Author's response to reviews

Title: Small intestinal bacterial overgrowth mimicking acute flare as a pitfall in patients with Crohn's Disease

Authors:

Jochen Klaus (jochen.klaus@uniklinik-ulm.de)
Ulrike Spaniol (ulrike.spaniol@uniklinik-ulm.de)
Guido Adler (guido.adler@uniklinik-ulm.de)
Richard A Mason (richard.mason@uhhs.com)
Max Reinshagen (m.reinshagen@klinikum-braunschweig.de)
Christian von Tirpitz (christian.vontirpitz@kliniken-bc.de)

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Author's response to reviews: see over
Dear Dr. J. A. Le Good,
Senior Scientific Editor,
BMC-series journals

Thank you very much for the review comments provided. This time it is up to us to be very sorry for the delay in doing the revision of our manuscript as recommended by the two referees. Enclosed we now resubmit the revised research article

Small intestinal bacterial overgrowth mimicking acute flare as a pitfall in patients with Crohn’s Disease

for again consideration of publication in APT Gastroenterology.

We would like to give a point-by-point response to all the concerns of the two referees.

**Referee 1:**

**Major essential revisions**

1. The only major concern that I feel has not been adequately addressed is the relationship between the abnormal breath test and the issue of intestinal resection. The authors state that resection was a predictor of positive test. Is this because resection leads to lack of ileocecal valve and overgrowth or is it due to rapid transit from the resection and not overgrowth at all. I think this should at least be discussed.

Done. As given in the discussion section, the relationship between an abnormal breath test and intestinal resections, especially ileocecal resections, and an alteration in the oro-cecal transit time is some what difficult to explain. As stated, a false positive finding in the HGBT might be due to rapid transit from prior resection. On the other hand, Castiglione et al reported a prolongation of oro-cecal transit time in CD patients, especially pronounced in patients with prior ileocecal resection [8]. This may reflect stasis due to recurrence of strictures in these patients, with stasis and not only the removal of ileocecal valve being discussed as a cause of SIBO itself [10]. Nevertheless, a rapid transit time can never be excluded to produce an abnormal and false positive breath test, but a H2 lactulose breath test to rule out rapid transit can only be used to establish the oro-cecal transit time in absence of SIBO [1,3]. (see discussion)

**Minor essential revisions**

2. Did the authors exclude patients with adhesions or bowel obstruction? This could also lead to mechanical issues leading to bacterial overgrowth.

Done. Patients presenting with clinical symptoms such as nausea and vomiting or abdominal colic suspicious clinically to arouse from strictures or obstructions were excluded from the study and underwent standard work-up and therapy of their underlying CD according to treatment guidelines. Nevertheless, strictures and adhesions in patients with CD are often asymptomatic and it is difficult to make statements on the presence of strictures without radiological or endoscopic findings.
For ethical and practical reasons we could not set a radiological or endoscopical procedure to be a standard inclusion criteria for this study and a history of bowel preparation for colonoscopy within four weeks preceding study inclusion was an exclusion criteria.

3-In the results (methods) section (page 7) there is an extensive defense for using the glucose breath test. This is too long. If the authors want to defend the use of glucose breath test, they should do so in the discussion section of the paper. This is not appropriate for the methods.

Done. We shortened this part of the paper and included it to the discussion section.

Referee 2:

Major essential revisions
None

Minor essential revisions
1-Minor essential revisions The title should be changed and indicate that SIBO is a complication of CD associated to flare up of disease. In patients with a high CDAI it seems difficult to consider SIBO as a secondary event.

We didn’t change the manuscripts eye-catching title because we want to draw attention to the fact, that we show SIBO can really mimic an acute flare of the underlying CD itself, and a high CDAI may not only represent an inflammatory flare but can be high also because of a SIBO associated increase in the daily bowel movements and abdominal complains. Some SIBO patients had a high, some a normal CDAI, as non-SIBO patients had [10]. If anti-inflammatory treatment of an acute flare with a normal or high CDAI by a standard regimen according to the guidelines fails, SIBO should be ruled out by non-invasive HGBT to be the cause of the patient’s medical condition. (see discussion)

2-Minor essential revisions The introduction should clearly state that the method used id indirect and will only detect hydrogen produced by some (not all) anaerobic bacteria. SIBO is possible without hydrogen formation. Glucose is used as external substrate for these bacteria. Lactulose would be a better substrate because not resorbed by the small intestine and only used by bacteria. In SIBO, lactulose can be used as a substrate. In absence of SIBO, it is used to establish orocecal transit time.

Done. We stated in the introduction section that the direct confirmation of SIBO is possible only by microbiological examination of aspirate from the proximal small bowel [1,4]. The H2 glucose breath test (HGBT) has only become the indirect non-invasive standard procedure because of the difficulty of integrating the first method into clinical routine.

The H2 glucose breath test (HGBT) is reported in the literature to have a sensitivity of 62-93% and a specificity of 78-100% in detecting SIBO [1,3]. The H2-lactulose breath test (HLBT), however, which detects bacterial overgrowth by determining the orocecal transit time, shows a sensitivity of only 16.7-68% and a specificity of 44-70% [1,3] and was therefore used only to rule out a hydrogen non-producers status [1,3]. Due to the degree of clinical symptoms during the HGBT, three patients with negative
HGBT findings underwent the H2 lactulose breath test (HLBT) and a hydrogen non-producer status was determined. (see introduction and discussion)

3-Minor essential revisions The used HGBT method should be justified in the introduction section and not in the methodology section (page 7 and 8).

Done. But according to referee 1 we included this part of the paper in the discussion section, and not in the introduction section. (see discussion)

4-Minor essential revisions Antibiotherapy is evoked in the introduction and discussion but not used for the studied population. It should be discussed that an antibiotic treatment will not show a long-lasting effect because the anatomic disorders remain present and will allow recurrence.

Done. (see discussion)

5-Minor essential revisions The references cited need revisions to use always the same type of citations. Names of journals are sometimes complete and sometimes shortened. Ref 4 "Auflage" should be changed to "edition"

Done. (see references)

Thank you very much for the valuable comments that have helped to improve the paper significantly. We do hope that appropriate revisions have been made in response to the point of critique and again we want to say sorry for our delay in resubmitting the revised research paper.

We are looking forward to hear from you

Yours sincerely