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**Treatment of laryngopharyngeal reflux disease: A systematic review**

Lechien JR *et al*. Laryngopharyngeal reflux treatment

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**Abstract**

***BACKGROUNG***

For a long time, laryngopharyngeal reflux disease (LPRD) has been treated by proton pump inhibitors (PPIs) with an uncertain success rate.

***AIM***

To shed light the current therapeutic strategies used for LPRD in order to analysis the rationale in the LPRD treatment.

***METHODS***

Three authors conducted a PubMed search to identify papers published between January 1990 and February 2019 about the treatment of LPRD. Clinical prospective or retrospective studies had to explore the impact of medical treatment(s) on the clinical presentation of suspected or confirmed LPRD. The criteria for considering studies for the review were based on the population, intervention, comparison, and outcome framework.

***RESULTS***

The search identified 1355 relevant papers, of which 76 studies met the inclusion criteria, accounting for 6457 patients. A total of 64 studies consisted of empirical therapeutic trials and 12 were studies where authors formally identified LPRD with pH-monitoring or multichannel intraluminal impedance-pH monitoring (MII-pH). The main therapeutic scheme consisted of once or twice daily PPIs for a duration ranged from 4 to 24 wk. The most used PPIs were omeprazole, esomeprazole, rabeprazole, lansoprazole and pantoprazole with a success rate ranging from 18% to 87%. Other composite treatments have been prescribed including PPIs, alginate, prokinetics, and H2 Receptor antagonists.

***CONCLUSION***

Regarding the development of MII-pH and the identification of LPRD subtypes (acid, nonacid, mixed), future studies are needed to improve the LPRD treatment considering all subtypes of reflux.

**Key words**: Laryngopharyngeal; Reflux; Laryngitis; Treatment; Proton pump inhibitors

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**Core tip:** The treatment of laryngopharyngeal reflux disease (LPRD) has not changed since three decades and it is based on proton pump inhibitors (PPIs). However, the superiority of PPIs over placebo is still controversial and there are a significant number of non-responder patients to treatment. The development of multichannel intraluminal pH impedance monitoring led to the identification of subtypes of LPRD including acid, nonacid and mixed LPRD. The treatment of each subtype could be different in order to have better response rate.

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**INTRODUCTION**

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastric or duodenal content reflux, which induces morphological changes in the upper aerodigestive tract[1]. LPR-related symptoms concern approximately 4 to 10% of outpatients visiting Otolaryngology–Head and Neck Surgery Departments[2] and up to 50% of patients in Division of Laryngology[3]. To date, several controversies persist about the diagnostic and the therapeutic management of LPRD. Although proton pump inhibitors (PPIs) are considered as the main treatment of LPRD since many decades[4], the superiority of PPIs over placebo is still controversial[5]. Thus, more than 40% of patients have less or no symptom relief with an empirical therapeutic trial based on PPIs[5,6]. The aim of this systematic review is to shed light the current therapeutic strategies used for the management of LPRD in order to analysis the rationale in the treatment of LPRD.

**MATERIALS AND METHODS**

The criteria for considering studies for the review were based on the population, intervention, comparison, and outcome framework[7].

***Types of studies***

Clinical prospective or retrospective studies published in peer-reviewed journals were included. Studies had to explore the impact of medical treatment(s) on the clinical presentation of suspected or confirmed LPRD. Only studies published in English literature were included.

***Participants, inclusion/exclusion criteria***

Papers were included if they attempted rigorous diagnosis of LPRD through symptoms, exam findings, or objective testing. Patients with positive pH-monitoring or multichannel intraluminal impedance-pH monitoring (MII-pH) were considered as “LPRD patients”; those with a clinical diagnosis based on symptoms ± findings were considered as “suspected LPRD patients”. Studies focusing on patients who did not respond to treatment were not included.

***Outcomes***

The primary outcome was review of types and effectiveness of treatment administered to LPRD patients. The secondary outcome was based on the above to define a rational approach to the management of LPRD.

***Intervention and comparison***

Authors had to treat their patients with conventional medical treatment including PPIs, prokinetics, histamine H2-receptor antagonists (H2R), alginate, magaldrate, baclofen and other drugs that have been reported at least once as treatment of LPRD or gastroeosophageal reflux disease (GERD). Diet and behavioral changes have also been considered as treatment. Studies that reported patients treated with surgery were carefully excluded. The studies had to clearly describe the therapeutic scheme, *i.e.*, drug(s), doses and potential association of drug(s) with other therapeutic approaches (speech and swallowing therapies, *etc.*).

***Search strategy***

Lechien JR, Barillari MR, and Calvo-Henriquez C conducted a PubMed search to identify papers published between January 1990 and February 2019. Studies were screened if they had database abstracts, available full texts or titles referring to the condition. The following keywords were used: “laryngopharyngeal reflux”; “reflux laryngitis”; “gastroesophageal reflux”; “treatment”; and “therapeutic”. These investigators provided a critical analysis of the publication’s content and summarized the data of the selected papers in the publication in order to determine final article selection.

**RESULTS**

The search identified 1355 relevant papers, of which 76 studies met the inclusion criteria, accounting for 6457 patients. A total of 64 studies consisted of empirical therapeutic trials (Table 1)[8-72], and 12 were studies where authors formally identified LPRD with pH-monitoring (*n* = 10) or MII-pH (*n* = 2) (Table 2)[40,56,60,73-83].

