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The management of suspected or confirmed laryngopharyngeal reflux patients with recalcitrant symptoms: A contemporary review

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Abstract

Objective: To summarise current knowledge about the prevalence, aetiology and management of recalcitrant laryngopharyngeal reflux (LPR) patients—those who do not respond to anti-reflux medical treatment.

Methods: A literature search was conducted following the PRISMA guidelines to identify studies that reported success of anti-reflux medical treatment with emphasis on studies that attempted to be rigorous in defining a population of LPR patients and which subsequently explored the characteristics of non-responder patients (ie aetiology of resistance; differential diagnoses; management and treatment). Three investigators screened publications for eligibility from PubMED, Cochrane Library and Scopus and excluded studies based on predetermined criteria. Design, diagnostic method, exclusion criteria, treatment characteristics, follow-up and quality of outcome assessment were evaluated.

Results: Of the 139 articles screened, 45 met the inclusion criteria. The definition of non-responder patients varied substantially from one study to another and often did

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not include laryngopharyngeal signs. The reported success rate of conventional therapeutic trials ranged from 17% to 87% and depended on diagnostic criteria, treatment scheme, definition of treatment failure and treatment outcomes that varied substantially between studies. The management of non-responders differed between studies with a few differential diagnoses reported. No study considered the profile of reflux (acidic, weakly acid, non-acid or mixed) or addressed personalised treatment with the addition of alginate or magaldrate, low acid diet, or other interventions that have emerging evidence of efficacy.

Conclusion: To date, there is no standardised management of LPR patients who do not respond to traditional treatment approached. A diagnostic and therapeutic algorithm is proposed to improve the management of these patients. Future studies will be necessary to confirm the efficacy of this algorithm through large cohort studies of non-responder LPR patients.

Level of evidence: 2a.

1 | INTRODUCTION

Laryngopharyngeal reflux (LPR) is an inflammatory condition of upper aerodigestive tract tissues related to direct and indirect effects of gastroduodenal content reflux, which causes morphological changes in the upper aerodigestive tract.[1] The most prevalent LPR symptoms are globus pharyngeus, hoarseness, cough, throat clearing and post-nasal drip.[2-4] In less than 50% of cases, these complaints are associated with gastro-oesophageal reflux disease (GERD) symptoms such as heartburn and regurgitation. LPR-related symptoms impair quality of life[3,5] and require prolonged treatment, which is associated with a significant cost.[6]

For three decades, an increasing number of publications have described the changes in laryngopharyngeal signs and symptoms when patients with presumed LPR are treated empirically with proton pump inhibitors (PPIs).[7] Treatment success with this approach for LPR is equivocal, and thought to be less than treatment success for typical GERD.[8] Usually, that patients are defined as non-responders (or patients with recalcitrant LPR) if they did not respond to a 6-month therapy.[4,7]

Why patients with presumed LPR do not respond better to PPIs has not been as frequently studied. Relatively little is known about the aetiology of LPR recalcitrant to PPIs, or to what additional therapies might be indicated. The management of non-responder patients varies between studies and remains non-evidence-based.

The first aim of this systematic review is to assess the rate of non-responder suspected or confirmed LPR patients after medical anti-reflux treatment. A second goal is then to characterise the aetiology and management of non-responders. Based on this systematic review of current literature, the authors propose a potential diagnostic and therapeutic algorithm for management of patients with recalcitrant LPR.

Key points

- The success rate of conventional PPI empirical therapeutic trials ranged from 17% to 87% and depended on diagnostic criteria, treatment scheme, definition of treatment failure and treatment outcomes that varied substantially between studies.
- There is no standardised management of LPR patients who do not respond to traditional treatment approached.
- Many digestive, ear, nose and throat conditions associated with LPR are not taken into consideration in the management of non-responder patients and may be detected with additional examinations including oesophageal manometry and GI endoscopy.
- No study considered the profile of reflux (acidic, weakly acid, non-acid or mixed) or addressed personalised treatment with the addition of alginate or magaldrate, low acid diet, or other interventions that have emerging evidence of efficacy.

2 | MATERIALS AND METHODS

This study was performed by the experts of the LPR Study Group of the Young Otolaryngologists of the International Federation of Oto-Rhino-Laryngological Societies (YO-IFOS). The criteria for study selection were based on the population, intervention, comparison and outcome (PICO) framework.

2.1 | Types of studies

Two types of studies have been included in this review of LPR patients. First, in order to study therapeutic response, studies reporting success rate of anti-reflux medical treatment have been included. Second, we included studies that explored the characteristics of resistant patients in at least one of the following categories: aetiology of resistance; potential differential

diagnoses; further management strategies. Papers included were published as original papers in peer-reviewed journals in English or French. Studies of initial treatment included both prospective and retrospective studies that reported therapeutic response of anti-reflux medical treatments using PPIs ± H-2 blockers ± alginate ± magaldrate ± dietary and behavioural changes. Studies that addressed specifically those LPR patients who were resistant to these medical strategies were included for review as well, regardless of what additional medical or surgical treatments were utilised.

2.2 | Subjects

Included studies had populations of adult LPR patients with age > 18 years. Those patients who were diagnosed with LPR on the basis of rigorous application of validates ratings for signs/symptoms, pH monitoring or multichannel intraluminal impedance-pH monitoring were considered "LPR patients." Patients whose diagnosis was made clinically without objective testing or application of validated scoring systems for signs/symptoms were considered as "suspected LPR patients" for purpose of the review.

2.3 | Outcomes

Studies were assessed for their definition of response to treatment; the rates of therapeutic response to primary medical strategies; aetiology of LPR (acid, weakly acid, non-acid, mixed); differential diagnoses listed as potential sources of persistent laryngopharyngeal complaints; and the management of non-responder patients.

