

**Name of journal: World Journal of Methodology**

**ESPS Manuscript NO: 18011**

Point to point response to the reviewers

Reviewer 1

C1: The terms GERD and GERC have been used interchangeably in this paper. I suggest they are separated.

R1: We accept the suggestion as Reviewer 1 raised. The term DERD has been deleted and replaced by gastroesophageal reflux disease.

C2: Causes of chronic cough should be discussed briefly. The major reason of chronic cough being post nasal drip, asthma and then GERD.

R2: We have revised the manuscript according to the opinion raised by Reviewer 1. The revisions can be seen in Line 4-5, first paragraph, Page 3.

C3: Relationship between asthma and GERD (increased negative pressure in thorax causing reflux) should be addressed.

R3: As the Reviewer 1 mentioned, the relationship between asthma and reflux is very complex. It is well known the microaspiration or esophageal acidification induced by gastroesophageal reflux can cause bronchospasm and even the onset of asthma. In contrast, asthma can also predispose to gastroesophageal reflux by a variety of mechanisms such as increased intrathoracic pressure; vagal dysfunction; altered function of the crural diaphragm and decreased pressure of the lower esophageal sphincter due to asthma treatment. In the case of chronic cough, cough variant asthma and cough due to reflux may exist in isolation or in combination. According to the algorithm used in clinical practice, these two etiologies may be diagnosed and treated in sequence or simultaneously. However, refractory GERC is a disorder unresponsive to standard medical anti-reflux therapy, more difficult

to manage than naïve GERC. Although asthma may play a role in the pathogenesis of refractory cough due to reflux by precipitating the reflux, TLESR and esophageal hypersensitivity which we have discussed in the text, refractory chronic cough due to reflux is not directly associated with asthma. Therefore, we think the addition of relationship between asthma and GERD to the text may deviate or scatter the focus in our review to refractory cough due to reflux.

C4: Mechanism of cough in GERD, neural arc involved should be mentioned.

R4: According to the suggestions raised by Reviewer 1, we have added the mechanism of cough in GERD to Line 21-24, the page 5.

C5: Complete work up of patients includes imaging of sinuses and chest, pulmonary function tests should be mentioned before it is attributed to GERD.

R5: We have added the complete workup for the cause investigation of chronic cough to line 13-24, Page 8 as Reviewer 1 required.

C6: I believe if the evidence cited in every section of paper ( evidence that GERD causes cough, studies talking about medication efficacy should be presented in table form as well. It will make the paper more easy to read and compare the evidence).

R6: We have done these as required by adding the table 1-2 to the revised manuscript.

## Reviewer 2

C1: This is a useful narrative review of chronic reflux cough. The review would be improved by a summary table of the pros and cons of the various methods of diagnosis, the work-up of the differential and a comparison of the approaches to therapy. A key points box would be a useful adjunct.

R1: This comment is almost the same as C6 from the Reviewer 1. We have done these as required by adding the table 1-2 to the revised manuscript.

C2: There are some minor grammar and spelling issues throughout the document.

R2: We have checked the manuscript and wish to correct all the grammar and spelling errors.

## Reviewer 2

C1: Dear Author, I read with interest your review article. It is well written and discusses all topic in GERD related chronic cough. I desire to underline that you could added the finding of a research article recently accepted for publication in Alimentary Pharmacology and Therapeutic. This paper discovers that baseline impedance (IB) values might improve the ability of MII-pH analysis to recognize patients who better respond to PPI therapy. The authors described that the presence of a pathological AET or pathological IB in patients with chronic cough is associated with a greater probability of PPI response. IB is a promising variable in patients with chronic cough, as it increases the diagnostic yield of MII-pH and allows confirmation of the GERD diagnosis in these patients. (ARTICLE: Reflux pattern and role of impedance-pH variables in predicting PPI response in patients with suspected GERD-related chronic cough. Ribolsi M, Savarino E, De Bortoli N, Balestrieri P, Furnari M, Martinucci I, Casale M, Greco F, Salvinelli F, Savarino V, Marchi S, Cicala M. Aliment Pharmacol Ther. 2014 Oct;40(8):966-73. doi: 10.1111/apt.12919. Epub 2014 Aug 11. (PMID: 25109844)

R1: Thanks for the suggestion raised by Reviewer 3. We have mentioned the findings in line 19-22, Page 9 of our revised manuscript and used the article as the reference 34.

C2: Minor suggestion: Change Ggastroesophageal in Gastroesophageal (1st

word in Background)

R2: We have corrected the spelling error.

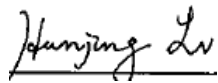
Dear editor;

Thank you for your providing us with a chance to revise and resubmit our Manuscript No.18011 entitled “**Refractory Chronic Cough due to Gastroesophageal Reflux: Definition, Mechanism and Management**” to **World Journal of Methodology**. The editor-in-chief’s comments have been most helpful in revising the manuscript. The revisions, highlighted by the Track Changes function in the text, have been completed according to the opinions of editor-in-chief. Attached is the point to point reply to all the comments the reviewers made.

We wish that our revision would be sufficient to warrant the publication of our manuscript. Thank you for your help and consideration.

Sincerely yours,

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### Point to point response to the reviewers

C1: Overall I agree with the 3 reviewers on their remarks and decisions for this interesting review article. The authors have made serious revision on their manuscript according to the reviewers' suggestions. My advice optional for you is the following. To make this paper more attractive and illustrative, the authors may consider adding a figure of color diagram depicting the elements in discussion. An example can be found on-line here

<https://heathmatters.wordpress.com/tag/esophagus/>.

R1: We accept the opinion suggested by editor-in-chief. A figure describing the diagnostic algorithm for refractory chronic cough due to reflux is added to the manuscript, and the revision also can be seen in the text, Line 24, page 9 and line 1, page 24