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SYSTEMATIC REVIEW

Treatment of laryngopharyngeal reflux disease: A systematic review

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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

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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 H_2 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

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 H_2-receptor antagonists (H_2R), 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 H_2R 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,

Table 1 Empirical therapeutic trials

Ref.	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) Gr2: suspected LPR (n = 8)	Pre to post-score improvement: +	Gr1-2: 12 wk placebo/lanzoprazole (30 mg 2/d) and Diet
El-Serag *et al*[15], 2001	Placebo RCT	Ib	Gr1: suspected LPR (n = 10) Gr2: suspected LPR (n = 10)	54% of symptom resolution	Gr1-2: 12 wk placebo/lansoprazole (30 mg 2/d)
Langevin *et al*[16], 2001	Placebo RCT	Ib	Gr1: suspected LPR (n = 14) Gr2: suspected LPR (n = 16)	Pre to post-score improvement	Gr1-2: 12 wk placebo/omeprazole (40 mg/d)
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) Gr2: CT (n = 23)	Improvement of ≥ 1-point RSI and RFS: 68%	24 wk lansoprozole (30 mg, 2/d) and diet
Garrigues *et al*[22], 2003	Pros Uncontr	IIIb	Suspected LPR (n = 91)	Symptom improvement/resolution: 86-41% Laryngoscopic sign resolution: 83%	24 w omeprazole (20 mg, 2/d)
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) Gr2: healthy (n = 113)	Symptom improvement of Gr1: 65%	Gr1-2: 5 wk omeprazole (20 mg, 1-2/d) and diet
Williams *et al*[25], 2004	Pros Uncontr	IIIb	Suspected LPR (n = 20)	Improvement of ≥ 1-point level LGS: 63% Improvement of symptom score: 40%-45%	12 wk omeprazole (20 mg, 3/d) and diet
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)

[1]No 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.

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.

Table 2 Studies that identified LPRD with objective diagnostic tools

Ref.	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 Cross-sectional	IV	Gr1: LPR (*n* = 21); Gr2: suspected LPR (*n* = 24)	Symptom VAS improvement: 60%	12 wk pantoprazole (40mg, 2/d) and diet
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.

Histamine H_2R

PPIs have been associated with H_2R in four studies[28,66,70,72]. In comparison with twice daily PPIs, the use of H_2R does not make sense regarding their short duration of action (6 to 12 h)[94,95]. The studies comparing the efficacy of PPIs *vs* H_2R + PPIs did not report a clinical evidence of the use of H_2R 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

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.

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.

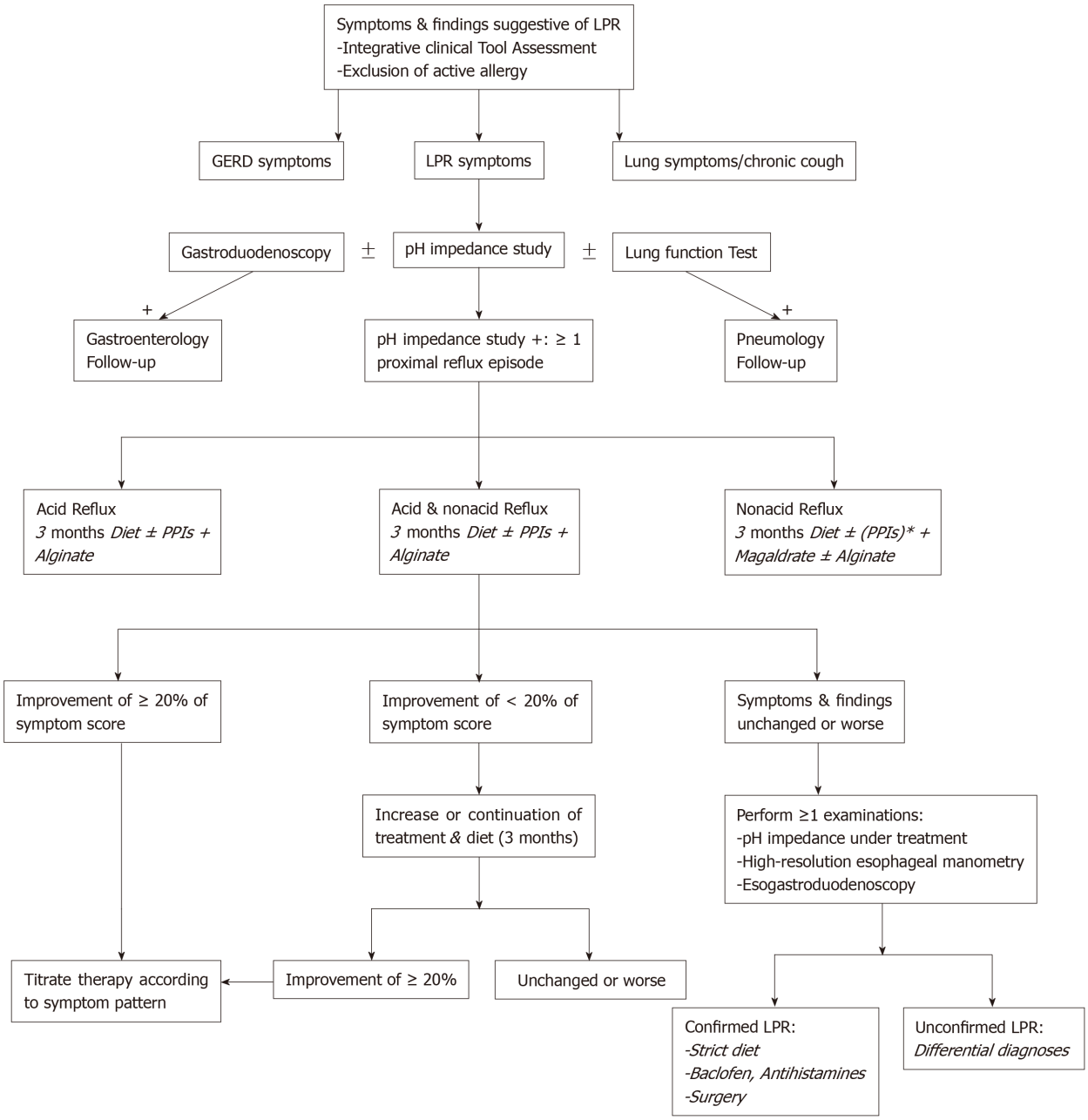

Figure 1 Personalized therapeutic approach for specific laryngopharyngeal reflux disease subtypes. In this algorithm, proximal reflux event was defined as an episode that reached two impedance sensors in the hypopharynx or proximal esophagus. Acidic event consisted of a gaseous or liquid reflux with 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. [1]For nonacid LPR, PPIs are not necessary regarding their low efficacy.

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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