2.4 | Search strategy

An electronic search of PubMed, Cochrane, and Scopus databases was conducted to identify articles published between January 1990 and November 2018 describing the success rate of PPIs and/or the characteristics and management of patients with recalcitrant LPR disease. The keywords used were "reflux"; "laryngopharyngeal"; "laryngitis"; "treatment"; "non-responder"; "resistant"; "resistance"; "recalcitrant"; "refractory"; "persistent"; and "failure". Additional references were obtained from citations within the retrieved articles. Three independent authors (JRL, SS and VM) screened and selected each study that had database abstracts and available full texts. The PRISMA checklist for reviews was used to conduct this study.[9]

2.5 | Characteristics of studies

The investigators analysed trials for number of subjects, study design, inclusion and exclusion criteria, evidence level (EL), treatment types, therapeutic outcomes and rates of response to treatment. In keeping with a previous paper,[1] and in order to study the probable causes of resistance to treatment relative to possible inclusion of non-LPR patients within each study, the exclusion criteria used in each study were extracted and classified in seven categories:

1. Patients with ear, nose and throat (ENT) & respiratory toxic or infectious disorder(s) within the last month;
2. Smokers, alcoholics and subjects with active allergy;
3. Patients with anti-reflux treatment already started in the previous month (ie PPIs; H_2 receptor antagonists; over-the-counter antacids; prokinetic agents and reflux surgery);
4. Patients with current or past history head and neck malignancy, radiotherapy, trauma or surgery;
5. Patients with benign laryngeal lesions including cysts, nodules, polyps and papillomatosis
6. Patients with severe neurologic and psychiatric disorders (ie severe depression; dementia; psychosis);
7. Patients with other ENT diseases/diagnoses whose complaints might confound LPR diagnosis.

Also, extracted from each study were clinical outcomes, consisting of response to treatment assessed by clinical symptom questionnaires, signs or simply history/observation taken by the clinician. In cases of discrepancies between extracted data by different investigators, re-review was performed collectively by JRL, VM and SS and consensus analysis of the content of the publication was made. Risk of bias was assessed using the Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group and Evidence Partners.[10]

3 | RESULTS

3.1 | Therapeutic success and definition of response to treatment

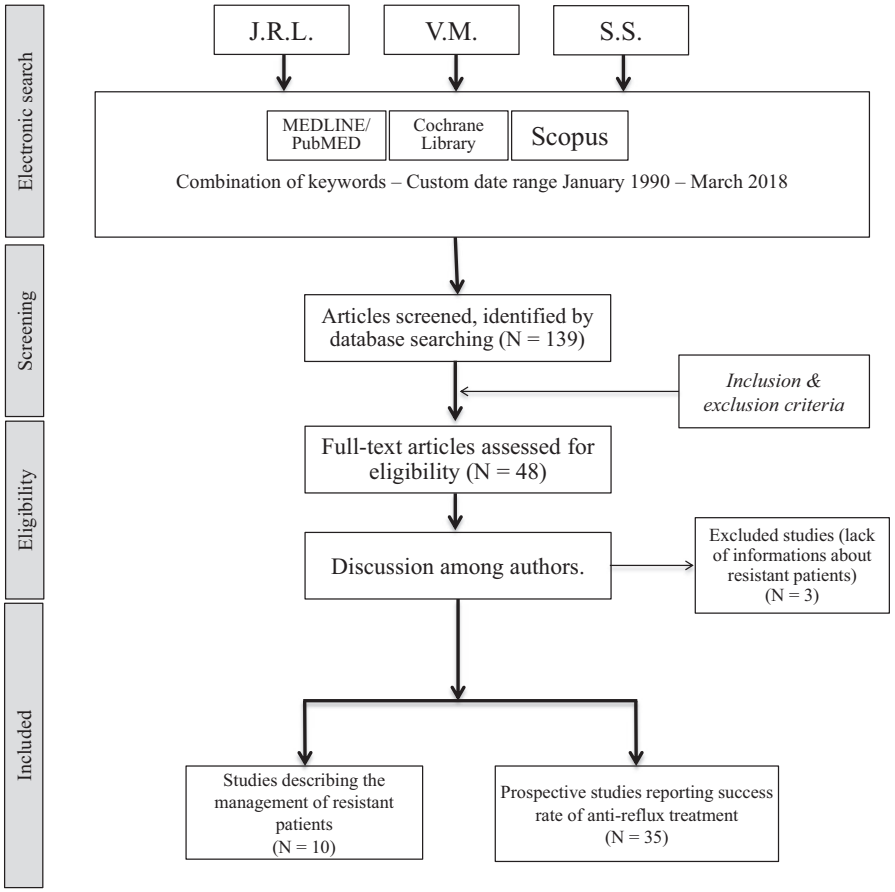
3.1.1 | Type of treatment

Figure 1 shows the PRISMA chart flow of the electronic search. From the 139 identified papers, 45 studies met our inclusion criteria. Among these, 35 reported success rate of PPIs ± other drugs ± diet and behavioural changes (Table 1).[11-45] In these studies, the medication used for LPR treatment consisted of PPIs alone in 30 studies; PPIs + prokinetic drugs in three studies; and PPIs + H_2 receptor antagonists in one study. In another study, authors used PPIs and voice therapy. Diet and behavioural changes were prescribed in 14 studies and explicitly were not prescribed in 8 studies (Table 1); information about diet was not mentioned either positively or negatively in the remaining 13 studies. Treatment duration among the studies varied from 4 to 24 weeks (Table 1) for most studies, though one study assessed long-term response after 169 weeks of treatment.[45]

3.1.2 | Characteristics of studies

The inclusion and exclusion criteria vary substantially across studies. Some authors did not exclude some conditions that are associated

FIGURE 1 PRISMA flow chart



with symptoms and findings similar to those seen with LPR (ie smokers, allergy, alcoholism)[11,32] or did not define their exclusion criteria (Table 1).[21-27,31,37,44,45] For diagnosis, single or dual-probe pH monitoring was used in 5 studies,[13,14,16,36,45] oropharyngeal pH-metry in one study[43] and the rest of the studies based the diagnosis on symptoms ± clinical findings. Some studies based the diagnosis on the occurrence of GERD with/without oesophagitis.[23,29] Symptoms and findings composing the composite clinical scores used to assess the therapeutic response also differ greatly from one clinical instrument to another.

3.1.3 | Definition of response to treatment

The definitions of response to treatment differed from one study to another (Table 2). Many validated and non-validated composite symptom and sign tools have been used. In nine studies, the response to treatment was based on the resolution of symptoms as reported by the patient or using a composite score. In the rest of studies, the response to treatment was defined on the basis of at least ≥1-point improvement of symptoms according to a clinical score (Tables 1 and 2). Only a few studies based the definition of response to treatment on the improvements of both symptoms and signs. As illustrated in Table 1, there is troublesome heterogeneity between studies regarding diagnostic method, exclusion criteria, treatment, definition of response to treatment and therapeutic outcomes. Hence, current literature does not permit establishment of a mean rate of response to treatment. At best, we can state that the therapeutic success rate based on the reported improvement of symptoms ranges from 18% to 87% (Table 1).

