

## Detailed response to reviewers' comments (90507)

Dear Editor:

First of all, we are truly grateful to the reviewers' comments and suggestions. Based on the comments we received, careful and thorough modifications have been made to the manuscript. All corrections are highlighted in yellow in the revised manuscript. Our point-by-point responses are listed as follows:

### Reviewer: 1

#### Comments to the Author

This comprehensive review provides a thorough examination of laryngopharyngeal reflux disease (LPRD), encompassing its pathophysiology, clinical manifestations, diagnostic methods, and treatment strategies. The author delves deeply into the etiology of LPRD, covering both reflux and reflex theories, as well as its associations with other respiratory conditions. Additionally, the article intricately describes the relationship between LPRD and gastroesophageal reflux disease (GERD), emphasizing its role as an extra-esophageal manifestation of GERD. The pathophysiology section meticulously dissects the mechanisms of injury to laryngopharyngeal tissues by different reflux substances such as hydrochloric acid, bile, gastric enzymes, among others.

1. However, when discussing treatment methods, the article could delve more into recent research advancements and future therapeutic trends.

#### Response:

Thank you for your kind suggestions. Reviewing the latest literature, the latest treatment methods such as speech therapy and behavior therapy have been added to the treatment methods. The details are as follows:

#### *Speech therapy*

In addition to pharmacologic therapy, speech therapy (a therapy that focuses on language and breathing) has also been shown to be an effective treatment and is recommended by CHEST guidelines[57]. In a study[58] of patients with chronic cough, researchers found that compared with a control group, patients who received 6 months of PPI therapy and 3-5 sessions of breathing therapy and speech pathology intervention (guidance on healthy lifestyles such as relaxation, stress management, exercise, and diet) had significant improvements in symptoms (cough, breathing, voice, upper airway, and limited daily activities) after treatment. The results suggest that speech therapy may potentially improve laryngeal allergy symptoms in patients with chronic cough. The researchers found that 100% of patients experienced an improvement in their cough symptoms. Further research in this field is still needed in the future.

#### *Behavioral therapy*

In cognitive behavioral therapy[59], psychiatrists use a range of behavioral therapies, including stress management, cognitive reconstruction, coping strategies, problem solving,

and anxiety management, to improve patients' throat symptoms and have been shown to be a safe and effective option. Studies have found that hypnotherapy treats [60, 61] patients with allergic laryngeal symptoms and foreign body sensation in the pharynx. The researchers found that patients experienced a significant reduction in the severity and symptoms of throat discomfort after relaxation breathing therapy, which involves adjusting breathing and relaxing muscles, and esophageal-oriented hypnotic-assisted relaxation therapy. In another study, nine patients with functional heartburn who received esophageal directed hypnotherapy seven times a week experienced significant improvements in heartburn symptoms, visceral anxiety, and quality of life. In a recent study, it was found that, based on the available evidence, hypnotherapy for patients presenting with dysphagia, foreign body sensation, indigestion, and functional heartburn is reasonable cognitive behavioral therapy (CBT), which has been well studied in patients with functional bowel disease. Future research is needed in behavioral therapy for laryngeal hypersensitivity and laryngeal dysfunction.

57. Gibson, P., G. Wang, L. McGarvey, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest* . 2016.149: 27–44.

58. Vertigan, A.E., D.G. Theodoros, P.G. Gibson & A.L. Winkworth. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax*. 2006. 61: 1065–1069.

59. Riehl, M.E. & J.W. Chen. The proton pump inhibitor nonresponder: a behavioral approach to improvement and wellness. *Curr. Gastroenterol. Rep.* 2018. 20: 34.

60. Riehl, M.E., J.E. Pandolfino, O.S. Palsson & L. Keefer. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. *Dis. Esophagus* .2016. 29: 490–496.

61. Riehl, M.E., S. Kinsinger, P.J. Kahrilas, et al. Role of a health psychologist in the management of functional esophageal complaints. *Dis. Esophagus*. 2015. 28: 428–436.

2 The mention of surgical interventions is relatively limited, and a more extensive exploration of the latest studies and developments might provide readers with additional information on treatment options.

**Response:**

Thank you for your kind suggestions. Related contents are added in the section of surgical treatment, and the surgical methods, indications and prognosis are expounded in detail. The details are as follows:

Swoger et al. [51] evaluated the difference between surgical treatment and PPI in a retrospective controlled trial and found a significant difference in fundoplication. There is a close relationship between fundoplication and improved RSI scores, and fundoplication as an effective treatment for LPR patients has significantly benefited many patients. However, how to judge the effect of surgical treatment and accurately select suitable patients for surgical treatment is the current difficulty. It would be irresponsible to recommend that every LPR patient undergo major abdominal surgery. Previous studies often judge the effect of treatment according to the subjective judgment of patients, which has great subjectivity and individual differences. Therefore, when selecting and evaluating the effect of treatment, patient-reported results must be given priority in a patient-centered approach, and reflux and symptoms must be evaluated in detail in combination with pH monitoring and RSI score. At the same time, fundoplication is more effective than PPI treatment, but it is more risky. The most common

complaint is dysphagia. In one study[52], all patients experienced dysphagia after surgery. The patient may have dysphagia in the initial postoperative period, but it resolves spontaneously after 2 weeks. But 13 patients (4.53%) reported prolonged dysphagia after surgery. And the second most common complaint was postoperative gas/abdominal distension. In one study[53], abdominal distension occurred in all 12 patients during the first 2 weeks. Sahin et al. [54] showed that postoperative complications included emphysema (10.8%), intraoperative bleeding (4.4%), pleural displacement (2.9%), and postoperative hernia (1.4%), and seven patients (2.4%) required a second surgical intervention due to postoperative complications and one patient (0.4%) required a repeat procedure due to surgical failure.

