August 28, 2013

Dear Editor,
Thank you very much for reviewing our paper and for your favorable comments. We feel the reviewers' suggestions and comments have allowed us to improve our manuscript substantially. Please find enclosed the edited manuscript in Word format (file name: 4917-edited.doc).

Title:A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

Author: Linda Anne Feagins, Ramiz Iqbal, Stuart Jon Spechler

Name of Journal:*World Journal of Gastroenterology*

ESPS Manuscript NO: 4917
The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
2 Revision has been made according to the suggestions of the reviewer
3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

Linda A. Feagins, MD
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Response to reviewers' comments

(1) Reviewer 1: A well-written case-control study, focused on important problem
(2) Reviewer 2: The manuscript has studied the association between IBD flares and potential triggering factors. The results are of clinical significance.

We greatly appreciate the comments from reviewers 1 and 2 that our study is well-written, focused on an important problem, and of clinical significance.

(3) Reviewer 3: 1. The statistical treatment and presentation of results are unclear. Arguably the multivariable logistic regression results should be featured, not the crude (i.e., unadjusted) test of differences in proportions (Figure 1). It is fine to present results in a Figure instead of a table but please present the ORs for all exposures of interest from a single, mutually adjusted model.

Thank you for this suggestion. We now include the ORs and 95% confidence intervals for each result in the text. Figure 1 has been improved and now includes the ORs on the figure, as suggested.

2. The presentation of analysis methods (page 7) is unclear. It states that multivariate logistic regression was used, and variables were "evaluated." But does this mean they are in the same model and mutually adjusted, or does it mean a series of models each with just one independent variable were run? (The given reference for Bursac and colleagues is not helpful; if a variable selection procedure such as backward elimination was used, it should be described.) Was age or sex included? Why not consider IBD disease duration or race in the analysis of flares as well as in the adherence analysis? The selection of variables between these two analyses seems without justification.
The details on the method for purposeful selection analysis are now included in the methods section along with details of which variables were evaluated in the initial selection model and which remained in the final models.

3. Some potentially relevant factors are not discussed or are unclear in the analysis. Was logistic regression adjusted for age? What about BMI? Changes in diet? For NSAIDs use, were data gathered on dose, frequency of use, and etc or only "yes/no"?
Please see the response for the question above. The details for the multivariate analysis are now included in the methods section. While we agree that BMI and diet would be interesting to consider, these data were unfortunately not collected in our study. Yes, frequency data on NSAIDs was recorded but was not reported, as this variable was not significant in the analysis.

4. In Results page 8, 1st paragraph it is noted that use of immunomodulators was higher in the control group. Is this to imply that use of other medications is a risk factor for flares (or conversely that immunomodulator use is more effective at preventing flares)? Wouldn't this be an important point?

Yes, we found a baseline difference in our groups in regards to controls using more

immunomodulators. Moreover, this was found in the logistic regression analysis to be significantly associated with decreased rates of flares. This finding is now emphasized in the discussion.

5. Along the same lines, it is unclear how it can be concluded that non-adherence per se is the issue if one medication is better than the other and furthermore the class of medications is related to non-adherence. Ideally adherence would be compared between users of similar medications. But this is not clear in this study, and should be clearly detailed.

We agree that in retrospect, we should have collected specific compliance data from patients in regards to each specific medication they were taking. We, unfortunately, collected adherence data in aggregate. We did not find any association between specific medication use and adherence, and this is detailed in the results and discussion. We now highlight the fact that specific medication use was not related to adherence.

6.Discussion: page 10. "This prospective study…" is incorrect. The study described is retrospective because exposure information (e.g., adherence) was collected after incidence of disease (flares). Some of the data are perhaps prospective (from medical records) but on the whole it seems retrospective.

Thank you for pointing this out. We have now removed the word "prospective".

7. P-values cannot be 1.0 (i.e., exactly 1). Please change to P>0.99 or whatever the case may be.
Thank you for this comment. We have corrected our p-values, as the reviewer suggests.

8. Although the VA does provide access to treatment and medications it seems an overstatement to say variations in access "plays little role" in adherence. Isn't it possible that some veterans must travel far to reach the VA center in Dallas? If it takes a day off of work to drive 4 hours there and 4 hours back, for example, that is a big barrier. Would it be worth considering home address or distance traveled to the clinic? Or could more detail be provided on why the barriers within the VA system truly are low enough to be negligible?
The reviewer brings up a good point. We have removed the statement "plays little role" from our conclusions.

9. Please include the number of patients invited to participate (Methods, page 6) and the response rate (or %).

We unfortunately did not specifically collect this data on response rate. However, the participation rate for our study was very high with very few people declining to participate. I would guess that the rate was >95%.

(4) Reviewer 4: *This paper aims to explore the association between IBD inflammation flares and potential triggers. The research question is an important one given the physical, emotion, and economic costs of disease relapse. While the sample is relatively large and the question is of import, there are several major and minor ways the article could be strengthened. Below are*

questions, comments, and suggestions for the authors to consider.
ABSTRACT 1. The abstract is nicely written and sets up the paper well. Authors may want to reconsider the use of "definitively proven" in the abstract and introduction. This is the case with many studies of this nature and this study does not "definitively" prove triggers as well.

The statement in regards to "definitively" prove has been removed, as the reviewer suggests.

