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Proposed approach to the challenging management of progressive GERD

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Response to reviewer comments

Reviewer 1

This review article provides a thorough review of the current literature on GERD progression and the associated physiological and pathological changes. The authors proposed that endoscopically normal patients who partially respond or do not respond to PPI therapy should undergo routine biopsies at the squamocolumnar junction to identify histological changes that may predict future progression and thus allow earlier intervention and prevention of the development Barrett's esophagus. Generally speaking, this topic is important and this article is comprehensive and well-written and proved current available evidence for the readers who are treating such GERD patients. The reviewer only has a few suggestions as follow:

1. The authors have stressed the important of esophageal motility, such as the esophageal body contractions and LES pressure, on the progression of GERD. With the advent of high-resolution manometry and impedance-pH monitoring, physicians now have better assessment of the esophageal motility as well as the nature of all reflux episodes. The authors may have some discussion of the application of these updated medical tools for the evaluation of GERD progression.

Author response: we thank the reviewer for this suggestion and have added a section entitled 'Medical tools for the evaluation of GERD progression', where we discuss endoscopy, ambulatory reflux monitoring and manometry techniques and their potential value in the identification of patients with progressive disease (manuscript file: page 9, line 233–278).

2. The authors have proposed endoscopically normal patients who partially respond or do not respond to PPI therapy undergo routine biopsies at the squamocolumnar junction to identify histological changes that may predict future progression. Although such proposal has its advantages for early identification and prevention of GERD progression, several

important issues should be taken into account, such as the cost, biopsy number, and its associated risks of bleeding. Before making such strong proposal, the authors are suggested to review and discuss this important points to make this review more evidence-based.

Author response: We remind the reviewer that our proposed approach is currently based on the hypothesis that routine biopsy of the SCJ in a subpopulation of patients with GERD who are undergoing endoscopy to investigate an incomplete response to PPI therapy, and who have no visible evidence of a columnar-lined esophagus, will identify patients who are at risk of progression and who are candidates for preventative treatment. This hypothesis is supported by findings from the ProGERD study, but must be tested in the clinical setting to determine whether GERD progression can be prevented in this subgroup of patients, and to assess the cost-effectiveness of routine biopsy and the associated risks. Given the absence of clinical data, an evidence-based discussion of our proposal is currently not possible. We have added some text to clarify this for the reader (manuscript file: page 13, line 367–373) and hope that the reviewer finds this acceptable:
'*Our hypothesis will need to be tested in the clinical setting to determine whether potentially progressive disease can be identified through routine biopsy of the SCJ in this subgroup of patients, and whether progression can be prevented through earlier intervention. In addition, the number of biopsies required, the cost-effectiveness, and the associated risk of bleeding*[25] *must be considered before acceptance of this proposed approach in clinical practice.'*

3. Figure 2 is very nice to illustrate several important landmarks during retroflex endoscopic view with the comparison of normal white-light and NBI endoscopy. However, the NBI technology was only mentioned in the figure legend but not in the main text. The authors may have a new paragraph to discuss about commonly used endoscopic tools to facilitate the evaluation of the ECJ and SCJ.

Author response: we agree with the reviewer that discussion of the advantages of NBI compared with conventional endoscopy would be of value. In response to comment one from the reviewer, we have added a section that discusses medical tools for the evaluation of GERD progression. Conventional endoscopy and the advantages of using NBI are discussed within this section (manuscript file: page 9, line 233–278).

4. Figure 4. It is unusual to arrange 24-h pH monitoring before the endoscopy in clinical setting. In addition, manometry is usually performed before the pH monitoring. The order of this algorithm should be seriously considered and be supported with enough evidences.

Author response: we agree with the reviewer that manometry is usually performed before pH monitoring and have revised the algorithm to reflect this (manuscript file: page 26).

Reviewer 2

I have revised this review article focused on GERD progression. I have no comments to do.

Author response: We thank the reviewer for reviewing our manuscript.

Comments from the Editor

1. Please rearrange all the authors' affiliations with Department, University or Institute, City, Postcode, Country, etc. (without any symbol or figure like * or 1).

Author response: All author affiliations have been included in the requested format (manuscript file: page 1, line 11–14).

2. Please add ORCID numbers in the format 'full name (number).

Author response: ORCID numbers have been added for all authors except Tom R DeMeester, who will provide his ORCID on acceptance of the manuscript (manuscript file: page 1, line 16). We hope this is acceptable to the Editor.

3. Please provide the author contributions. Authors must indicate their specific contributions to the published work. This information will be published as a footnote to the paper. See the format in the attachment file-revision policies.

Author response: author contributions have been provided in the requested format (manuscript file: page 1, line 20–24).

4. Please provide the corresponding author address definite to the street number.

Author response: the street number has been added to the contact details of the corresponding author (manuscript file: page 2, line 38).

5. In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Author response: an audio core tip has been recorded and uploaded with the submission files.

6. Please provide all authors abbreviation names and manuscript title here. The abbeviation names should be the same as the copyright. *World J Gastrointest Endosc* 2018; In press.

Author response: the requested text has been added (manuscript file: page 4, line 95). In addition, the references in the text have been formatted according to journal specification.