3.2 | Aetiology and management of non-responder patients

Among the 35 studies that assessed the success rate of treatment, only two studies provided additional information about the management of non-responder patients.[24,33] Metz et al performed additional pH monitoring and confirmed the LPR diagnosis in 3 of the 4 non-responder patients.[24] They did not provide additional information about the therapeutic course of these patients. Masaany et al performed GI endoscopy in their 3 non-responder patients and did not find abnormalities or explanations for the therapeutic resistance.[33] Other authors have identified several conditions associated with atypical GERD or resistant LPR, that is, cervical patch inlet (oesophageal heterotopic gastric mucosa),[46] coeliac disease,[47] oesophageal/upper oesophageal sphincter dysmotility/dysfunction,[48,49] gastroparesis,[49] food intolerance and oeosinophilic oesophagitis.[49-51]

As described in Figure 1, from the initial electronic search, 10 cohort studies which did not discuss primary treatment outcomes overall (ie not part of the 35 studies above) did otherwise specifically address aetiology or management of non-responder patients.[52-60]

TABLE 1 Studies evaluating the response to treatment rates

References	EL	Characteristics	Inclusion/exclusion criteria	Treatment	DT	Outcome defintion & tools	SR
El-Serag, 2001[11]	Ib	Suspected LPR (N = 11)	LPR symptoms & signs Exclusion: 1	Lansoprazole (30 mg, 2/d) Diet: -	12 wk	Laryngeal symptom resolution Tool: Laryngeal composite score	54%
Langevin, 2001[12]	Ib	Suspected LPR (N = 14)	LPR symptoms Exclusion: 4,5,7	Omeprazole (40 mg/d) Diet: -	12 wk	Laryngeal symptom resolution Tool: Laryngeal composite score	79%
Eherer, 2003[13]	Ib	LPR (N = 10)	Laryngeal symptoms Dual-probe pH-metry Exclusion: 1,2,4	Pantoprazole (40 mg, 2/d) Diet: -	12 wk	Laryngeal symptom improvement Laryngeal sign improvement Tools: Laryngeal composite scores	80% 100%
Steward, 2004[14]	Ib	LPR (N = 21)	LPR symptoms & signs Dual-probe pH-metry Exclusion: 1,2,3,4,5,6,7	Rabeprazole (20 mg, 2/d) Diet: +	8 wk	Laryngopharyngeal symptom improvement Tool: 4-point Likert Scale of improvement: 3, 4 = symptoms much better or gone.	53%
Vaezi, 2006[15]	Ib	Suspected LPR (N = 95)	LPR symptoms & signs Exclusion: 1,2,3,4,5,7	Esomeprazole (40 mg, 2/d) Diet: -	16 wk	Laryngopharyngeal symptom resolution Tool: patient evaluation (yes/no)	15%
Wo, 2006[16]	Ib	LPR (N = 19)	LPR symptoms Triple-probe pH-metry Exclusion: 3,7	Pantoprazole (40 mg/d) Diet: -	12 wk	Laryngeal symptom improvement Tool: Laryngeal composite score (/120)	40%
Reichel, 2008[17]	Ib	Suspected LPR (N = 30)	RSI > 13 & RFS > 7 Exclusion: 2,3,4,5,6,7	Esomeprazole (20 mg, 2/d) Diet: -	12 wk	Laryngeal symptom resolution Tool: patient evaluation (yes/no)	78%
Ezzat, 2011[18]	Ib	Gr1: suspected LPR (N = 42) Gr2: suspected LPR (N = 45)	LPR symptoms & signs Exclusion: 3,4,5,6,7	Gr1: Pantoprazole (40 mg/d) & Itopride (50 mg, 3/d), & diet Gr2: Pantoprazole (40 mg/d) & Placebo & diet	8 wk	Laryngeal sign resolution Gr1-2 Tool: total finding disappeared	48%-20%
Siupsinkiene, 2003[19]	IIb	Suspected LPR (N = 113)	LPR symptoms & signs Exclusion: 1,2,3	Omeprazole (20 mg, 1-2/d) Diet: +	5 wk	Laryngeal symptom improvement Tool: >50% reduction of a composite score	65%
Park, 2005[20]	IIb	Gr1: suspected LPR (N = 30) Gr2: suspected LPR (N = 30)	LPR symptoms & signs Exclusion: 3	Gr1: Lansoprazole (30 mg, 2/d), diet Gr2: Omeprazole (20 mg, 2/d) & Ranitidine (300 mg/d), diet	16 wk	Laryngeal symptom improvement Gr1-2 Tool: >50% reduction of a composite score Laryngeal symptom resolution	68%-46% 50%-18%

(Continues)

TABLE 1 (Continued)

References	EL	Characteristics	Inclusion/exclusion criteria	Treatment	DT	Outcome defintion & tools	SR
Hunchaisri, 2012[21]	IIb	Gr1: suspected LPR (N = 32)	RSI > 13	Gr1: Domperidone (10 mg, 3/d) &	12 wk	RSI	73%
		Gr2: suspected LPR (N = 33)	Exclusion: NA	Omeprazole (20 mg, 2/d), diet		Tool: >50% reduction of RSI	67%
				Gr2: Omeprazole (20 mg, 2/d), diet			
Hanson, 1995[22]	IIIb	Suspected LPR (N = 141)	LPR symptoms & signs	Omeprazole (20 mg, 1/d)	6 wk	Laryngopharyngeal symptom resolution	51%
			Exclusion: NA	Diet: +		Laryngopharyngeal sign improvement	51%
						Tool: patient/physician evaluation (yes/no)	
Jaspersen, 1996[23]	IIIb	Suspected LPR (N = 21)	LPR symptoms & signs	Omeprazole (40 mg, 1/d)	4 wk	Unblinded laryngeal sign improvement	100%
			Oesophagitis-Exclusion: NA	Diet: NA		Tool: reduction of laryngitis grading (I-III)	
Metz, 1997[24]	IIIb	Suspected LPR (N = 10)	LPR symptoms & signs	Omeprazole (20 mg/d)	4 wk	Oesophageal & LPR symptom resolution	60%
			Exclusion: NA	Diet: +		Tool: composite symptom score	
DelGaudio, 2003[25]	IIIb	LPR responder (N = 19)	LPR symptoms & signs	Esomeprazole (40 mg, 1/d)	8 wk	Laryngopharyngeal symptom improvement	63%
			Exclusion: NA	Diet: +		Tool: >50% reduction of composite score &	
						no persistant/worsened symptom item	
Bilgen, 2003[26]	IIIb	Suspected LPR (N = 36)	LPR symptoms & signs	Lansoprozole (30 mg, 2/d)	24 wk	Reduction of ≥ 1-point of modified RSI	68%
			Exclusion: NA	Diet: +		Reduction of ≥ 1-point of RFS	68%
Garrigues, 2003[27]	IIIb	Suspected LPR (N = 91)	LPR symptoms & signs	Omeprazole (20 mg, 2/d)	24 wk	LPR symptom improvement	86%
			Exclusion: NA	Diet: NA		LPR symptom resolution	41%
						Normal laryngoscy	83%
						Tool: composition symptom/sign scores	
Williams, 2004[28]	IIIb	Suspected LPR (N = 20)	LPR symptoms & signs	Omeprazole (20 mg, 3/d)	12 wk	Improvement of ≥ 1-point level in	63%
			Exclusion: 1,2,3,4,5,7	Diet: +		Composite laryngoscopic Grading Score	
						Improvement of composite symptom score	40%-45%