INTRODUCTION 2. The first paragraph is a little confusing and needs references. For instance, "Physicians may not systematically seek to identify triggers in their patients with IBD exacerbations, furthermore, and the causes of many exacerbations go unrecognized." This seems like two different points that are related. Authors should consider breaking up points. Also, while this conclusion makes intuitive sense, is their empirical support for this statement? Authors should also reconsider the use of "importance" in the last sentence as the importance is clear.

The introduction has been rewritten and improved per the reviewer's suggestions.

3. Write out NSAIDs in Introduction. While it is written out in the abstract, acronyms should be written in text too.

Thank you for this suggestion. This has been corrected.

4. A broader problem with the introduction is the lack of empirical review pertaining to all the triggers of an IBD flare. While type of medication and stress receive a large portion of the review, there is almost no information pertaining to why tobacco use and medication non-adherence contributes to a flare up. A more descriptive literature review of these possible triggers are necessary.

We have expanded the introduction to bring a broader understanding of the problem with regards to flare-ups to the reader. Further, we have expanded the data on how tobacco use may cause flares. Lastly, since we have included much of the data on non-adherence in the discussion, we did not go into more depth on this in the introduction in order to not repeat these data.

5. The aims and importance of this research could be strengthened. What is the impact of flares? Why should we care? The authors mention the veteran affairs health system offers a unique system in which to study patients, this transition seems awkward and it is not clear why this is the case. Also, what do the authors' mean by "patients who served in the military simply have to enroll and can receive free or low cost health care." Does this mean they have to enroll in the VA and receive medical treatment there? Or that they can enroll and receive free and low cost treatment. While I do not think the authors' mean study enrollment, it is confusing what enrollment refers to and the degree of choice.

Thank you for these comments. We have added additional statements into the introduction to emphasize the impact of flares on patients. We have clarified for veterans, that enrollment is in regards to receiving healthcare, not participation in a study.

METHODS 7. On pg. 6, "The study protocol conforms to the ethical guidelines of the 1975

Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institutional review board of the Dallas VA Medical Center." all research has to adhere to these guidelines, not sure if this statement is necessary unless it is a journal guideline.

As suggested by the reviewer, we have removed this statement from this section.

8. Recruitment requires more details. How and where were potential participants approached? How many individuals were approached? How many declined?

As detailed in the methods, patients with flares were identified by gastroenterologists when seen in the course of clinical care at the DVAMC. This has been clarified in the methods. Patients were approached in clinic or their inpatient room, after notification of the study team by the treating gastroenterologist. In regards to numbers of patients approached, please see the response 9 to reviewer #3.

9. General study procedures are missing. Later in the manuscript an interview is mentioned. Who conducted the interview? It sounds like some information is self-report based on the interview, some information is collected from retrospective chart review, and disease activity is collected or generated? Did patients fill out any self-report measures? Did gastroenterologists complete disease activity forms at the time of the interview or is this done routinely? If disease activity was generated retrospectively, was any data checked by multiple raters to determine accuracy. Was written consent obtained?

Thank you for these comments. Yes, all patients gave written consent to participate in the study (included in first paragraph of methods section). We describe in our methods that patients enrolled in the study are queried (asked to recall) by a study team member in regards to the potential triggers for flares over the prior 3 months. At this same encounter, a measurement of disease activity is calculated (CDAI or Mayo score depending on type of IBD) by the study team based on patient interview of their symptoms. The methods section has been improved to clarify these points.

10. Were labs collected as part of the study or where charts reviewed? If retrospective, what time frame was used to include a lab? What parameters were set for this? Stool assessment is unclear. Only 40 of flare group had this collected? This is not mentioned in methods.

Thank you for this comment. Labwork was not mandated by study participation. However, the majority of the patients had routine labs at their clinic visit, and these data were collected as available. This has been clarified in the methods section.

11. Measures need citations, psychometric details, range of scores, et
Normal values for the data in table 2 are now included along with units. Citations for the CDAI score and mayo scores are included in the references.

(5) Reviewer 5: The submitted manuscript tries to figure out trigger factors for an IBD flare in a cohort of patients evaluated at a veteran affairs institution. In this case control study encompassing 134 patients only medication non adherence was identified to be related to a disease flare,

especially in ulcerative colitis. This finding is off relevance as it contradicts previous knowledge. Neither smoking nor NSAID use or stress factors had any impact which has been reported in the past. The paper is well written and offers no apparent criticism. Although the number of patients included is rather small it is no major drawback. However, the percentage of smokers is rather small. I assume, that the authors did not perform a matched analysis which would have improved the manuscript. Did the investigators observe a major recall bias? Hence, what was the ratio of invited/included patients in each group? Antibiotic use has been linked to the first diagnosis of IBD in general. Data regarding flares in established IBD is limited. The finding that immunomodulator use was more prevalent in the control group warrants some thoughts. In contrary, no difference was observed regarding biologics. This distribution should be mentioned in the discussion and highlights the efficacy of immunomodulators.

Thank you for your comments that the paper is well written with no major criticisms. As the reviewer guesses, we did not perform a matched analysis. Further, while we assume there is some recall bias, as is inherent to a case-control study where patients are surveyed about past exposures, we did not perform any specific study within this study to assess the amount of recall bias. Lastly, we did not keep specific data on the number of patients who declined study participation, but in general study participation at our institution is very high, >95%. Discussion of immunomodulators has been added to the discussion, as above.