The main therapeutic scheme consisted of once or twice daily PPIs (*n* = 63) for a duration ranged from 4 to 24 wk. The most used PPIs were omeprazole, esomeprazole, rabeprazole, lansoprazole and pantoprazole (Table 3). The efficacy of these treatments was reported in the majority of studies using different outcomes, yielding the comparison between studies difficult (Tables 1 and 2). Overall, authors reported a success rate with PPI therapy ranging from 18% to 87%. Other composite treatments have been prescribed including PPIs, alginate, prokinetics, and H2R antagonists (Table 4).

**DISCUSSION**

LPRD has been defined as a different entity other than GERD in the end of the nineties[84]. Since then, the number of clinical studies dedicated to the treatment of LPRD have progressively increased[1]. This review has shown that the most preferred treatment for LPRD is still the administration of once or twice daily PPIs. This therapeutic approach is however associated with an uncertain success rate and, depending of the therapeutic outcomes used, a significant number of patients are found to be resistant to treatment. According to a recent systematic review, the non-response rate would be close to 40% of patients[85]. The critical analysis of the different therapeutic schemes and their related success rate has to consider the respective pharmacological properties of the drugs used.

***PPIs***

PPI decreases the H+ gastric secretion by covalent binding with H+/K+ ATPase. The inhibition of proton pump increases the pH of the gaseous refluxate droplets and limits the extracellular activity of pepsin on upper aerodigestive tract tissues[86]. From a pathophysiological standpoint, PPIs have no impact on the intracellular activity of pepsin[87], and a low impact on the activity of trypsin and non-conjugated bile salts, which could injure the laryngopharyngeal mucosa in a nonacid environment[88,89]. Moreover, the PPI intake does not change the total number of daily reflux episodes[90].

This review shows that the doses and administration frequency of PPIs varies from one to another study. PPIs have a short half-life (90 min) and an oral unique dose of 20 mg inhibits 70% of the pump enzymes[91]. In practice, the half-life of the inhibition of gastric acid secretion lasts an estimated 24 h. Approximately 20% of proton pumps are newly synthesized over a 24-h period with greater pump synthesis at night than during the day. With regard to the 90 min blood half-life of PPI, the addition of bedtime administration will not add to inhibition of nocturnal acid breakthrough, because the drug will have disappeared by the time nighttime acid secretion is evident. Assuming that about 70% of pumps are activated by breakfast and that the PPI is given 30 to 60 min beforehand, it can be calculated that steady state inhibition on once-a-day dosing is about 66% of maximal acid output. In other words, and regarding the pharmacological properties of the drug, increasing the dose has virtually no effect once optimal dosage has been reached. However, increasing the dose frequency does have some effect; a morning dose and an evening dose before meals results in about 80% inhibition of maximal acid output[91,92]. Thus, twice daily PPI could be better because a more complete control of both daytime and nocturnal esophageal acid exposure[93]. In LPRD literature, only the study by Park *et al*[28] compared once *vs* twice daily PPIs in LPRD. These authors suggested a superiority of twice daily *vs* once daily PPI(s), which seems to be in accordance with the pharmacological properties of PPIs[28,93]. Pharmacologically, the use of twice daily 20 mg PPIs could be the most effective approach in order to inhibit the acid secretion but, as mentioned above, this approach has low effect on nonacid or weakly acid LPRD variants.

***Histamine H2R***

PPIs have been associated with H2R in four studies[28,66,70,72]. In comparison with twice daily PPIs, the use of H2R does not make sense regarding their short duration of action (6 to 12 h)[94,95]. The studies comparing the efficacy of PPIs *vs* H2R + PPIs did not report a clinical evidence of the use of H2R in LPRD[28,72]. Moreover, the association of once daily PPI with ranitidine at bedtime being more expensive approach than 6-mo twice daily PPIs[66].

***Prokinetics***

The addition of prokinetics to PPIs is still controversial in GERD[96], despite their role in the increase of the esophageal sphincter pressure[94,97,98]. Six studies showed interest in the role of prokinetics for the management of LPRD[17,38,48,51,57,79] and these authors reported mixed evidence about the superiority of PPIs and prokinetics over PPIs alone[99]. Precisely, two RCTs suggested that the addition of prokinetics to PPI(s) would be associated with better symptom improvement[38,51], while the study by Hunchaisri *et al*[48] did not find similar findings. The controversy about the efficacy of prokinetics in LPRD illustrates the lack of evidence in the occurrence of esophageal dysmotility disorder in this condition[100,101].

***Alginate and magaldrate***

The development of MII-pH led to the identification of new subtypes of LPRD, being acid, weakly acid, mixed and nonacid LPRD. In that way, three recent studies found that the majority of patients have in fact nonacid or mixed LPRD[102-104]. The pathophysiological mechanisms of nonacid and mixed LPRD are still unknown but they could involve the activity of trypsin, conjugated and non-conjugated bile salts in the mucosa of the upper aerodigestive tract[1,105]. Precisely, non-conjugated bile salts and trypsin are effective in pH above 6.0 while conjugated bile salts are more effective in acid environment. Consequently, the use of alginate or magaldrate could make sense in the primary management of LPRD.

