

Objective: Answering Reviewers

Title: Eosinophilic esophagitis: New insights in pathogenesis and therapy

Authors: Guarino Michele Pier Luca, Cicala Michele, Behar Jose

Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics*

ESPS Manuscript NO: 20624

- Responses to the Editor comments:

Please revise your article according to the reviewers' comments/suggestions and provide point-by-point responses to each in the letter format specified in the attached files.

Response: The article has been changed accordingly to the reviewers' comments/suggestions and point-by-point responses are listed below.

Conflict of interest This file must be signed by the corresponding author and provided in a PDF format.

Response: we attached a PDF file.

The references of 45 and 67 are the same, please revise. Thank you!

The references of 88 and 90 are the same, please revise.

Response: references have been changed.

- Responses to Reviewers comments:

Reviewer **03338934**

Dear Editor of World Journal of Gastroenterology Guarino and colleagues reviewed new insights in the pathogenesis and treatment of Eosinophilic esophagitis (EoE). The authors describe the prevalence, clinical, endoscopic, histological features. Extensively explaining the pathogenesis and treatment There are few minor concerns with the manuscript.

1. Page 4, first paragraph last sentence "Occasionally it is associated with esophageal infiltration of other segments of the gastrointestinal tract". It is important to add the reference for this sentence. To the best of my knowledge EoE is isolated to the esophagus.

Response: thank you for the correction. The sentence has been changed accordingly.

2. Unexplained gender difference. I recommend discussing the Thymic stromal lymphopoietin (TSLP) in pathogenesis of EoE.

Response: this aspect is discussed in the “GENETIC VERSUS ENVIRONMENTAL ETIOLOGICAL FACTORS” section.

3. Clinical presentations. The symptom of dysphagia has been emphasized with almost no mention of clinical presentation in children.

Response: a sentence has been added in the “Clinical presentation” section.

4. The significance of treated with high dose PPI is not to exclude only GERD but also PPI-responsive esophageal eosinophilia. The clinical and endoscopic features of PPI REE and EoE is indistinguishable however the authors mention only dysphagia as a compliant responding to PPI in a subset of patients.

Response: thank you, we agree with you as dysphagia is not the only symptom. The sentence has been changed.

5. Endoscopic finding: Reference for 1/3 patients may have normal endoscopic appearance.

Response: the reference number 15 has been added.

6. Reference supporting biopsies from patient with GERD have <15 eosinophils present only in the distal segment.

Response: the reference by Lucendo AJ et al., Endoscopy. 2007, has been added.

7. Treatment: Important to mention topical steroid are off label. Describe evidence or lack of evidence of adrenal suppression with use of topical steroids

Response: thank you, two sentences have been added in the “treatment” section.

8. Intravenous IL blockers? Which once are available and FDA approved

Response: We added this sentence: While these approaches are often effective, no pharmaceutical agents have yet been approved by the Food and Drug Administration.

9. The sentence “some patients appear to respond to steroids” is unclear as identification of allergic dietary antigens is one of the mainstay of treatment.

Response: we agree with you, the sentence was confusing and has been deleted. the elemental diets and the specific dietary restrictions are more deeply described below.

Reviewer **03261357**

Dear authors, I congratulate you for the extensive and pertinent review conducted on an increasingly prevalent condition in clinical practice that is eosinophilic esophagitis.

However, some more detailed consideration should be made concerning some issues related to the disease, in line with the extensive description given in relation to other points of the article:

1 - A reference to the correlation between symptoms and endoscopic findings and the correlation between the latter and the histological findings should be made. It may be still interesting to make a comment about combination of findings and the likelihood of diagnosis.

Response: thank you. A sentence and a reference have been added in the “Clinical presentation” section.

2 - There is no mention made concerning the complications of the disease, especially the risk of perforation after food impaction.

Response: A sentence and a reference have been added in the “Natural History” section.

3 - A topic related to the prognosis should be added.

Response: A sentence and a reference have been added in the “Natural History” section.

Reviewer 00050080

This review involves everything regarding EoE. It is very informative. However, this manuscript is too long, so readers have to spend much time to read this manuscript. And contents of this manuscript is redundant in many part. I think review in medical journal should be well constituted and summarized. This review is absence of perspective on this point.

Response: The article has been summarized and changed accordingly to the reviewers' comments/suggestions.

JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

Very good paper, however, the section entitled "Clinical Presentation" 2nd paragraph, should have 2-3 references that show that eosinophilic esophagitis involves the full extent of the esophagus with more than 15 eosinophils per HPF. This would be an important distinguishing feature compared to reflux. It might also imply that diagnosis could be established by biopsy of the proximal esophagus. The authors might specifically comment on this issue.

Dear Editor,

Thank you for your constructive suggestions. The bibliography has been added in the "Clinical Presentation" section and a comment has been added about the suggested issue.

Best regards

Michele Cicala