(Continues)

TABLE 1 (Continued)

References	EL	Characteristics	Inclusion/exclusion criteria	Treatment	DT	Outcome defintion & tools	SR
Dore, 2007[29]	IIIb	Suspected LPR (N = 266)	GERD symptoms	PPIs (20 mg, 2/d), or	12 wk	Symptom resolution/improvement	68%-12%
			LPR symptoms	Lanzoprazole (30 mg, 2/d), or		Tool resolution: patient evaluation (yes/no)	20%
			Exclusion: 3,4	Diet: +		Improvement: reduction of composite VAS	
						Symptom score	
Qua, 2007[30]	IIIb	Suspected LPR (N = 32)	LPR symptoms & signs	Lanzoprazole (30 mg, 2/d)	8 wk	Improvement of LSS Gr1-2	67%-18%
		Gr1: GERD (N = 21)	Exclusion: 1,2,3,4,5,6,7	Diet: -		Tool: 4-point Likert Scale of improvement	
		Gr2: non-GERD (N = 11)				Improvement of laryngeal signs Gr1-2	86%-36%
						Tool: reduction of laryngitis grading	
Oridate, 2008[31]	IIIb	Suspected LPR (N = 52)	LPR symptoms	Rabeprazole (20mg/d)	9 wk	Reduction of > 50% of modified RSI	50%
			Exclusion: NA	Diet. NA		Reduction of > 50% of GERD score	78%
Lee, 2011[32]	IIIb	Suspected LPR (N = 455)	LPR symptoms & signs	Rabeprazole (10/20 mg/d)	12 wk	Reduction of > 50% of RSI	75%
			Exclusion: 3	Diet: +			
Masaany, 2011[33]	IIIb	Suspected LPR (N = 47)	RSI > 13 & RFS > 7	Pantoprazole (40 mg, 2/d)	16 wk	Reduction of ≥ 10-point of RSI	79%
			Exclusion: 3,4,6	Diet: NA			
Park, 2012[34]	IIIb	Gr1: suspected LPR (N = 50)	RSI > 13 & RFS > 7	Omeprazole (20 mg, 2/d) ± voice	12 wk	Reduction of ≥ 5-point of RSI Gr1-2	46%-68%
		Gr2: suspected LPR (N = 50)	Exclusion: 1,2,5,7	therapy (Gr 2); Diet: -		Reduction of ≥ 3-point of RFS Gr1-2	18%-50%
Becker, 2012[35]	IIIb	Suspected LPR (N = 30)	LPR symptoms	Pantoprazole (40 mg, 2/d)	12 wk	Symptom improvement	20%
			Exclusion: 3,4	Diet: NA		Tool: patient interview (yes/no)	
Lien, 2013[36]	IIIb	Gr1: GERD & LPR (N = 65)	LPR symptoms & signs	Esomeprazole (40 mg, 2/d)	12 wk	Reduction of > 50% of RSI (Gr1)	63%
		Gr2: LPR (N = 42)	Triple-proble pH-metry	Diet: +		Reduction of > 50% of RSI (Gr2)	17%
			Exclusion: 1,2,3,4,7				
Beech, 2013[37]	IIIb	Suspected LPR (N = 74)	RSI > 13 & signs	Lansoprazole (30 mg, 2/d)	24 wk	Reduction of ≥ 1-point of RSI	71%
			Exclusion: NA	Diet: +			
Vailati, 2013[38]	IIIb	Suspected LPR (N = 22)	RSI > 13	Pantoprazole (40 mg, 2/d)	12 wk	Reduction of ≥ 1-point of RSI	59%
			Exclusion: 2	Diet: NA			
Semmanaselvan, 2015[39]	IIIb	Suspected LPR (N = 50)	RSI > 13 & RFS > 7	Rabeprazole (20 mg/d) +	12 wk	Reduction of ≥ 1-point of RSI	87%
			Exclusion: 1,3,4	Domperidone (30 mg/d), diet: NA		Reduction of ≥ 1-point of RFS	98%

(Continues)

TABLE 1 (Continued)

References	EL	Characteristics	Inclusion/exclusion criteria	Treatment	DT	Outcome defintion & tools	SR
Batioglu, 2016[40]	IIIb	Suspected LPR (N = 84)	RSI > 13 & RFS > 7	Lansoprazole (30mg, 2/d)	12 wk	Reduction of ≥ 1-point of RSI	21%
			Exclusion: 4,5	Diet: NA		Reduction of ≥ 1-point of RFS	56%
Dulery, 2016[41]	IIIb	Suspected LPR (N = 24)	LPR symptoms	Esomeprazole (40mg, 2/d)	8 wk	Total symptom resolution	10%
			Exclusion: 1,4	Diet: NA		Tool: composite symptom score	
Lechien, 2017[42]	IIIb	Suspected LPR (N = 80)	RSI > 13 & RFS > 7	Pantoprazole (20mg, 2/d)	12 wk	Post-treatment RSI < 13 and RFS < 7	74%
			Exclusion: 1,2,3,4,5,6,7	Diet: +			
Friedman, 2011[43]	IV	Gr1: LPR (N = 73)	Restech (Gr1)	PPI (20 or 40mg, 2/d)	24 wk	Improvement of main complaint Gr1-2	49%-41%
		Gr2: suspected LPR (N = 70)	RSI > 7 & RFS > 13 (Gr2)	Diet: +		Resolution of main complaint Gr 1-2	14%-3%
			Exclusion: 1,4				
Waxman, 2014[44]	IV	LPR (N = 43)	RSI > 13	Omeprazole (40 mg, 2/d)	4 wk	Reduction of ≥ 1-point of RSI	67%
			Exclusion: NA	Diet: NA			
Nennstiel, 2016[45]	IV	Suspected & LPR (N = 45)	LPR symptoms/ pH-metry	Pantoprazole (40 mg, 2/d)	169 wk	Symptom VAS improvement	60%
			Exclusion: NA	Diet. NA			

Note: PPIs = Rabeprazole; Pantoprazole; Esomeprazole.