51. Swoger J, Ponsky J, Hicks DM, Richter JE, Abelson TI, Milstein C, Qadeer MA, Vaezi MF. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol*. 2006;4(4):433-41.

52. Iqbal M, Batch AJ, Spychal RT, Cooper BT. Outcome of surgical fundoplication for extraesophageal (atypical) manifestations of gastroesophageal reflux disease in adults: A systematic review. *J Laparoendosc Adv Surg Tech*. 2008; 18: 789–796.

53. Suzuki T, Seki Y, Okamoto Y et al. Hypopharyngeal multichannel intraluminal impedance leads to the promising outcome of antireflux surgery in Japanese population with laryngopharyngeal reflux symptoms. *Surg Endosc Other Interv Tech*, 2017: 1–11.

## **Reviewer: 2**

### **Comments to the Author**

This review extensively covers the pathophysiology, clinical features, diagnosis, and treatment of LPRD, offering readers a comprehensive and in-depth understanding. The author employs a wealth of research data and literature references, enhancing the credibility and reliability of the article. The elucidation of different perspectives on the etiology of LPRD, such as reflux and reflex theories, is particularly clear, aiding readers in comprehending the diversity and complexity of LPRD. Providing insights into these aspects could offer readers a clearer understanding of the future developments in the field of LPRD. Overall, this review provides a valuable and detailed exploration of LPRD, contributing substantially to the understanding of this complex medical condition.

1 Others, there is a relatively limited discussion on future research directions and development trends in LPRD towards the end of the article. Further research avenues could include the development of novel treatment strategies, a deeper exploration of etiology, and the advancement of more accurate diagnostic methods.

### **Response:**

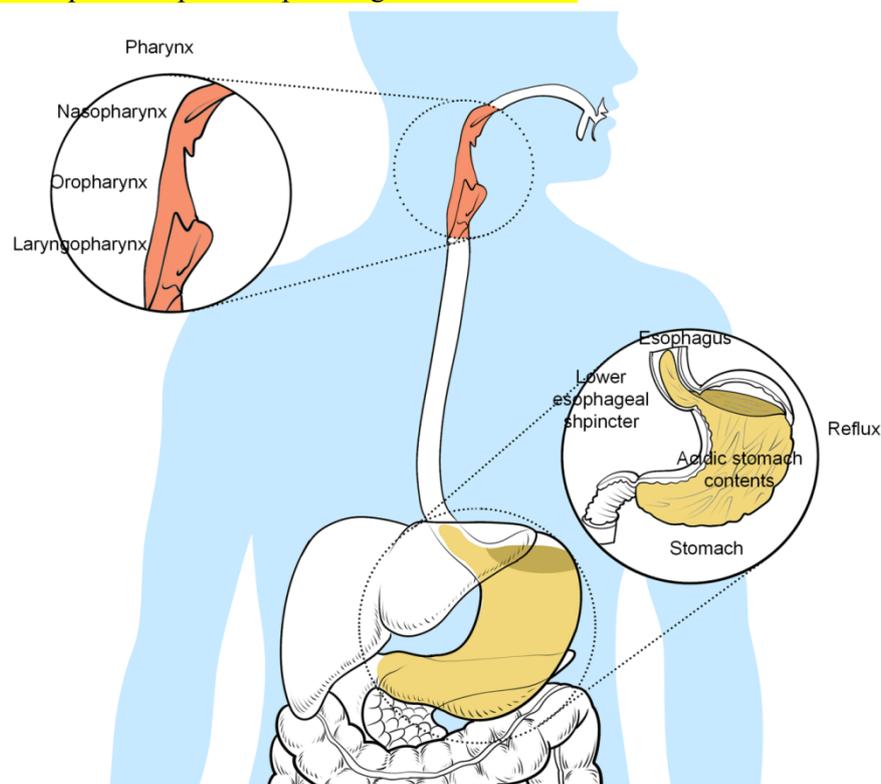
Thank you for your kind suggestions. In the article, the prospect part is added, and the future treatment strategy and the future research direction of drugs are expounded in detail. The details are as follows:

### **PROSPECT**

For LPRD caused by different reflux substances, 24-hour MII pH, salivary pepsin and bile acid tests should be established in clinical practice, which not only helps to diagnose the

cause, but also facilitates the observation of the therapeutic effect and course of different drugs, so as to provide patients with a more personalized treatment plan. For patients with non-acid reflux or refractory LPRD, PPI indications and discontinuation plans require multidisciplinary evaluation involving gastroenterologists, otolaryngologists, and even psychiatrists. The poor efficacy of some PPIs patients indicates that the molecular mechanism of non-acid components on laryngopharyngeal mucosal injury needs further study. In addition, more clinical prospective studies are needed to evaluate the reliability of biomarkers such as pepsin and bile acids as diagnostic and prognostic indicators of LPRD. At the same time, more clinical prospective studies are needed to evaluate the selection of laparoscopic surgical treatment methods and indications in order to provide more effective treatment strategies for more patients.

**3. In addition, we revised Figure 1 and added a text description of the stomach contents to the figure to explain the possible pathological mechanism.**



**Figure 1 Pathogenesis of laryngopharyngeal reflux**

Laryngopharyngeal reflux disease (LPRD) is an inflammatory disease of the upper aerodigestive tract caused by reflux of gastroduodenal content. The stomach contents usually include gastric acid, nonacid substances, bile and pepsin. Reflux of the upper respiratory tract mainly involves the pharynx, larynx and nasal cavity.

Your faithfully,

Xuewei Zhu