Alginates form a raft floating over gastric contents that can be maintained within the stomach for up to 4 h. Gaviscon is endowed with bio-adhesive potential, a property due primarily to its polymer chain length and ionizable groups that provides a protective biofilm on the mucosa of esophagus and, potentially, upper aerodigestive tract[106]. Interestingly, these drugs are able to reduce the number of acid reflux events[94,107].

In practice, McGlashan *et al*[34] have demonstrated the superiority of alginate over placebo in the treatment of LPRD patients. More recently, Wilkie *et al*[69] found that a treatment based on the single use of alginate is quite competitive with a treatment combining PPIs and alginate. Our recent results also support that the addition of alginate or magaldrate to PPIs seems to significantly improve symptoms in patients with mixed and nonacid LPRD[102].

***Diet and behavioral changes***

Diet and behavioral changes remain the first therapeutic step of the LPRD treatment. Additionally, this approach is the best cost-effective empirical treatment for patients with mild LPRD. In practice, patients who respect diet and behavioral changes have better symptom improvement than those who did not respect diet[108]. Furthermore, recent studies suggested that a well-conducted diet could be as efficiently as PPI treatment[65,70].Alkaline, protein, low-fat and low-acid diet is effective because these types of foods are well digested, also decreasing the number of transient relaxations of esophageal sphincters and thereby the related number of LPRD episodes.

***Perspectives***

The development of MII-pH as diagnostic tool is an important step in the improvement of daily clinical practices related to LPRD. MII-pH studies showed that there are a large number of patients with nonacid or mixed LPRD, which are both less controlled by conventional PPI therapy. It is highly likely that a significant part of the patients who were called “resistant LPRD patients” within the three last decades, had nonacid or mixed LPRD. With regard to the properties of anti-reflux drugs, alginate is a future candidate as single drug or additional drug to PPIs in the future studies. The concomitant use of twice daily PPIs and twice or thrice daily alginate or magaldrate could provide a consistent protection against the mucosal irritation of pepsin, trypsin and bile salts. Naturally, the administration of diet and behavioral changes is still required in all patients in order to improve the treatment efficacy. According to a recent management algorithm of LPRD (Figure 1)[1], MII-pH testing could be used as diagnostic and therapeutic control tool, providing better identification of the LPRD subtypes and better treatment. Because the compliance of LPRD patients to medical treatment and diet can be poor, the administration of a personalized treatment based on the patient MII-pH results and the lifestyle habits could improve the patient compliance to LPRD treatment.

**Article Highlights**

***Research background***

For a long time, laryngopharyngeal reflux disease (LPRD) has been treated by proton pump inhibitors (PPIs) with an uncertain success rate.

***Research motivation***

The low success rate of PPIs as well as the cost of unsuccessful empirical therapeutic trials are important in otolaryngology. Many treatments of LPRD exist and we want to provide an analysis of the current therapeutic approach of this prevalent disease.

***Research objectives***

To shed light the current therapeutic strategies used for LPRD in order to analysis the rationale in the LPRD treatment.

***Research methods***

Three authors conducted a PubMed systematic review respecting PRISMA statements.

***Research results***

The majority of studies consists of empirical therapeutic trials using PPIs as single drug. The success rate of PPIs ranges from 18% to 87% and there is an important heterogeneity between studies according to the diagnostic, the therapeutic outcomes and the duration of treatment.

***Research conclusions***

The majority of treatments in LPRD are empirical and based on PPIs. The empirical therapeutic trial with PPIs is however associated with an uncertain success rate.

