

Dear Editor,

Thank you for your review of our manuscript entitled “A focus on gastroesophageal reflux disease (GERD) in patients with cystic fibrosis” (NO: 56068). We greatly appreciate the constructive comments. We have read your comments and those of the reviewers and have revised the manuscript. Below, I would like to outline our responses to these comments.

We used point-to-point response to reviewers' comments. In addition, you will find, colored in red, suggested modifications in the text.

Thank you again for your interest in our work. We hope that this revision meets with your approval. We await your review of our revised manuscript.

Reviewer reports:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors, Your paper titled: A focus on gastroesophageal reflux disease in patients with cystic fibrosis is informative and will be interesting for different professionals who treat CF patients. I only have one major remark and it is regarding the selection of articles of publication. Can you explain the methodology how, when and in which databases the search for relevant studies has been done?

Response: as requested, the methodology adopted to perform this study has been reported (please, see 165-178 lines).

Below I list some minor specific questions/remarks and am kindly asking you to address them: • p. 3, l. 70: I believe that you have to add in or something else before which in the next sentence: ... by CF, in which ... • p. 4, l. 151: noncardiac chest pain is not a cardiac symptom, please, correct. Other listed symptoms are also not cardiac, probably some words ... other symptoms such as laryngitis ... are missing. • p. 4, l. 157: hematemesis is not blood flow with vomiting, please, correct. • p. 4, l. 160: I suggest you to leave out (or rewrite that some are already known but probably not all of them) the sentence ... Mechanisms of GER in CF are still unknown ... as you discuss different mechanisms of GER in CF, although, I agree, that all are not known, yet. • p. 5, l. 172: please, add the appropriate ref. no. for

the last sentence in the first paragraph. • p. 5, l. 175: there is a mistake, instead of microaspirations (as is written correctly in the paper below) micro-inhalations are written. •

Response: following your indications, we corrected grammar and typo mistakes and performed a full revision with a native language speaker. The appropriate ref. has also been added (please, see 413 line)

p. 9, l. 261: You wrote that surgical options for those who do not respond to PPI are not recommended, but, on the other hand you discuss Nissen fundoplication as a possible treatment in uncontrolled GERD in the part 7. GERD treatment in patients with CF (p. 19, l. 291). You have to be more precise, when surgery is not a good option and when is it necessary?

Response: to be more precise, flow chart on medical and surgical treatment have been added.

• p. 11, l. 306: a meta-analysis [42] has been performed in general population, not in patients with CF, please add this explanation. • p. 11, l. 309: there must be a mistake in this sentence, as it is not clear. Please, define whether you discuss complication of GER or PPI treatment? •

Response: we clarified the above mentioned sentences (please, see 366 and 368-369 lines).

p. 12, l. 327: please, state also the upper limit of healthy BMI for CF patients as obesity is also a problem in a subgroup of these patients, and obesity is also a risk factor for GERD. Please, correct or explain the above questions and comments. Yours sincerely, Reviewer

Response: as requested, we clarified the above mentioned sentences (please, see 412-415 lines)

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is an interesting study focusing on GERD in patients with cystic fibrosis. As a general comment, a more precise and accurate target on the CF patients could be. Although description of mechanisms is very attracting, a further at length and in depth analysis could be desirable. The chapters with GERD characteristic could be more catching if putative differences between general population and CF patients were mentioned. Especially, chapter 3 referred to GERD and respiratory diseases association in a general way. Impact of GERD in pulmonary function of CF patients could be extended, as it presents the main adverse effect on the disease. In the diagnosis, there is none special mention in tricks, if there are any, for CF patients especially; there are only reports for the well-known diagnostics tests used in general population. Tables do not provide any new information and there is a clear displacement of them. A flow chart could be more helpful.

Response: as requested, more detailed information on CF patients and GERD has been provided (please, see 235-239 lines; 263-293 lines).

The table 6 has been removed and a flow-chart has been added.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is a good review article for the GERD in patients with cystic fibrosis. I'd like to comment some request for revisions. Page 7, line 196 Please correct the wrong words. COPD > COPD Page 9, line 261 Author mentioned that surgical options are not recommended for patients who do not respond to PPI therapy. However, when gastroesophageal reflux is confirmed objectively, failure in PPI therapy is one of the surgical indications. There are several guidelines for surgical treatment of GERD recommending surgical treatment for refractory GERD. Although antireflux surgery for patients with PPI-refractory GERD has been known to be less effective than for patients who respond to PPI therapy, "no response to PPI" is still a common reason for having antireflux surgery. In addition, antireflux surgery may benefit the selected group of patients with pulmonary disease and proven GERD. Therefore, I'd like to recommend additional description about the role of surgical treatment for GERD patients with pulmonary disease such as CF. Page 11, line 308 Correction of wrong words is needed. Complications gastric > gastric complication

Response: as requested, more detailed information on surgical options has been provided (please, see 374-393 lines). The typo-errors have also been corrected.

We are grateful to you and reviewers for the truly helpful comments.

These changes will improve the quality of our paper.

Sincerely,

Sara Manti, MD, PhD

Department of Clinical and Experimental Medicine,

Pediatric Respiratory Unit,

San Marco Hospital,

University of Catania,

Catania, Italy.

E-mail: saramanti@hotmail.it