Peer Review File

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Reviewer A

This is a very broad topic and I appreciate the effort put in to summarize such a vast topic.
Recommend adding abdominal breathing. Abdominal breathing is a simple office based measure that can help significantly to the patient and help in better symptom control and potentially escalate the medicine.
RCT PMID 22146488

Authors would like to thank Reviewer A for the favorable feedback. We have added referenced paper and another, newer study (Halland et al) to the text.

Reviewer B

The authors present a narrative review on GERD and its significance in the primary care physician's practice. I enjoyed the paper but have the following comments/concerns:

1. There are MANY typos, grammatical errors, etc in the manuscript which is surprising given the country of origin. Please correct prior to re-submission.

2. In the Intro, the authors state that GERD is the second most common GI-related disease seen by the GP. Might be nice to tell the reader the most common GI-related disease!

3. I am not familiar with the term "esophageal syndrome" and "extra-esophageal syndrome" but rather typical and atypical reflux symptoms. In the typical category, I would always list volume reflux/water brash/acid regurgitation which is not specifically listed.

4. I am not sure dysphagia is a classic reflux symptom. It can be when it is caused by a Schatzki ring/para-esophageal hernia but it is more of an alarm symptom in other situations. I think this should be clarified in the text.

5. I am not sure I believe that reflux is a well-established cause of laryngeal carcinoma. Surely, smoking is a much higher risk factor. A patient needs to reflux acid up to the level of the neck for this to occur which is not terribly common.

6. The authors should specify the Mediterranean diet in the text.

7. I am an upper GI surgeon, and therefore a big supporter of laparoscopic fundoplication, but even I feel the authors have painted a very dark picture of medical therapy for GERD. The literature would support a success rate of up to 85% for controlling reflux in patients with

GERD. The 15% who are not adequately controlled are generally those with volume reflux, or those who have ongoing esophagitis on maximal medical therapy. And the authors should clarify that the lower success rate of PPI for controlling atypical symptoms is because, quite often, these symptoms are not caused by reflux.

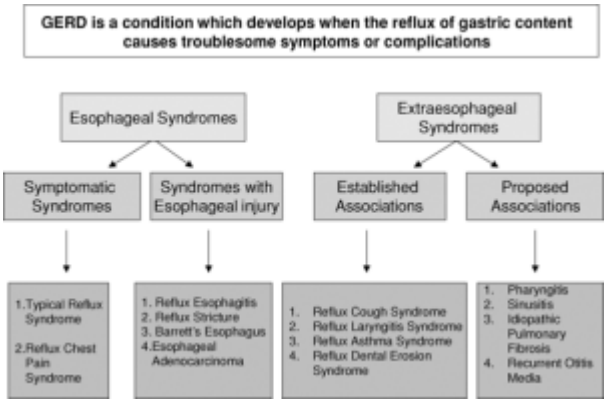
8. There are some excellent recent papers on the side-effects (or not) of PPIs and these have not been referenced in this paper. Please include a recent review by Michael Vaezi which states quite definitively that the only proven long-term side-effect to PPI therapy is bacterial overgrowth in the gut. None of the others have been proven definitively, and this paper should remain objective in its reporting of such complications.

9. PPI therapy does not "mask" the symptoms, it removes the symptoms (caused by acid) in up to 85% of patients. This section is misleading.

10. Laparoscopic or robotic fundoplication is the standard of care in patients whose symptoms are not adequately controlled by PPI therapy, in those who predominantly have volume reflux, and in those with a large hiatus hernia. The LINX device is not offered in many countries, for example it is not offered in Australia. The endoscopic therapies are highly controversial and again, not offered in many countries. I feel a sentence stating their efficacy (or not) is beyond the scope of this paper.

Authors appreciate Reviewer B for the constructive criticism.

1. We proofread the manuscript to address mentioned problem.
2. We rephrased the paragraph to add the most common diagnosis, which is an abdominal pain.
3. We appreciate Reviewer B comment. These are well established definitions from the landmark paper by Vakil at al. PMID 16928254. Please see the figure. We have rephrased the paragraph to cross-reference to more familiar for Reviewer B terminology of typical and atypical symptoms.



4. We appreciate Reviewer B attention to this matter and rephrased the paragraph to clarify the issue.
5. Whereas we acknowledge Reviewer B skepticism, this data is derived from metanalysis that included nearly 40 thousand patients and believe the data is reliable. PMID 32841763
6. We added definition of the Mediterranean diet from the paper to the manuscript.