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**Table 1 Empirical therapeutic trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **References** | **Design** | **EL** | **Characteristics** | **Outcomes** | **Treatment** |
| Hanson *et al*[8], 1995 | Pros Uncontr | IIIb | Suspected LPR (*n* = 141) | Symptom and sign resolution: 51% | 4 wk omeprazole (20 mg, 1/d) and diet |
| Jaspersen *et al*[9], 1996 | Pros Uncontr | IIIb | Suspected LPR (*n* = 21) | Laryngeal sign improvement: 100% | 4 wk omeprazole (40 mg, 1/d) |
| Shaw *et al*[10], 1997  | Pros Uncontr | IIIb | Suspected LPR (*n* = 96) | Pre to post-score improvement: + | 12 wk omeprazole (20 mg/d) |
| Wo *et al*[11], 1997  | Pros Uncontr | IIIb | Suspected LPR (*n* = 21) | Pre to post-score improvement: + | 8 wk omeprazole (40 mg, 1/d) and diet |
| Metz *et al*[12], 1997  | Pros Uncontr | IIIb | Suspected LPR (*n* = 10) | Symptom and sign resolution: 60% | 4 wk omeprazole (20 mg/d) |
| Habermann *et al*[13], 1999  | Pros Uncontr | IIIb | Suspected LPR (*n* = 29) | Pre to post-score improvement: + | 6 wk pantoprazole (40 mg/d) |
| Havas *et al*[14], 1999 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 7) | Pre to post-score improvement: + | Gr1-2: 12 wk placebo/lanzoprazole (30 mg 2/d) and Diet |
| Gr2: suspected LPR (*n* = 8) |
| El-Serag *et al*[15], 2001  | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 10) | 54% of symptom resolution | Gr1-2: 12 wk placebo/lansoprazole (30 mg 2/d) |
| Gr2: suspected LPR (*n* = 10) |
| Langevin *et al*[16], 2001 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 14) | Pre to post-score improvement | Gr1-2: 12 wk placebo/omeprazole (40 mg/d) |
| Gr2: suspected LPR (*n* = 16) |
| Hamdan *et al*[17], 2001  | Pros Uncontr | IIIb | Suspected LPR (*n* = 22) | Pre to post-score improvement: + | 4 wk pantoprazole (40 mg, 2/d), cisapride (20 mg, 2/d) and diet |
| Rodríguez-Téllez *et al*[18], 2002  | Pros Uncontr | IIIb | Suspected LPR (*n* = 21) | Pre to post-score improvement: + | 12 wk omeprazole (20 mg, 2/d) |
| Habermann *et al*[19], 2002  | Pros Uncontr | IIIb | Suspected LPR (*n* = 24) | Pre to post-score improvement: + | 6 wk pantoprazole (40 mg/d) |
| DelGaudio *et al*[20], 2003  | Pros Uncontr | IIIb | Gr1: LPR responder (*n* = 19) | 50% symptom improvement: 63% | 8 wk esomeprazole (40 mg 1/d) and diet |
| Bilgen *et al*[21], 2003 | Pros Contr | IIIb | Gr1: suspected LPR (*n* = 36) | Improvement of ≥ 1-point RSI and RFS: 68% | 24 wk lansoprozole (30 mg, 2/d) and diet |
| Gr2: CT (*n* = 23) |
| Garrigues *et al*[22], 2003 | Pros Uncontr | IIIb | Suspected LPR (*n* = 91) | Symptom improvement/resolution: 86-41% | 24 w omeprazole (20 mg, 2/d) |
| Laryngoscopic sign resolution: 83% |
| Beaver *et al*[23], 2003  | Pros Uncontr | IIIb | Suspected LPR (*n* = 49) | Pre to post-LPR sign score improvement: +1 | 6 wk lansoprazole (30 mg, 2/d) or pantoprazole (40 mg, 2/d) or Omeprazole/Rabeprazole (20 mg, 2/d) |
| Siupsinskiene *et al*[24], 2003  | Pros Contr | IIb | Gr1: suspected LPR (*n* = 113) | Symptom improvement of Gr1: 65% | Gr1-2: 5 wk omeprazole (20 mg, 1-2/d) and diet |
| Gr2: healthy (*n* = 113) |
| Williams *et al*[25], 2004  | Pros Uncontr | IIIb | Suspected LPR (*n* = 20) | Improvement of ≥ 1-point level LGS: 63% | 12 wk omeprazole (20 mg, 3/d) and diet |
| Improvement of symptom score: 40%-45% |
| Issing *et al*[26], 2004  | Pros Uncontr | IIIb | Suspected LPR (*n* = 22) | Improvement of symptom score: + | 8 wk esomeprazole (20 mg, 2/d) |
| Sereg-Bahar *et al*[27], 2005 | Pros Uncontr | IIIb | Suspected LPR (*n* = 43) | Pre to post-RFS improvement: +1 | 8 wk esomeprazole (40 mg/d) and diet |
| Park *et al*[28], 2005 | Pros Contr | IIb | Gr1: suspected LPR (*n* = 30) | Symptom improvement (Gr1-2):68%-46% | Gr1: 16 wk lansoprazole (30 mg, 2/d) and diet |
| Gr2: suspected (*n* = 30) | Sign improvement (Gr1-2): 50%-18% | Gr2: Omeprazole (20 mg, 2/d) and ranitidine (300 mg/d) and diet |
| Gr3: suspected (*n* = 25) |  | Gr3: esomeprazole (40 mg, 1/d) and diet |
| Vaezi *et al*[29], 2006 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 95) | Symptom resolution: 15% | Gr1-2: 16 wk placebo/esomeprazole (40 mg, 2/d) |
