are aiming to examine every participant in person in the outpatient clinic. However, whenever participants are unable to attend their physical follow up appointment after 12 months (for various reasons, i.e. moved away, no transportation, etc.) we will ask them several symptom related questions to make an estimation about the presence of a fistula.

Rephrasing the sentence:

“A perianal fistula is diagnosed based on findings from physical examination. When patients did not attend their appointment they will receive a telephone call after 12 months where the doctor asks for symptoms as serosanguineous discharge and pain. An external opening with or without serosanguineous discharge is considered a fistula. In case of doubt an endo-anal ultrasonography or MRI scan is performed.”

3. Is there a time limit for non-responders for the follow-up questionnaire?

Response:

- Yes, the baseline questionnaire should be completed within the first week, after which the second questionnaire is sent out. These should also be completed within one week. The next three questionnaires are scheduled at 3, 6, 12 months for which each questionnaire a period of one month is accepted, after which the researcher will contact them once more to obtain the missing data.

New sentence: “There is a time limit set to one month to complete the questionnaires at 3, 6 and 12 months.”

4. If the patient develops a recurrence of the abscess, and it reveals an underlying/missed fistula, how is it going to be reported? A recurrence or a fistula or both? I would like to suggest to clarify this in the protocol.

Response:

- It will be reported as both. A fistula has formed but also repeated drainage of an abscess was required.

New sentence: “In case of repeated drainage of recurrent perianal abscess, and an underlying fistula is objectified, both recurrence and fistula are scored.”

5. Sample calculation is based on assumptions, derived from a rather questionable quality literature (as we all know in the case of perianal sepsis) that the fistula formation between 30-50%. I am concerned about the risk of underpowered study, as the study is including first time anal abscess. A recently published RCT on the subject (aspiration+antibiotics vs surgical drainage) showed no significant difference and the formation of the fistula was 15%. Can you elaborate more on the sample calculation?
RCT: Sørensen KM, Möller S, Qvist N. Needle aspiration treatment vs. incision of acute simple perianal abscess: randomized controlled study. Int J Colorectal Dis. 2021 Mar;36(3):581-588. doi: 10.1007/s00384-021-03845-6. Epub 2021 Jan 15. PMID: 33447866.

Response:

- Our sample size calculation was based on the marginal available literature regarding antibiotics in addition to drainage, also taking our study design and hypothesis into account. The meta-analysis performed in 2019 showed a reduction of 36% when drainage was accompanied by antibiotics. Also, a single-blinded single-centre RCT in 2017 showed a reduction of 50% in fistula formation (15% instead of 30% in the control group). Based on these numbers we have made our calculations as it is the only available literature out there.

6. “The abscess is adequately drained”. I would recommend a more detailed description of the incision-drainage procedure, as there might be risk of lacking homogeneity in a multicenter study with some differences in daily surgical practice, especially in the absence of a standardized procedure, which might have an impact on the study results.

Response:

- As there are various forms of perianal abscesses: small, large, horse-shoe shaped, etc. we chose not to standardize the way of drainage but we chose to leave this up to the surgeon. However, we are collecting data on drainage method, e.g. simple, elliptic, contra incision. Whether a drain is left behind (no, drain, gauze, other).

New sentence: “We chose to conduct a pragmatic study that mimics the current daily practice in the Netherlands best. Therefore we chose not to standardize the surgical procedure but leave this up to the surgeon.”

7. In case of un-blinding due to suspected side effects to study medications and the participant does not fully receive the prescribed study medications, is he/she going to be included in the analysis of the primary end point?

Response:

- Yes, we will perform an intention-to-treat analysis

Reviewer: 2

Mr. Michael El Boghdady, Guy's and St Thomas’ Hospitals NHS Trust

Comments to the Author:

I would like to congratulate the authors for this protocol.

Authors mentioned they will study Antibiotics (Abx) vs no Abx, while in the Abx group: Ciprofloxacin and Metronidazole will be used.

We agree this is one of the most common regimes, however, microbiology guidance varies from one country to another and from one hospital to another. In the UK, the ACPGBI recommends the use of antibiotics only if the perianal abscess is complicated, while there was no recommendation in uncomplicated perianal abscesses. A previous study looked at a local variation in clinical practice based on microguidance:

El Boghdady, M., Zhao, S., Najdawi, A. et al. Post-Operative Antibiotics Prescription for Perianal Abscesses: International Microguidelines Required. Indian J Surg (2022). https://doi.org/10.1007/s12262-022-03504-2

Cipro + Metronidazole are not always the guidance, however, the use of Metronidazole has been widely used, as there are reports to decrease postop pain.
Can authors explain if their local or national guidance recommend this combination of antibiotics for treatment of perianal abscesses postop. Any national or local guidelines recommending these or is it department/surgeons' preference?

Response:

- The choice for this combination of antibiotics was based on available literature where the combination of drainage and antibiotics was successful (Ghahramani L, et al. Antibiotic therapy for prevention of fistula in-ano after incision and drainage of simple perianal abscess: A randomized single blind clinical trial. Surg. 2017). Also, this combination provides complete coverage of the bacterial spectrum (gram-, gram+ and anaerobic bacteria). However, it is our experience also that because there is no recommendation of routine administration of antibiotics in case of perianal abscess that each hospital will use different regimes. Our Dutch national guideline recommends one-time prophylaxis with Cefalozoline and Metronidazole in case of gastro-intestinal (including coloproctological) procedures. As Cefalozoline is not available in tablet form, we chose an widely available alternative with similar coverage of the bacterial spectrum. Hopefully, as a result from this trial we can update our National guideline with the recommendation to use this regime of antibiotics.

Reference: Dutch National guideline [https://adult.nl.antibiotica.app/sites/default/files/2019-09/SWAB%20richtlijn%20perioperatieve%20profylaxe%202019.pdf](https://adult.nl.antibiotica.app/sites/default/files/2019-09/SWAB%20richtlijn%20perioperatieve%20profylaxe%202019.pdf)