7. We appreciate this Reviewer B comment. Review of the best evidence on the effectiveness of the medical therapy in management of GERD is presented in this section and we have nothing to change.
8. Thank you for the excellent reference to this paper. However, it is worthwhile to note that authors do not dispute the findings in publications, but rather point to low absolute increase in the risk of PPI and call to balance this small increase in risk with therapeutic benefits of PPI use. This has been added to the discussion.
9. Thank you for the excellent feedback. We rephrased the paragraph to clarify the thought process.
10. We agree that details of surgical and endoscopic interventions are beyond the scope of this paper and expertise of family practitioners. Nothing in this paragraph address the details of the procedures. Procedures were listed to draw attention of primary care physicians to a vast array of options currently available and encourage them to consider referral to specialists.

Reviewer C

This is a review of GERD for primary care providers. The following suggestions may help to strengthen the manuscript

--The authors should introduce functional esophageal disorders such as functional heartburn and reflux hypersensitivity, in the section of Failure of Therapy. These conditions are very common, and in some studies, account for the majority of "PPI failures" (Abdallah et al, CGH 2019)

--I would recommend discussing the importance of differentiating GERD from dyspepsia/functional dyspepsia in the Presentation section

--In the PPI Side Effects section, I would consider discussing Dr. Moayyedi's recent RCT regarding PPI and no association of many of these conditions (Moayyedi et al, Gastroenterology, 2019)

--In the Escalation of Care section, Stretta is mentioned; however, a recent meta-analysis found that Stretta does not reduce acid exposure (Lipka et al, Clin Gastroenterol Hepatol. 2015 Jun;13(6):1058-67) and Stretta is not recommended in the most recent ACG GERD Guidelines

--As noted above, I feel that discussion of functional esophageal disorders is much more important to the PCP than a discussion of antireflux surgery

--In the escalation section, I would mention that bariatric surgery (specifically Roux en Y gastric bypass) is the recommended antireflux surgery for patients with BMI > 35

--I would consider adding a section on diagnostic testing, that would include:
PPI trial, the limited value of upper endoscopy (aside from screening for Barrett's esophagus), esophageal manometry to rule out motility disorder such as achalasia, and pH testing in PPI non-

responders to confirm the diagnosis, and rule out functional esophageal disorder mentioned above

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Authors would like to thank Reviewer C for the positive feedback and recommendation on improving the manuscript.

- We have added the section on functional esophageal disorders and their role in the failure of medical therapy.
- We have added discussion on functional esophageal disorders to presentation section.
- We added a sentence on Moyyyedi publication.
- We are aware of the controversy about Stretta, however feel that details of intervention selection are outside of the primary care expertise and the scope of this manuscript and would like to leave these details to other authors.
- We agree with this statement and addressed above recommendations as suggested.
- We appreciate Reviewer C recommendation, but again would like to leave it to another discussion for GERD experts. This manuscript is intended to be an all-inclusive overview of the condition as a whole.

Reviewer D

The authors touched upon an extremely pertinent problem – management of GERD in the primary care practice settings.
Primary care physicians are essentially gate keepers for the management of such complex and continuously growing problem. However, in the majority of cases, this problem remains grossly underappreciated and ignored.
Authors presented the history, definition, presentation, diagnosis and management of the condition. Especially useful were discussion of the quality-of-life impact in patients with GERD, world-wide prevalence of the condition and effectiveness of the diet and lifestyle modification.
Role of PPI in the initial treatment of the GERD was well reviewed and evidence were presented logically. Especially important was an accent on the complications of the chronic PPI use and its overutilization.
The review is well written in the easy-to-understand manner and would a valuable tool in the armamentarium of primary care physicians. Minor edits were added to the text, after correction of which the paper should be accepted for publication.
(See Attachment)

We appreciate Reviewer D kind words and feedback. All suggested edits were incorporated into the revised manuscript.

Reviewer E

Good comprehensive paper on GERD management from a family medicine perspective.

Lines 86-87. “antireflux mechanism on the other, such as low esophageal sphincter, the crural diaphragm and angle of His”. This sentence is a little oversimplified. I think more discussion on the

actual anatomy needs to be included. The crura of the diaphragm, not the crural diaphragm. Discuss the actual intrinsic thickening of the muscle fibers of the lower esophagus at the GEJ. And discuss the valve mechanism of the angle of His. There are papers on this for which you can cite.

Lines 275-276: agree with this statement.
For the failure of initial therapy and escalation of care paragraph. I would talk a little more about the laparoscopic and robotic options, specifically the fundoplications and a general idea of what they are, as this is a narrative review.

I would also talk about surgery as a standard of care in the conclusion, especially since it presents with the most durable anti-GERD therapy – would bring in a few more articles pertaining to the improvement in GERD questionnaire scores and being off of PPIs in the long run.

We appreciate Reviewer E positive response and valuable input.

- We clarified anatomical components of the GEJ.
- We appreciate support of this paragraph.
- We feel that this manuscript is aimed at primary care physicians and prefer to avoid granular discussion of details of surgical interventions selection and their details.