| Gr2: suspected LPR (*n* = 50) |
| Dore *et al*[30], 2007 | Pros Uncontr | IIIb | Suspected LPR (*n* = 266) | Symptom improvement/resolution: 68%-12% | 12 wk rabeprazole/pantoprazole (20 mg, 2/d), and diet or esomeprazole (20 mg, 2/d) or lanzoprazole (30 mg, 2/d),  |
| Qua *et al*[31], 2007 | Pros Contr | IIIb | Suspected LPR (*n* = 32) | Gr1-2: Symptom improvement: 67%-18% | 8 wk lanzoprazole (30 mg, 2/d) |
| Gr1: GERD (*n* = 21) | Gr1-2: LGS improvement: 86%-36% |
| Gr2: non-GERD (*n* = 11) |  |
| Oridate *et al*[32], 2008 | Pros Uncontr | IIIb | Suspected LPR (*n* = 52) | > 50% improvement of RSI and GERD: 50%-78% | 9 wk rabeprazole (20 mg/d) |
| Pre to post-improvement of DLS: + |
| Reichel *et al*[33], 2008 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 30) | RSI improvement: 78% | Gr1-2: 12 wk placebo/esomeprazole (20 mg, 2/d) |
| Gr2: suspected LPR (*n* = 28) |
| McGlashan *et al*[34], 2009 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 24) | Pre to post-RSI improvement | Gr1-2: 24 wk placebo/gaviscon (4/d) and diet |
| Gr2: suspected LPR (*n* = 25) |
| Vashani *et al*[35], 2010 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 16) | Pre to post-RSI improvement: + | Gr1: 6 wk voice therapy + Omeprazole (20 mg, 2/d) |
| Gr2: suspected LPR (*n* = 16) |   | Gr 2: Placebo (2/d) |
| Fass *et al*[36], 2010 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 24) | Pre to post-symptom improvement: + | Gr1-2: 12 wk placebo/esomeprazole (20 mg, 2/d) and diet |
| Gr1: suspected LPR (*n* = 17) | Pre to post-RFS improvement: - |
| Lam *et al*[37], 2010 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 42) | Pre to post-RSI and RFS improvement: + | Gr1-2: 18 wk placebo/rabeprazole (20 mg, 2/d) and diet |
| Gr2: suspected LPR (*n* = 40) |   |
| Ezzat *et al*[38], 2011 | Placebo RCT | Ib | Gr1: suspected LPR (*n* = 42) | RFS improvement (Gr1-2): 48%-20% | Gr1-2: 8 wk pantoprazole (40 mg/d) and itopride (50 mg, 3/d) |
| Gr2: suspected LPR (*n* = 45) | Pre to post-symptom improvement: + | /Pantoprazole and placebo and diet  |
| Chiba *et al*[39], 2011 | Pros Uncontr | IIIb | Suspected LPR (*n* = 27) | Pre to post-GERD Score improvement: + | 8 wk lanzoprazole (30 mg/d) or rabeprazole (10 mg/d) |
| Friedman *et al*[40], 2011 | Retrospective | IV | Gr1: LPR (*n* = 73) | Improvement of main complaint Gr1-2: 49%-41% | 24 wk PPI (20 or 40 mg, 2/d) |
| Gr2: suspected LPR (*n* = 70) | Resolution of main complaint Gr 1-2: 14%-3% |
| Lee *et al*[41], 2011 | Pros Uncontr | IIIb | Suspected LPR (*n* = 455) | Reduction of > 50% of RSI: 75% | 12 wk rabeprazole (10/20 mg/d) and diet |
| Masaany *et al*[42], 2011 | Pros Uncontr | IIIb | Suspected LPR (*n* = 47) | Reduction of ≥ 10-point of RSI: 79% | 16 wk pantoprazole (40 mg, 2/d) |
| Naiboglu *et al*[43], 2011 | Pros Uncontr | IIIb | Suspected LPR (*n* = 50) | Pre to post-RSI and RFS improvement: + | 12 wk lansoprazole (30 mg/d) and diet |
| Patigaroo *et al*[44], 2011 | Pros Uncontr | IIIb | Suspected LPR (*n* = 50) | Pre to post-RSI and RFS improvement: + | 16 wk esomeprazole (20 mg, 2/d)/pantoprazole (40 mg/d) |
| Lansoprazole (30 mg, 2/d) |
| Habermann *et al*[45], 2012 | Pros Uncontr | IIIb | Suspected LPR (*n* = 1044) | Pre to post-RSI and RFS improvement: + | 12 wk pantoprazole (20 or 40 mg, 2/d) |
| Park *et al*[46], 2012 | Pros Contro | IIIb | Gr1: suspected LPR (*n* = 50) | Reduction of ≥ 5-point of RSI Gr1-2:46-68% | Gr1: 12 wk omeprazole (20 mg, 2/d)  |
| Gr2: suspected LPR (*n* = 50) | Reduction of ≥ 3-point of RFS Gr1-2:18-50% | Gr2: Omeprazole + voice therapy |
| Becker *et al*[47], 2012 | Pros Uncontr | IIIb | Suspected LPR (*n* = 30) | Reduction of RSI: 20% | 12 wk pantoprazole (40 mg, 2/d) |
| Hunchaisri *et al*[48], 2012 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 32) | RSI reduction: 73% | Gr1: 12 wk domperidone (10mg, 3/d) and omeprazole (20 mg, 2/d) and diet |
| Gr2: suspected LPR (*n* = 33) | > 50% of RSI reduction: 67% | Gr2: Omeprazole (20 mg, 2/d) and diet |
| Chung *et al*[49], 2012 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 22) | Pre to post-RSI and RFS improvement: + | Gr1: 8 wk Lanzoprazole (30 mg/d) |
| Gr2: suspected LPR (*n* = 20) |   | Gr2: Lanzoprazole + SGB  |
