November 20, 2013

Dear Editor,

Please find the edited manuscript in Word format (file name: 6449-edited.docx).

**Title**: Prevention of post-operative recurrence of Crohn's disease

**Authors**: Byron Philip Vaughn, Alan C Moss

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6449

The manuscript has been improved according to the suggestions of the editor:

1. Full names of authors have been added
2. Full telephone and fax have been added
3. Abstract has been added
4. 5-10 key words have been added
5. A Core tip has been added
6. Figure legend has been added
7. Pubmed citation numbers and DOI numbers have been added as able. First pages of those without have been submitted.

The manuscript has been improved according to the suggestions of the reviewers:

**1. Reviewer 1:**

The authors have attempted to review the topic of management of postoperative recurrence of Crohn's disease Comments:

1. If the objective is to present a cost effective algorithm, then TNF-Inhibitor is not cost effective currently as explained in the manuscript. Otherwise, could the authors explain why thiopurines are excluded from the postoperative algorithm as depicted in the manuscript, especially for low risk group?

***Authors reply:*** *As stated in the manuscript, the figure is intended to present the most cost effective method. To clarify, we have added that information into the figure legend (below). We agree with the reviewer regarding the role of thiopurines. As such as have added thiopurines as a potential alternative or adjunct therapy to antibiotics in low risk patients.*

*Legend to figure 1:*

*Suggested algorithm for deciding when to administer post-operative prophylaxis based on effectiveness of treatment. Other considerations such as cost and prior success or failure of treatment need to be individualized. Patients at high risk are those who have 2 or more of the following risk factors: smoking, penetrating disease, history of prior resection, and myenteric plexitis. Based on the available evidence, we suggest first surveillance endoscopy be done at 6 months time for all patients. Treatment escalation at 6 months should be considered for all patients with evidence of endoscopic recurrence (Rutgeerts ≥ i2). For select patients who achieve and maintain deep remission on therapy (Rutgeerts of i0 with normal histology), consideration can be given to de-escalation of therapy to either thiopurine alone or close monitoring.*

2. Figure 1 would benefit from clarifying in the figure the timing of the surveillance endoscopy while receiving maintenance medical therapy.

***Authors reply:*** *We agree with the reviewer that the timing of surveillance therapy is important. Based on recent updates from the POCER study, we suggest endoscopic assessment at 6 months in all patients. This was clarified in the legend to the figure (please see response to reviewer 1 question 1).*

**Reviewer 2**

This is a very well written review on "Prevention of Post-Operative Recurrence of Crohn's Disease (CD)". The authors review the natural history of postoperative CD, risk factors, available medical therapies, use of endoscopy, and propose an algorithm for postoperative follow-up and treatment. I have minor comments and suggestions:

1. P 6 line 3: Add Odds ratios (95%CI) from Cochrane mesalamine meta-analysis (REF 42) which will clarify your statement.

   ***Authors reply:*** *We agree with the reviewer that this would be helpful. The following text was added to page 6 line 27:*

   *(RR: 0.76 versus placebo, 95% CI: 0.62 – 0.94)*

2. 2. P 6 line 10: Similarly, add Odds ratios (95%CI) from Cochrane thiopurine meta-analysis (REF 42) which will clarify your statement.

***Authors reply:*** *We agree with the reviewer that this would be helpful. The following test was added to page 7 lines 6 – 8:*

*(RR: 0.59 versus placebo, 95% CI: 0.38 – 0.92)*
*(RR: 0.64 versus placebo, 95% CI: 0.44 – 0.94)*

3. 3. P7 Anti-TNF antibodies: At UEGW in Oct 2013, extended POCER data were presented including 18 months follow-up data. I suggest the authors to include these very recent data in the discussion. (21st United European Gastroenterology Week (UEGWEEK2013), 2013, OP057, OP052).