Exclusion criteria adopted in trials were extracted and were classified in seven categories (cat.): cat.1: authors carefully excluded patients with ENT & respiratory toxic or infectious disorder(s) within the last month; cat.2: smoker, alcoholic, and subjects with active allergy; cat.3: patients with anti-reflux treatment already started in the previous month (ie PPIs; H_2 receptor antagonists; over-the-counter antacids; gastroprokinetic; and surgery); cat.4: patients with current/history of malignancies, radiotherapy, laryngeal trauma, and head and neck previous surgery; cat.5: benign laryngeal lesions including cyst; nodules; polyps; and papillomatosis; cat.6: severe neurologic and psychiatric disorders (ie severe depression; dementia; psychosis); and cat.7: subjects with other ENT diseases that may lead to confounding ENT complaints.

Abbreviations: DT, duration time; EL, evidence-based level; GERD, gastro-oesophageal reflux disease; Gr, group; LPR, Laryngopharyngeal reflux; LSS, laryngeal symptom score; NA, not available; PPI, proton pump inhibitor; RFS, reflux finding score; RSI, reflux symptom score; SR, success rate; VAS, visual analog scale; w, weeks.

TABLE 2 Success rate definitions in included studies

Definition of response to treatment	N studies
Laryngeal/laryngopharyngeal symptom resolution regarding	
Composite score	6
Patient judgment (yes/no)	3
Laryngeal/laryngopharyngeal symptom improvement regarding	
Reduction of composite score	1
Improvement of main complaint	1
Reduction of > 50% of composite score	2
Reduction of > 50% of RSI	4
Reduction of ≥ 1-point of RSI	3
Reduction of ≥ 10-point of RSI	1
Laryngeal/laryngopharyngeal sign improvement regarding	
Reduction of ≥ 1-point of Composite score	4
Disappearing of findings	1
Laryngeal/laryngopharyngeal symptom & sign improvement regarding	
Reduction of composite symptom & sign scores	3
Reduction of > 50% of composite symptom & sign scores	1
Reduction of ≥ 1-point of RSI & RFS	3
RSI < 13 & RFS < 7	1
Reduction of ≥ 5-point of RSI & ≥3-point RFS	1

Abbreviations: RFS, reflux finding score; RSI, reflux symptom index.

Table 3 summarises the details of these studies relative to diagnosis, management, and treatment. In 4 studies, the inclusion criteria (definition of non-responder patients) was based on a < 50% symptomatic improvement of composite symptom score after 4 or 8 weeks of PPI therapy.[41,52,54,59] One study defined resistance as persistent symptoms and signs and/or continued proximal acid reflux on impedance-pH monitoring.[57] The rest of the studies defined non-responder patients on the basis of persistent symptoms ± findings after 1 month of PPI ± H_2 receptor antagonist therapy.

To evaluate non-responder patients, studies describe a variety of subsequent methods—some studies used more than once. In total, the 10 studies focused on describing management of recalcitrant LPR patients utilised impedance-pH monitoring (N = 5), oesophageal manometry (N = 4), barium oesophagram (N = 1), pH monitoring (N = 1) and GI endoscopy (N = 1) to try to identify the reason for resistance (Table 3). Differential diagnoses (ie allergic rhinitis, asthma, alcoholic pharyngitis and vocal fold disorders) were investigated in three studies.[52,54,56] Among these differential diagnoses, Carroll et al[56] identified 26% of patients with cofactors that could be associated with apparent resistance to treatment (ie persistence of LPR signs or symptoms) including allergic rhinitis, asthma, vocal fold lesions, post-viral vagal neuropathy, glottic incompetence, gastroparesis and oesophageal dysmotility. Investigating cofactors associated with resistance, Tsutsui et al found that 48% of non-responder patients suffered from oesophageal dysmotility.[60] Among these patients, ineffective oesophageal motility, achalasia, oesophageal spasms, nutcracker oesophagus and hypertensive LES were identified on manometry.[60]

Only 6 studies specified the treatment proposed for non-responder patients including fundoplication (N = 4), high-dose PPIs (N = 3) and restrictive diet (N = 1) with a variable rate of therapeutic success (7%-76%) (Table 3). The heterogeneity between studies with regard to inclusion, exclusion and diagnostic criteria; treatments; and therapeutic outcomes renders analysis and meaningful conclusions about LPR treatment and resistance impossible.

4 | DISCUSSION

The efficacy of PPI therapy in treatment of LPR disease has been controversial because some studies reported lack of evidence supporting superiority of PPIs over placebo.[1,61,62] Currently, using different definitions of response to treatment, authors report a success rate with medical therapy for LPR ranging from 18% to 87%, lower than the success rate of PPI therapy for classic GERD.[8] Unfortunately, heterogeneity among those LPR studies which assess response to primary medical therapy, as well as heterogeneity among the separate group of studies which evaluate recalcitrant patients in particular, make it difficult to know exactly why LPR remains difficult to treat.

Among the factors that complicate assessment of response LPR treatment, many studies are characterised by lack of clear definitions of responder and non-responder patients. In this systematic review, we found that the majority of studies based their definitions on symptom evolution without clear criteria or definition of the symptom improvement. Of the few papers that did assess changes in signs, only Portnoy et al assessed laryngeal signs in a blinded fashion,[57] with other papers using scoring systems for signs of LPR being subject to the risk of evaluation bias.[63,64] Even if tools are used appropriately, choice of assessment tool can be important; valid evaluation of therapeutic effectiveness requires the use of efficient and validated clinical instruments to assess treatment effect. However, as described in a recent meta-analysis, there are no comprehensive clinical tools including all laryngeal and extra-laryngeal symptoms and signs.[1] Some new clinical tools such as Reflux Symptom Score (RSS) and Reflux Sign Assessment (RSA) are newly validated (RSS)[65] or in process of validation (RSA) and should provide future responses to this point. Another source of potential bias in assignment of responder/non-responder status is time course of this assessment—many authors considered patients who did not respond to a 1-month PPI treatment as non-responders,[53,59,60] whereas symptoms and signs of reflux commonly continue to improve beyond the first month of treatment.[42,66] Any bias or systemic error in evaluation of response to medication limit meaningful comparisons, conclusions or meta-analyses concerning response of LPR patients to medication.