| Oridate *et al*[50], 2012 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 60) | Pre to post-RFS improvement: - | Gr 1: 4 wk rabeprazole (10 mg/d) |
| Gr2: suspected LPR (N=13) |  | Gr 2: No treatment |
| Chun *et al*[51], 2013 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 32) | Pre to post-RSI and RFS improvement: + | Gr1: 12 wk lanzoprazole (30 mg/d) |
| Gr2: suspected LPR (*n* = 29) |   | Gr2: Lanzoprazole and itopride (50 mg 3/d) |
| Beech *et al*[52], 2013 | Pros Uncontr | IIIb | Suspected LPR (*n* = 74) | Reduction of ≥ 1-point of RSI: 71% | 24 wk lansoprazole (30 mg 2/d) and diet |
| Improvement of pre to post-VSS: + |
| Vailati *et al*[53], 2013 | Pros Uncontr | IIIb | Suspected LPR (*n* = 22) | Reduction of ≥1-point of RSI: 59% | 12 wk pantoprazole (40 mg, 2/d) |
| Lee *et al*[54], 2014 | Pros Uncontr | IIIb | Suspected LPR (*n* = 180) | Pre to post-RSI and RFS improvement: + | 12 wk lansoprazole (15 mg, 2/d) and diet |
| Chappity *et al*[55], 2014 | RCT | IIb | Gr1: suspected LPR (*n* = 117) | Pre to post-score improvement: + | Gr1: 12 wk omeprazole (20 mg, 2/d) and diet |
| Gr2: suspected LPR (*n* = 117) | Gr2: Diet |  |
| Wan *et al*[56], 2014 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 35) | Pre to post-RSI and RFS improvement: + | 4 wk esomeprazole (20 mg, 2/d) and diet |
| Gr2: LPR (*n* = 23) |  |
| Semmanaselvan *et al*[57], 2015 | Pros Uncontr | IIIb | Suspected LPR (*n* = 50) | Reduction of ≥ 1-point of RSI/RFS: 87%-98% | 12 wk rabeprazole (20 mg/d) and domperidone (30 mg/d) |
| Ozturan *et al*[58], 2016 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 65) | Pre to post-RSI and RFS improvement: + | 8 wk esomeprazole, (20 mg, 2/d) and diet |
| Gr2: Control (*n* = 35) |   |
| Gupta *et al*[59], 2016 | Retrospective | IV | Suspected LPR (*n* = 188) | Pre to post-RSI and RFS improvement: + | 10 wk PPIs (2/d) |
| Nennstiel *et al*[60], 2016 | Retrospective | IV | Gr1: LPR (*n* = 21) | Symptom VAS improvement: 60% | 12 wk pantoprazole (40 mg, 2/d) and diet |
| Cross-sectional |  | Gr2: suspected LPR (*n* = 24) |   |  |
| Batıoğlu-Karaaltın *et al*[61], 2016 | Pros Uncontr | IIIb | Suspected LPR (*n* = 84) | Reduction of ≥ 1-point of RSI/RFS: 21%-56% | 12 wk lansoprazole (30 mg, 2/d) |
| Dulery *et al*[62], 2016 | Pros Uncontr | IIIb | Suspected LPR (*n* = 24) | Symptom resolution: 10% | 8 wk esomeprazole (40 mg, 2/d) |
| Joshi *et al*[63], 2017 | Pros Uncontr | IIIb | Suspected LPR (*n* = 100) | Pre to post-RSI and RFS improvement: + | 24 wk omeprazole (20 mg, 2/d) and diet |
| Pullarat *et al*[64], 2017 | Pros Uncontr | IIIb | Suspected LPR (*n* = 30) | Pre to post-RSI and RFS improvement: + | 8 wk pantoprazole (40 mg/d) |
| Zalvan *et al*[65], 2017 | Retrospective | IV | Gr1: suspected LPR (*n* = 85) | Reduction of ≥ 6-points of RSI Gr1-2: 54-63% | Gr1: 6 wk PPI (1 or 2/d) and diet |
| Gr2: suspected LPR (*n* = 99) |  | Gr2: Diet |
| Carroll *et al*[66], 2017 | Retrospective | IV | Suspected LPR (*n* = 97) | RSI < 13: 49% | 12 wk omeprazole (40 mg/d) and ranitidine (300 mg/d) |
| Lechien *et al*[67], 2018 | Pros Uncontr | IIIb | Suspected LPR (*n* = 80) | Post-therapy RSI < 13 and RFS < 7: 74% | 12 wk pantoprazole (20 mg, 2/d) and diet |
| Mozzanica *et al*[68], 2018 | Pros Uncontr | IIIb | Suspected LPR (*n* = 34) | Pre to post-RSI, RFS, VoiSS improvement: + | 8 wk omeprazole (20 mg, 2/d) and diet |
| Wilkie *et al*[69], 2018 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 39) | Reduction of RSI: 94% | Gr1: 12 wk gaviscon advance (4/d) and diet |
| Gr2: suspected LPR (*n* = 33) | Pre to post-RSI improvement: - | Gr2: Gaviscon (4/d) and PPI (NA) and diet |
| Yang *et al*[70], 2018 | Retrospective | IV | Suspected LPR (*n* = 105) | Reduction of ≥ 1-point of RSI: 91% | 8 wk PPI (40 mg/d) ± H2 blocker (300 mg/d) and diet |
| Kirti *et al*[71], 2018 | Pros Uncontr | IIIb | Suspected LPR (*n* = 80) | Unblinded RFS < 7: 95% | 8 wk PPI (2/d) and diet |
| Suzuki *et al*[72], 2019 | Pros Contro | IIb | Gr1: suspected LPR (*n* = 20) | Pre to post-RSI, RFS improvement: + | Gr1: 8 wk esomeprazole (20 mg/d)  |
| Gr2: suspected LPR (*n* = 20) |   | Gr2: 8 wk famotidine (20 mg/d) |

