

Format for ANSWERING REVIEWERS



April, 3rd 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8985-wjgp-review).

Title: INTESTINAL MICROBIOTA: THE EXPLOSIVE MIXTURE IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE?

Author: Roberto Bringiotti, Enzo Ierardi, Rosa Lovero, Giuseppe Losurdo, Alfredo Di Leo, Mariabeatrice Principi

Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 8985

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

Reviewer 1

In the review article of Bringiotti et al. (Intestinal microbiota...) the authors aimed to summarize the current data of the role of microbiome in the pathogenesis of IBD. The review is a precious work, however, there are some points that need revision. The review is too descriptive. The own opinion of the authors is needed from the manuscript. According to the scientific literature what do the authors think:

- What can be immunomechanistic reason of the "different-type-colitis" inducing effect of different bacteria?

The different type of colitis appears to be due more to a different balance among bacterial species than to a single species (see also successive answer). Moreover, a relevant role may be played with microbial interaction with genetic and environmental factors of the host (i. e. NOD2 polymorphism, familiarity at al). This aspect is reported in revised manuscript.

- Are there any animal studies where IBD itself was transmitted from a diseased animal to another, but non-diseased one?

Couturier-Maillard et al demodstrated that reciprocal microbiota transplantation from healthy wild type mice may reduce IBD risk in Nod2-deficient mice and lead to long-term changes in intestinal microbial communities. Conversely, disease risk was enhanced in wild-type mice that were recolonized with dysbiotic fecal microbiota from Nod2-deficient mice. These evidences suggest the possibility of a "IBD transmission from a diseased animal to another."

- In case of non-colitic localized IBD (small intestinal localization, extraintestinal manifestations, gastric/oesophageal manifestation) what can be the pathogenic role of microbiome?

Microbiota composition may influence the onset of IBD in a selected part of the digestive system. El Aidy et al investigated the responses of the jejunal mucosa to bacterial colonization in germ-free mice, showing a consequent shift to anaerobic metabolism, a condition that may strongly influence the mucosal oxygenation in IBD. Moreover, in an experimental model of small bowel CD, a single strain of *E. coli* (LF82) has been demonstrated to stimulate the production of pro-inflammatory cytokines, an

effect that was counteracted by lactoferrin, another microbial product. This aspect is detailed in revised manuscript.

- Dysbacteriosis is a consequence or a trigger factor of IBD?

On the bases of current knowledge, dysbacteriosis appears to be a trigger factor in predisposed individuals more than an epiphenomenon of IBD.

After discussing these aspects (major revision), and after a revision of English language, I suggest to accept the manuscript for publication in WJGP.

Linguistic revision was performed by a native speaker.

Referee n. 2

This well written review covers all aspects of microbiota role in intestinal patogenesis.

References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Pathophysiology*

Sincerely yours,

Enzo Ierardi, Professor, Gastroenterology, Department of Emergency and Organ Transplantation, 70124

Bari (Italy); e-mail: enzo.ierardi@fastwebnet.it

Telephone: +39-0805592577

Fax: +39-0805593088