With the development of impedance-pH monitoring, an increasing number of physicians distinguish acid, non-acid and mixed reflux; non-acid and mixed reflux accounting for a substantial number of LPR patients.[67,68] The efficacy of PPIs for LPR should be better for acid than non-acid and mixed reflux, as PPIs do not limit refluxate mechanically

TABLE 3 Studies assessing aetiology or the management of non-responder LPR patients

References	EL	Characteristics	Initial diagnosis	Definition of non-responder	Non-responder management	Non-responder treatment	DT	Outcomes	SR
Swoger, 2006[52]	IIb	Gr1: non-responder LPR	LPR symptoms & signs	<50% symptomatic improvement of composite symptom score after high-dose PPIs during 4 mo	1. Oesophageal manometry	Gr1: fundoplication	52 wk	Symptom improvement Gr1-2	10%-7%
		N = 10	Positive dual-p pH-metry		2. pH and bilirubin monitoring	Gr2: Omeprazole (80 mg/d)		Intergroup comparison	Gr1 = 2
		Gr2: non-responder LPR	GI endoscopy		under PPIs + barium oesophagram	or Lansoprazole (120 mg/d)		Sign improvement Gr1-2	50%-30%
		N = 15	Exclusion: 3		3. Evaluation of cofactors	Diet: +		Intergroup comparison	Gr1 = 2
Tokashiki, 2013[53]	IIb	Gr1: Resistant LPR	Persistant LPR symptoms	Persistent symptoms after 2 or >2	No additional examination	Gr1: Rikkunshito	4 wk	Improvement of	
		N = 11	≥2 wk PPI therapy	weeks of treatment (lansoprazole 30 mg, 4/d)		Gr2: Lanzoprazole (30 mg/d)		Sore throat (VAS)	S (Gr2)
		Gr2: Resistant LPR	GSRS ≥ 3			& Rikkunshito		Globus sensation (VAS)	S (Gr1-2)
		N = 11	Exclusion: 3,6,7			Diet: -			
Qaader, 2005[54]	IIIb	Gr1: LPR (N = 72)	LPR symptoms & signs	<50% symptomatic improvement of composite symptom score after high-dose PPIs during 4 mo	1. Evaluation of cofactors	Gr1: Omeprazole, (40mg, 2/d)	54 wk	Reduction of > 50% of	10%
		Gr2: LPR (N = 10)	Positive dual-p pH-metry			or Lansoprazole (60mg, 2/d)		Composite symptom score	
			GERD, GI endoscopy			Gr2: Fundoplication		Reduction of composite	80%
			Manometry			Diet: +		laryngeal symptom score	
			Exclusion: 3					Normal laryngoscopy	30%
Koufman, 2011[55]	IIIb	Resistant LPR (N = 20)	LPR symptoms & signs	No reduction of RSI after PPI & anti-H2 during 2 mo	No additional examination	Restrictive diet	2 wk	Reduction of RFS	t1 > t0
			Positive dual-p pH-metry					Reduction of RSI	95%
			Exclusion: 1,4,7						

(Continues)

TABLE 3 (Continued)

References	EL	Characteristics	Initial diagnosis	Definition of non-responder	Non-responder management	Non-responder treatment	DT	Outcomes	SR
Carroll, 2012 (50)	IIIb	Resistant LPR (N = 33)	LPR symptoms & signs	Persistent symptoms after 3-mo high-dose PPIs (omeprazole 40 mg ± anti-H2) and diet	1. Exclusion of allergic rhinitis, asthma, vocal fold lesions.	-	-	Manometry dysmotility	22%
			Positive MII pH-metry					Resistant acid reflux	22%
			Manometry		2. High resolution manometry			Non-acid reflux	52%
					3. MII pH-metry			Differential diagnoses	26%
Dulery, 2016[41]	IIb	Gr1: Resistant LPR	LPR symptoms & signs	<50% symptomatic improvement of composite symptom score after high-dose PPIs during 2 mo	1. MII pH-metry	-	-	MII pH-metry:	
		N = 24	Positive MII pH-metry					-Proximal, distal, pharyngeal	Gr1 = 2
		Gr2: CT (N = 46)	Exclusion: 1, 2, 3, 4, 6					episodes	
Portnoy, 2013[57]	IV	Resistant LPR	LPR symptoms & signs	Persistent symptoms & signs (RFS) and/or continued proximal acid t the pH-impedance monitoring after 3-mo of high-dose PPI therapy	1. Second MII pH-metry	High-dose PPI therapy +		MII pH-metry change	NS
		N = 35	Positive MII pH-metry			Antihistamine		Reduction of RFS	70%
			Exclusion: 3, 5	a		Fundoplication in case of failure			
Weber, 2014[58]	IV	Resistant LPR (N = 25)	LPR symptoms & signs	Persistent symptoms & signs after	1. Second MII pH-metry	Fundoplication		Reduction of RFS	NS
		Professional voice users	Positive MII pH-metry	3-mo treatment of twice daily PPIs				Reduction of reflux episodes	S
			Exclusion: 3					MII pH-metry after surgery	
								Patient satisfaction	76%
Ribolsi, 2012[59]	IIb	Gr1: Resistant LPR N = 28	GERD & LPR symptoms	<50% of symptom improvement of composite symptom score after 1-mo PPI therapy	1. MII pH-metry	-	-	Acid, weakly acid, mixed LPR	Gr1 > 2
			Exclusion: NA		2. Manometry			Upright LPR	Gr1 > 2
		Gr2: Responder GERD N = 55			3. GI Endoscopy			Reduction of reflux episodes of non-responders during trt	NS

(Continues)

TABLE 3 (Continued)