1No statistical analysis. CT: Control; DLS: Dysmotility-like symptoms; GERD: Gastroeosophageal reflux disease; GI: Gastrointestinal; Gr: Group; LGS: Laryngitis grading system; LPR: Laryngopharyngeal reflux; PPI: Proton pump inhibitor; Pros Contr: Prospective controlled study; Pros Uncontr: Prospective uncontrolled study; RCT: Randomized controlled trial; RFS: Reflux finding score; RSI: Reflux symptom index; VAS: Visual analog scale; VoiSS: Voice symptom scale; VSS: Voice subjective score.

**Table 2 Studies that identified LPRD with objective diagnostic tools**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **References** | **Design** | **EL** | **Characteristics** | **Outcomes** | **Treatment** |
| Noordzij *et al*[73], 2001  | Placebo RCT | Ib | Gr1: LPR (*n* = 15); Gr2: LPR (*n* = 15) | Pre to post-symptom improvement: +; Pre to post-sign improvement: - | Gr1-2: 8 wk placebo/omeprazole (40 mg, 2/d)  |
| Belafsky *et al*[74], 2001 | Pros Uncontr | IIIb | LPR (*n* = 39) | Pre to post-RSI and RFS improvement: + | 24 wk omeprazole/rabeprazole (20 mg, 2/d) or lansoprazole (30 mg, 2/d) and diet |
| Belafsky *et al*[75], 2002 | Pros Uncontr | IIIb | LPR (*n* = 25) | Pre to post-RSI improvement: + | 26 wk PPIs (2/d) and diet |
| Eherer *et al*[76], 2003 | Placebo RCT | Ib | Gr1: LPR (*n* = 7); Gr2: LPR (*n* = 7) | Symptom/sign improvement: 80%-100% | Gr1-2: 12 wk placebo/pantoprazole (40 mg, 2/d) |
| Steward *et al*[77], 2004 | Placebo RCT | Ib | Gr1: LPR (*n* = 21); Gr2: LPR (*n* = 21) | Symptom improvement: 53% | Gr1-2: 8 wk placebo/rabeprazole (20 mg 2/d) and diet |
| Wo *et al*[78], 2006 | Placebo RCT | Ib | Gr1: LPR (*n* = 19); Gr2: LPR (*n* = 20) | Symptom improvement: 40% | Gr1-2: 12 wk placebo/pantoprazole (40 mg/d) |
| Jin *et al*[79], 2008 | Pros Uncontr | IIIb | LPR (*n* = 40) | Pre to post-RSI and RFS improvement: + | 20 wk lansoprazole (30 mg/d) and mosapride (5 mg, 3/d) or levosulpride (25 mg, 3/d) |
| Friedman *et al*[40], 2011 | Retrospective | IV | Gr1: LPR (*n* = 73); Gr2: suspected LPR (*n* = 70) | Improvement of main complaint Gr1-2: 49%-41%; Resolution of main complaint Gr 1-2: 14%-3% | 24 wk PPI (20 or 40 mg, 2/d) and diet |
| Lien *et al*[80], 2013 | Pros Contr | IIIb | Gr1: GERD and LPR (*n* = 65); Gr2: LPR (*n* = 42) | Reduction of > 50% of RSI (Gr1-2): 63%-17% | 12 wk esomeprazole (40 mg, 2/d) and diet |
| Wan *et al*[56], 2014 | Pros Contr | IIb | Gr1: suspected LPR (*n* = 35); Gr2: LPR (*n* = 23) | Pre to post-RSI and RFS improvement: + | 4 wk esomeprazole (20 mg, 2/d) and diet |
| Waxman *et al*[81], 2014 | Retrospective | IV | LPR (*n* = 43) | Reduction of ≥ 1-point of RSI: 67% | 4 wk omeprazole (40 mg, 2/d) |
| Nennstiel *et al*[60], 2016 | Retrospective | IV | Gr1: LPR (*n* = 21); Gr2: suspected LPR (*n* = 24) | Symptom VAS improvement: 60% | 12 wk pantoprazole (40mg, 2/d) and diet |
| Cross-sectional |
| Tseng *et al*[82], 2018 | Placebo RCT | Ib | Gr1: LPR (*n* = 39); Gr2: LPR (*n* = 40) | Pre to post-RSI and RFS improvement: + | Gr1-2: 8 wk alginate/placebo and diet |
| Agrawal *et al*[83], 2018 | Pros Uncontr | IIIb | LPR (*n* = 33) | Reduction of > 50% of RSI: 45% | 8-12 wk omeprazole and diet |