***Authors reply:*** *We agree with the reviewer that these updates are important and have included them in the text along with a discussion. Page 8 lines 12 – 19 now read:*

*However, patients on a thiopurine who had recurrence had an escalation of therapy to adalimumab. Thus at 18 months, there was no difference between endoscopic recurrence in patients who received adalimumab immediately post operatively and those who had tailored therapy based on 6 month endoscopy[60]. Thus early data from ongoing trials suggests that prophylaxis with anti-TNF antibodies may be highly effective compared to other treatments, although careful patient selection is likely required to identify whom to administer prophylaxis to.*
*Ref:*
*60. De Cruz P, Kamm M, Hamilton A, Ritchie K, Gearry R, Gearry R. Strategic timing of anti-TNF therapy in postoperative Crohn's disease: Comparison of routine use immediately postoperatively with selective use after demonstrated recurrence at 6 month endoscopy. Results from POCER. 2013. Presented at 21st United European Gastroenterology Week. 2012 Oct 12 - 16. Berlin Germany 61.*

*Additionally the following test was added to page 10 line 17-25:*
*Recently, preliminary results of the POCER study were presented, supporting the use of endoscopically tailored therapy. In this trial, all patients received thre months of antibiotics and high-risk patients (smoker, penetrating disease, ≥ second operation) received a thiopurine (or every other week adalimumab if thiopurine intolerant). Patients were then randomized to active care with a colonoscopy at 6 months and step up of therapy if evidence of recurrence (Rutgeerts score ≥ i2) or standard of care. At 18 months, significantly less endoscopic recurrence was seen in the active care group versus the standard of care group (49% v. 67% respectively, p = 0.028)*
*Ref:*
*74. De Cruz P, Kamm M, Hamilton A, Ritchie K, Krejany S, Gorelik A, Liew D, Prideaux L, Lawrance I, Andrews J, Bampton P, Sparrow M, Florin T, Gibson PR, Debinski H, Gearry R, Macrae F, Leong R, Kronborg I, Radford-Smith G, Selby W, Johnston M, Woods R, Elliot R, Bell S, Brown S, Connell W, Desmond PV. Optimizing post-operative Crohn's disease management: Best drug therapy alone versus endoscopic monitoring with treatment step-up. The POCER study. 2013. Presented at 21st United European Gastroenterology Week. 2012 Oct 12 - 16. Berlin Germany*

*Additionally the following text was updated to p12 line 3-7:*
*If the decision for tailored therapy is made, then endoscopic evaluation should take place at 6 months time as suggested by the recent POCER data[60,75]. In patients who are not high risk, then an empiric course of nitroimidazole antibiotic is likely to be cost effective, if the patient can tolerate the therapy, with or without maintenance thiopurine followed by endoscopic assessment at 6 months time[4,60,70,75].*

4. 4. P 8 line 8: Add Odds ratios (95%CI) from Cochrane probiotics meta-analysis (REF 42)

   ***Authors reply:*** *We agree with the review that this would be useful. As such the following text was added to page 9, line 5 and 6:*
   *(RR: 0.1.41 versus placebo, 95% CI: 0.59 –3.36)*
   *(RR: 0.64 versus placebo, 95% CI: 0.58 – 1.58)*

5. 5. Figure 1: I lack a legend of the figure. A figure should be self-explanatory and I suggest that "high" and "low" risk, "endoscopic recurrence", "deep remission" and the time of endoscopy is clarified in the figure legend.

   ***Authors reply:*** *We agree with the reviewers that this is important. As such a figure legend was added including definitions of terms. Please see figure legend in our response to reviewer 1 question 1.*

**Reviewer 3:**

This review article summarizes the results of the main papers regarding the effectiveness of the drugs used for the prevention of post-operative recurrence in Crohn's disease. The authors make a survey of the all drugs used to prevent post-operative recurrence and make a critical analysis of the results in function of their effectiveness, side effects and costs. As conclusion it is suggested a practical algorithm of post-operative prophylaxis based on the stratification risk to recurrence. The references quoted are comprehensive and updated. This paper may results of practical utility in clinical practice.

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

Sincerely,

Byron Vaughn, MD
BIDMC
Division of Gastroenterology
Boston, MA
USA
Phone: +1-617-667-2136
Fax: +1-617-667-5826
Email: bvaughn@bidmc.harvard.edy