References	EL	Characteristics	Initial diagnosis	Definition of non-responder	Non-responder management	Non-responder treatment	DT	Outcomes	SR
Tsutsui, 2012[60]	IIb	Gr1: Resistant LPR	GERD and globus	Persistent symptoms & signs after 1-mo of PPI therapy	1. MII pH-metry	-		Manometry dysmotility	48%
		N = 119	Laryngoscopy		2. Manometry			*Ineffective oesophageal motility*	32%
		Gr2: healthy subjects	Oesophagitis					*Achalasia*	7%
			Exclusion: NA					*Oesophageal spasms*	5%
								Nutcracker oesophagus	5%
								Hypertensive LES	<1%
								Oesophageal motility	Gr2 > 1

Abbreviations: DT, duration time; GERD, gastro-oesophageal reflux disease; Gr, group; LPR, Laryngopharyngeal reflux; MII-pH, multichannel intraluminal pH-impedance metry/monitoring; NS, non significant; PPI, proton pump inhibitor; RFS, reflux finding score; RSI, reflux symptom score; VAS, visual analog scale; EL, Evidence-based level; SR, Success rate.

but seek only to change its acid content.[69,70] It has even been suggested that a PPI prescription (as single medication) in non-acid and mixed LPR could exacerbate laryngopharyngeal mucosa injury from non-conjugated bile salts, trypsin, etc by providing the required alkaline pH for optimal activity of non-conjugated bile salts.[69,71,72] Thus, it is likely that many LPR patients with non-acid or mixed LPR did not receive adequate treatment during their initial therapeutic trial.

If diagnosis is accurate and medication regimen appropriate, another potential confounder is patient non-compliance with medication or inaccurate timing of medication relative to optimal biologic effect. Interestingly, no prospective study provided information about the therapeutic compliance of LPR patients. However, a recent cohort study reported that the lack of diet, behavioural changes, and the inadequate intake of drugs could be the first cause of non-response to treatment.[73] Thus, 62.7% of LPR patients reported an incorrect routine in taking their PPIs: taking it with other pills, taking it with food/drink, and uncertainty about which pill was for reflux. Similarly, a survey of 491 US physicians revealed that nearly 70% of primary care physicians and 20% of gastroenterologists advised patients to take their PPIs at bedtime or did not believe that the timing of dosing in relation to meals was important.[71] Instructions should be made clearly at initial treatment to avoid the cost (financial and physical) of an ineffective treatment.

To assess truly resistant patients, GI endoscopy and high-resolution oesophageal manometry could make particular sense to detect factors enhancing resistance such as severe hiatal hernia,[61] heterotopic oesophageal gastric mucosa,[46] Zenker's diverticulum,[74] oesophageal spasm and gastroparesis,[49,60,75] as well as impaired oesophageal motility,[49] stasis and intra-oesophageal reflux. Unfortunately, our systematic review showed that only a few studies investigated non-responder patients systematically. Overall, allergic rhinitis, asthma, laryngeal neuropathy and some disorders associated with oesophageal dysmotility have been identified as potentially relevant diagnoses.[1,4,49,76] Moreover, other diseases may mimic LPR complaints and findings, such as chronic rhinosinusitis, autoimmune laryngeal inflammation (rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc), fibromyalgia, laryngeal musculoskeletal disorders, laryngeal sensory neuropathies, aging voice and thyroid diseases, as well as gluten intolerance, food allergies, and other conditions that can be associated with similar symptoms to LPR (Table 4).[31,47,61,77,78] Obviously, concomitant cofactors such as active allergy (including food allergies) or untreated gluten intolerance can complicate the management of patient by confusing the reason for persistent signs such as laryngeal erythema, oedema and thick mucous and they should be considered alone with other diagnoses in all non-responder patients (Table 4).

4.1 | Perspectives in patients with recalcitrant LPR

In conclusion, although there are many published studies about LPR, only a few authors have addressed non-responder patients with confirmed or suspected diagnostic. Provided that LPR diagnosis is accurate and treatment appropriate, there are still myriad

TABLE 4 Differential diagnoses of laryngopharyngeal reflux or associated cofactors

Oesophageal disorders	Ear, nose, and throat disorders	Other
Mucosa disorders	Infections	Lung disorders
Eosinophilic oesophagitis	Chronic rhinosinusitis	COPD
Zenker diverticulum	Mycosis	Asthma
Oesophageal sclerodermia	Recurrent oropharyngeal angina	Psychological
Oesophageal candidosis	Tuberculosis	Addiction (alcohol, tobacco pharyngolaryntidis)
Heterotopic oesophageal gastric mucosa	Rheumatologic/auto-immune disorders	Stress
Neoplasia	Rheumatic arthritis	Anxiety
Oesophageal stasis	Sjogren's syndrome	Depression
Hiatal hernia	Laryngeal sarcoïdosis	Drugs associated with salivary hypofunction
Oesophageal stricture	Amyloïdosis	Digestive diseases associated with reflux
Oesophageal/sphincter motor disorders	Granulomatosis with polyangiitis	Lactose intolerance
Hypertonicity of upper oesophageal sphincter	Fibromyalgia	Gluten sensitivity
Hypertonicity of lower oesophageal sphincter	Allergy	Food allergy
Achalasia	Laryngeal musculoskeletal disorders	
Oesophageal spasm	Muscle tension dysphonia	
Absent/ineffective peristalsis	Functional laryngeal disorders	
Hypercontractile oesophagus	Cervical osteophytes	
Gastroparesis	Benign or malign tumours	
Oesophageal hypersensitivity	Anatomical disorders	
Other	Size & shape of the epiglottis	
Rumination	Lingual tonsil hypertrophy	
Aerophagia	Uvula hypertrophy	
	Retroverted epiglottis (touching the posterior pharyngeal wall)	
	Traumatic	
	Laryngeal fracture	
	Upper aerodigestive tract injury	
	Other	
	Laryngeal sensory neuropathies	
	Laryngeal hypersensitivity	
	Steroid inhaled laryngitis	
	Aging voice	
	Upper aerodigestive tract neoplasia	
	Thyroid disease (nodules, goitre, etc)	

Note: This table was constructed according to publications focusing on differential diagnoses of the main prevalent LPR symptoms (globus, dysphonia, throat clearing, and cough). Some of these conditions are LPR differential diagnoses or cofactors existing with LPR. All of them have to be investigated in case of lack of response to treatment. This is an improved table of differential diagnoses from previous review.[4]

potential issues that might lead LPR patients to be truly resistant to treatment—for instance, cofactors might include hiatal hernia,[61] oesophageal sphincter insufficiency,[49] diet,[79] non-acid/mixed LPR, heterotopic gastric mucosa such as inlet patch,[46] oesophageal visceral hypersensitivity,[61] vagally mediated laryngeal reflexes, etc). Although there are only a few studies that have been done, these factors should be considered in future studies to improve knowledge about resistance to treatment.

