**Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics
**ESPS Manuscript NO:** 4084
**Title:** Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia-
**Reviewer code:** 00182114
**Science editor:** Gou, Su-Xin
**Date sent for review:** 2013-06-14 15:42
**Date reviewed:** 2013-06-19 17:28

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A (Excellent) | [ ] Grade A: Priority Publishing | Google Search: | [ ] Accept |
| [ ] Grade B (Very good) | [ Y] Grade B: minor language polishing | [ ] Existed | [ Y] High priority for publication |
| [ Y] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | [ ]Rejection |
| [ ] Grade D (Fair) | [ ] Grade D: rejected | BPG Search: | [ ] Minor revision |
| [ ] Grade E (Poor) | | [ ] Existed | [ ] Major revision |
| | | [ ] No records | |

**COMMENTS TO AUTHORS**
Eosinophilic esophagitis ( E0E ) is a chronic inflammatory condition that has emerged as a major cause of esophageal disease over the past decade. The pathogenesis, although incompletely characterized, is thought to involve an allergic response to environmental or food allergens. Classic endoscopic findings of EoE is rings, linear furrows, white plaques, luminal narrowing, crepe-paper mucosa and frank esophageal stricture. But up to 20% of patients with EoE may have an esophagus that appears endoscopically normal, and the diagnosis of EoE will be missed if biopsies are not obtained. Current guidelines emphasize that EoE is a clinicopathologic condition with the following criteria: clinical symptoms of esophageal dysfunction; at least 15 eosinophils in one high-power field on esophageal biopsy; and lack of responsiveness to high dose PPI or normal pH monitoring of the distal esophagus. Challenges in diagnosis include lack of standardized esophageal biopsy protocols. Therefore, authors have identified reproducible methodologies for evaluating three potential biomarkers ( Mast cells, Major basic protein, Fibrosis ) in differentiating EoE from RE. They conclude MBP appeared to be the most promising method for differentiating EoE and RE. But I ask authors some question. 1.Please tell me the reason why you conclude MBP appeared to be the most promising method for differentiating EoE and RE. 2.As more is learned about the pathogenesis of EoE, an ultimate goal is to use biomarkers to definitively diagnose EoE. An ideal biomarker would be highly sensitive and specific, correlate with disease severity, responsive to treatment, reproducible, noninvasive, and cost-effective; such a biomarker does not yet exist for EoE. How about do you think immunohistochemistry staining for eosinophil granule constituents?

**Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics
**ESPS Manuscript NO:** 4084
**Title:** Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia-
**Reviewer code:** 00069066
**Science editor:** Gou, Su-Xin
**Date sent for review:** 2013-06-14 15:42
**Date reviewed:** 2013-06-20 18:27

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A (Excellent) | [ ] Grade A: Priority Publishing | Google Search: | [ ] Accept |
| [ ] Grade B (Very good) | [ Y] Grade B: minor language polishing | [ ] Existed | [ ] High priority for publication |
| [ Y] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | [ ]Rejection |
| [ ] Grade D (Fair) | [ ] Grade D: rejected | BPG Search: | [ Y] Minor revision |
| [ ] Grade E (Poor) | | [ ] Existed | [ ] Major revision |
| | | [ ] No records | |

**COMMENTS TO AUTHORS**
The part one of this study is good, since you want to seek the methods to see MBP, Mast cell density, and fibrosis. But the usage of these alternatives are not applicable since you have to do biopsy also to assess all the variable. The gold standard is also by biopsy, so what is it for if you also need to do biopsy to make all the preparat? You may be explore more about the pathophysiology with the pathology you found. Or it would be better if you have another data about the severity of the disease, so you can relate the pathology you found with the severity. The discussion should be focused on the validation of the methods as it is your part one and the primary aim of your study.

**Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics
**ESPS Manuscript NO:** 4084
**Title:** Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia-
**Reviewer code:** 02446446
**Science editor:** Gou, Su-Xin
**Date sent for review:** 2013-06-14 15:42
**Date reviewed:** 2013-06-26 07:37

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A (Excellent) | [ Y] Grade A: Priority Publishing | Google Search: | [ Y] Accept |
| [ Y] Grade B (Very good) | [ ] Grade B: minor language polishing | [ ] Existed | [ ] High priority for publication |
| [ ] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | [ ]Rejection |
| [ ] Grade D (Fair) | [ ] Grade D: rejected | BPG Search: | [ ] Minor revision |
| [ ] Grade E (Poor) | | [ ] Existed | [ ] Major revision |
| | | [ ] No records | |

