Tomelloso, November 21st, 2013

Dear Editor,

We are really grateful for the opportunity of revising our manuscript **"ANEMIA IN INFLAMMATORY BOWEL DISEASE: A NEGLECTED ISSUE WITH RELEVANT EFFECTS" (Re: 6306)** by Danila Guagnozzi and Alfredo J Lucendo, submitted to be considered in *World Journal of Gastroenterology*.

Changes have been made in the manuscript according to suggestions given by the reviewer. We feel that the current version has gained clarity and completeness.

Please find below a detailed response to each reviewer's comments.

We hope that you find this revised version of the manuscript suitable for publication in *World Journal of Gastroenterology*.

Sincerely yours,

Alfredo J Lucendo, MD, PhD.

REVIEWER #1

Well written article which covers the problem in detail. While the authors mention b12 and folate deficiency, they should comment further on how B vitamin deficiency should be treated.

A new paragraph including updated recommendation for treating vitamin B12 deficency in IBD has been included in the revised text.

Comment should also be made on the possibility of other common gut pathology (coeliac, colon cancer) which might manifest as new anaemia in a previously stable patient with Crohn's or UC.

We thank the reviewer for this comment. The revised version now includes information regarding this topic.

The reference list has been updated after inkling new references to relevant articles.

REVIEWER #2

Minor Criticism Consider using alternative terms for "iron seizure".

The term "iron seizure" has been replaces by "iron consfiscation".

Sulphasalazine should be spelled sulfasalazine; Creatinine misspelled on page 12

Both terms have been corrected in the revised version of the manuscript

Consider replacing S-ferritin with traditional "ferritin"

S-ferritin has been replaced with ferritin along the whole manuscript, according to the suggestions given by the reviewer.

Major Criticism -In the section on other causes of anemia, the authors should mention in more detail side-effects of common medications (6MP/azathiprine and biologics) and their potential role in bone marrow suppression and MDS. While rare, given their common use, would be important to discuss.

A new paragraph regarding the risk of developing a myelodysplastic syndrome after maintenance treatment of IBD with thiopurines has been added to the revised version of the manuscript. However, references to potential risk of anti-TNF-alpha biologic agents as causing myelodysplastic syndrome have not been included, since bibliographical data do not support the association. In fact, we should take into account that anti-TNF-alpha biologic agents are also used as specific therapy for myelodisplastic syndromes (Stasi R et al. *Leuk Lymphoma* 2005, Raza A. *Microsc Res Tech* 2000, Dufour C, et al. *Pediatr Blood Cancer* 2009).

Consider more discussion on vitamin B12 deficiency and replacement.

A new paragraph regarding the treatment recommendations for vitamin B12 deficiency have been added to the reviewed version of the manuscript.

A multifactorial nature to anemia is repeated in the paper; could the authors discuss how the different causes of anemia could/should be treated in a single patient – eg, bacterial overgrowth leading to B12 deficiency with concomitant side-effect of medication and recent GI bleeding from an IBD flare. While there is unlikely to be a standard approach, it would be important to emphasize to readers the nuances of diagnosing and treating anemia in IBD.

The section devoted to the treatment of anemia in IBD includes 1,300 words, and analyzes iron and erythropoietin supplementation, vitamine B12 and TNF-alpha administration. In each of these sections, practical guidelines are

provided, directed to restore the imbalance leading to anemia. Following the recommendations given by the reviewer, a final paragraph adverting the nuances of providing muti-therapy to multi-factorial causes of anemia in IBD has been added to the revised version of the manuscript.