GERD: Gastroeosophageal reflux disease; Gr: Group; LPR: Laryngopharyngeal reflux; PPI: Proton pump inhibitor; Pros Contr: Prospective controlled study; PROS Uncontr: Prospective uncontrolled study; RCT: Randomized controlled trial; RFS: Reflux finding score; RSI: Reflux symptom index; VAS: Visual analog scale.

**Table 3 Proton pump inhibitor therapeutic schemes used in the current literature**

|  |  |
| --- | --- |
| **Drugs and duration** | **Study numbers** |
| 4-5 wk  |
| Omeprazole 40mg 1/d | 1 |
| Omeprazole 20mg 1/d | 3 |
| Omeprazole 40mg 2/d | 1 |
| Esomeprazole 20mg 2/d | 2 |
| Rabeprazole 10mg 1/d | 1 |
| 6-7 wk |
| Pantoprazole 40mg 2/d | 1 |
| Pantoprazole 40mg 1/d | 2 |
| Lansoprazole 30mg 2/d | 1 |
| Omeprazole 20mg 2/d | 2 |
| 8-9 wk |
| Omeprazole 40mg 1/d | 1 |
| Omeprazole 20mg 2/d | 1 |
| Omeprazole 40mg 2/d | 1 |
| Esomeprazole 40mg 2/d | 1 |
| Esomeprazole 40mg 1/d | 2 |
| Esomeprazole 20mg 2/d | 2 |
| Esomeprazole 20mg 1/d | 1 |
| Lansoprazole 30mg 2/d | 1 |
| Lansoprazole 30mg 1/d | 2 |
| Rabeprazole 20mg 1/d | 1 |
| Rabeprazole 20mg 2/d | 1 |
| Rabeprazole 10mg 1/d | 1 |
| Pantoprazole 40mg 1/d | 2 |
| 12 wk |
| Omeprazole 40mg 1/d | 1 |
| Omeprazole 20mg 3/d | 1 |
| Omeprazole 20mg 2/d | 4 |
| Omeprazole 20mg 1/d | 1 |
| Esomeprazole 20mg 2/d | 3 |
| Esomeprazole 40mg 2/d | 1 |
| Lansoprazole 30mg 2/d | 4 |
| Lansoprazole 15mg 2/d | 1 |
| Rabeprazole 20mg 2/d | 1 |
| Rabeprazole 10mg 1/d | 1 |
| Pantoprazole 20 mg 2/d | 3 |
| Pantoprazole 40 mg 1/d | 1 |
| Pantoprazole 40 mg 2/d | 6 |
| 16-20 wk |
| Lansoprazole 30 mg 2/d | 2 |
| Esomeprazole 40 mg 2/d | 1 |
| Esomeprazole 40 mg 1/d | 1 |
| Esomeprazole 20 mg 2/d | 1 |
| Rabeprazole 20 mg 2/d | 1 |
| Pantoprazole 40 mg 2/d | 1 |
| Pantoprazole 40 mg 1/d | 1 |
| 24 wk |
| Omeprazole 20 mg 2/d | 2 |
| Omeprazole 20 mg 1/d | 1 |
| Lansoprazole 30 mg 2/d | 3 |

**Table 4 Composite treatments used in the current literature**

|  |  |
| --- | --- |
| **Drugs and duration** | **Study numbers** |
| PPIs and antihistamines |
| Omeprazole 20 mg 2/d and Ranitidine 300 mg/d (16 wk) | 1 |
| Omeprazole 40 mg/d and Ranitidine 300 mg/d (12 wk) | 1 |
| PPIs 40 mg/d and antihistamine 300 mg/d (8 wk) | 1 |
| PPIs and gastroprokinetic |
| Pantoprazole 40 mg 2/d and Cisapride 20 mg 2/d (4 wk) | 1 |
| Pantoprazole 40 mg 1/d and Itopride 50 mg 3/d (8 wk) | 1 |
| Omeprazole 20 mg 2/d and Domperidone 10 mg 3/d (12 wk) | 1 |
| Lansoprazole 30 mg 1/d and Itopride 50 mg 3/d (12 wk) | 1 |
| Rabeprazole 20 mg/d and Domperidone 30 mg/d (12 wk) | 1 |
| Lansoprazole 30 mg 1/d and Mosapride 5 mg 3/d (20 wk) | 1 |
| PPIs and alginate |
| PPIs (NA) and gaviscon 4/d (12 wk) | 1 |
| Aligante 3-4/d (8 wk) | 1 |
| Other |
| Famotidine 20 mg 1/d (8 wk) | 1 |
| Gaviscon 4/d (24 wk) | 1 |
| Gaviscon 4/d (12 wk) | 1 |

NA: Not available; PPIs: Proton pump inhibitors.

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**Figure 1 Personalized therapeutic approach for specific laryngopharyngeal reflux disease subtypes**. In this algorithm, proximal reflux event was defined as an episode that reached two impedance sensors in the hypopharynx or proximal esophagus. Acidic event consisted of a gaseous or liquid reflux with a pH ≤ 4.0 while nonacidic event was a gaseous or liquid reflux with a pH > 4.0. The LPR diagnosis was based on the occurrence of ≥ 1 proximal episode.Acid reflux episode consisted of an episode with pH > 4.0. Nonacid reflux episode consisted of an episode with pH ≤ 4.0. Because there are no guidelines in the definition of acid, nonacid and mixed laryngopharyngeal reflux disease (LPRD) disease, LPRD was defined as acid when the ratio of number of acid reflux episodes/number of nonacid reflux episodes was > 2. LPRD was defined as nonacid when the ratio of number of acid reflux episodes/number of nonacid reflux episodes < 0.5. Mixed reflux consisted of a ratio ranged from 0.51 to 2.0. 1For nonacid LPR, PPIs are not necessary regarding their low efficacy.