**COMMENTS TO AUTHORS**

-I reviewed your manuscript ntitled : "Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia". The material is quite interesting and makes an acceptable case for publication, considering that, the emergence of eosinophilic esophagitis over the past decade as an increasingly recognized clinipathologic entity has rekindled interest in a topic of common concern for allergists, immunologists,gastroenterologists and pathologists: namely, the role of eosinophils in gastrointestinal disease. However, there are some items in the paper which should be considered. -You represent a study of 40 cases of esophageal eosinophilia (Twenty specimens with >20 eosinophils/hpf classified as high eosinophil density (HE) and 20 specimens with <5 eosinophils/hpf classified as low esophageal density (LE). All specimens underwent (IHC) and trichrome staining. Mast cell density, extracellular MBP density, and presence of subepithelial fibrosis were assessed in a standardized manner. -The manuscript main claims are: 1.To validate reproducible methodologies and proof-of-concept for determining three potential biomarkers (Mast cell density, extracellular MBP density, and presence of subepithelial fibrosis) in differentiating Eosinophilic esophagitis (EoE) from Reflux Esophagitis (RE). Of the three, semi-quantitative assessment of extracellular MBP appears to be the most promising. 2.To determine whether the reproducible markers would reliably differentiate between patient with high esophageal density and patients with low esophageal density. 3.To explore the relationships between eosinophil density and potential biomarkers. -I have only two Comments: 1-In the introduction, first paragraph : it is stated that : " Mucosal eosinophils are increased in both reflux esophagitis and (RE)and Eosinophilic esophagitis (EoE)". I think you need here to clarify & justify other equally challenging diseases in

children; associated with abnormal accumulation of eosinophils in the esophagus such as:food allergy,Candida esophagitis,IBD,Celiac disease, drug allergy, viral esophagitis , etc…. 2- In the discussion section: please refer to the fact that, the approach to biomarkers even though attractive, is fraught with issues of reproducibility, sensitivity, specificity, and validity. Additionally, the markers of interest must be considered in the context of clinical course, disease progression, therapeutic intervention, and disease severity.

**Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics
**ESPS Manuscript NO:** 4084
**Title:** Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia-
**Reviewer code:** 00069814
**Science editor:** Gou, Su-Xin
**Date sent for review:** 2013-06-14 15:42
**Date reviewed:** 2013-06-26 16:20

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A (Excellent) | [ Y] Grade A: Priority Publishing | Google Search: | [ ] Accept |
| [ ] Grade B (Very good) | [ ] Grade B: minor language polishing | [ ] Existed | [ ] High priority for publication |
| [ Y] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | [ ]Rejection |
| [ ] Grade D (Fair) | [ ] Grade D: rejected | BPG Search: | [ Y] Minor revision |
| [ ] Grade E (Poor) | | [ ] Existed | [ ] Major revision |
| | | [ ] No records | |

**COMMENTS TO AUTHORS**
Dear authors: very interesting study. I only have two comments: 1- There is no figure legends 2- The clinical implication of this research is questionable.

**Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics
**ESPS Manuscript NO:** 4084
**Title:** Validation of methods to assess potential biomarkers in pediatric patients with esophageal eosinophilia-
**Reviewer code:** 01944824
**Science editor:** Gou, Su-Xin
**Date sent for review:** 2013-06-14 15:42
**Date reviewed:** 2013-06-26 22:49

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ ] Grade A (Excellent) | [ Y] Grade A: Priority Publishing | Google Search: | [ ] Accept |
| [ Y] Grade B (Very good) | [ ] Grade B: minor language polishing | [ ] Existed | [ ] High priority for publication |
| [ ] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | |
| [ ] Grade D (Fair) | | BPG Search: | [ ]Rejection |
| [ ] Grade E (Poor) | [ ] Grade D: rejected | [ ] Existed | [ ] Minor revision |
| | | [ ] No records | [ Y] Major revision |

**COMMENTS TO AUTHORS**
This is a potentially important study, and the authors are to be congratulated for attempting to identify specific biomarkers associated with prolonged esophageal injury and fibrosis in EoE. However, this reviewer would question the decision to limit analyses to subjects with eosinophil counts of >20 or <5/hpf. The mean counts of the latter group were, in fact, ~2 eos/hpf. This decision would appear to rule out patients with histopathologically significant GERD. I would also ask the following questions: 1. Where were biopsy specimens obtained? If all specimens derived from the distal esophagus, differentiation between EoE (typically more severe in the mid-esophagus) and GERD would be problemmatic. This of special importance since stricturing in EoE commonly occurs in the mid-esophagus. 2. Were patient records reviewed and, if so, the authors should provide clinical correlation. These data should include mean subject age in HE vs. LE groups, presenting symptoms, treatment prior to biopsy (which clearly may affect histologic analysis).