Realising that not all LPR is acidic, consideration of other approaches to limit reflux itself, rather than reduce acid content of refluxate, makes sense in the context of patients with refractory symptoms. Consider that super high-dose PPIs have been used as treatment of recalcitrant LPR patients with uncertain results.[57] The use of alginate or magaldrate is anecdotal although these drugs decrease acid reflux events during a critical time period corresponding to the first hour after the meals.[80] The majority

of authors considered fundoplication for resistant patients.[81] However, many drugs have been studied in recalcitrant GERD but never or less used in LPR. Prokinetic drugs could be used for recalcitrant LPR patients, especially those with oesophageal dysmotility. Baclofen is a γ-aminobutyric acid type B ($GABA_B$) agonist that has been used for many years to treat spastic muscle disorders (20 mg, thrice daily). Through direct action on lower oesophageal sphincter relaxation, Baclofen decreases the number of postprandial acid and non-acid reflux events via inhibition of transient lower oesophageal sphincter (LES) relaxation and reduces GERD symptoms.[80,82,83] However, the patient must understand that there are potential side effects, that is, somnolence, dizziness and drowsiness. One of the authors (RTS) has found that baclofen 10 mg b.i.d. or t.i.d. may be effect for LPR patients and the lower dose causes fewer side effects.[61] A recent study confirmed the usefulness of baclofen in resistant LPR patients.[83] Anecdotally and because the pathophysiology of LPR also involves an indirect effect, some drugs that impact mucosal hypersensitivity (such as tricyclic antidepressants (amitriptyline), trazodone and selective serotonin reuptake inhibitors) could be used in future randomised controlled trials studying resistant LPR patients; there is a literature that supports their use when refractory heartburn complaints despite pH probe demonstration of only normal degrees of oesophageal reflux lead to a diagnosis of "visceral hypersensitivity."

Though evidence for an overall approach is lacking, it might be that patients with refractory LPR need to address a variety of potential issues—the acid content of their refluxate, diet and lifestyle issues that promote reflux or re-activate tissue bound pepsin in the larynx and pharynx, and mechanical issues that might lead to continued non-acid or mixed reflux even if proton pumps are inhibited. With this comprehensive approach in mind, a combination of strict diet ± high-dose PPI (40 mg once or twice daily regarding the reflux subtypes) ± alginate ± malgaldrate (thrice daily after meals or depending of the patient lifestyle) seem reasonable as first-line treatment of recalcitrant LPR without cofactors. Strict low acid diet seems to be a key component of treatment.[55] The second line of

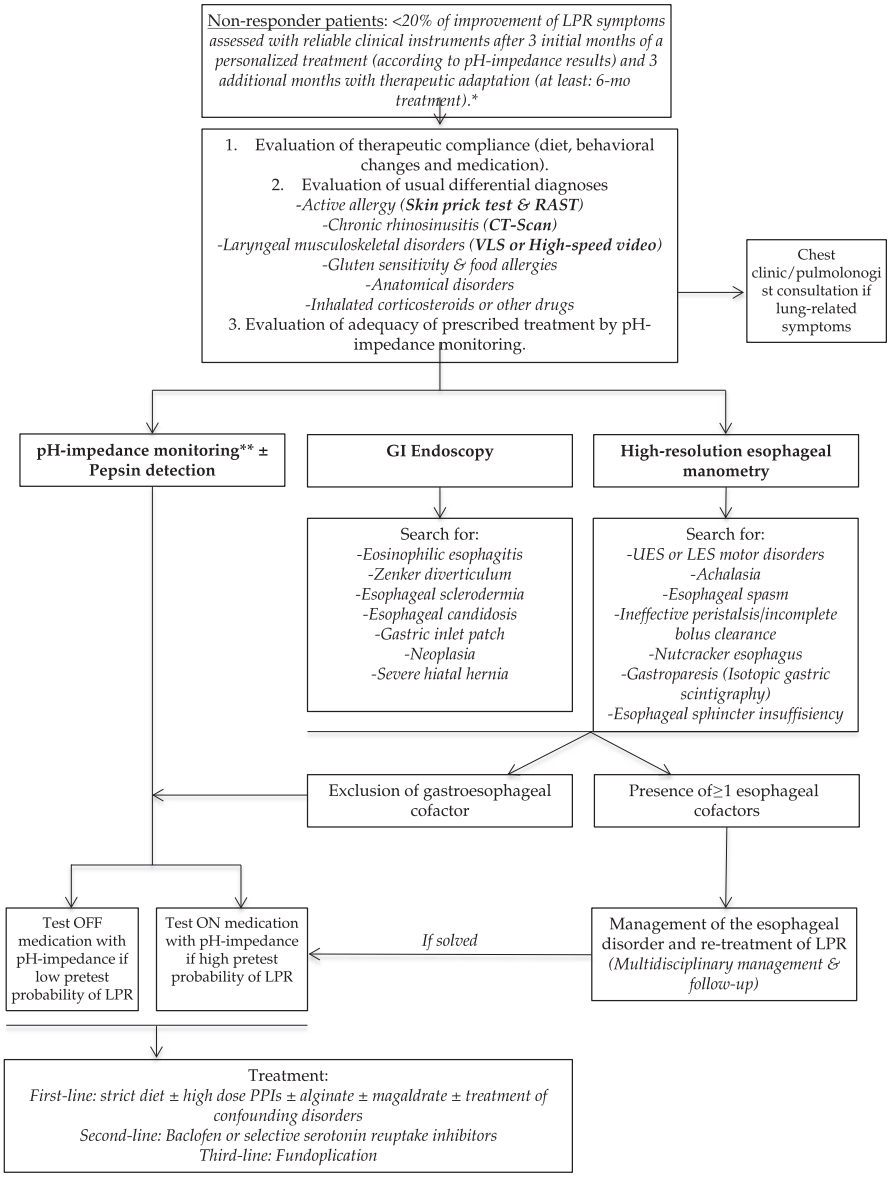


FIGURE 2 Algorithm of management of non-responder LPR patients. *Non-responder patients could be defined as individuals who have less than 20% improvement of symptoms through patient-reported outcome questionnaire after at least 6-month therapy. Patients with clinical improvements of 20-39, 40-59, 60-79 and > 80% could be defined as patients with mild, moderate, high and complete improvement, respectively, and should benefit from treatment adjustment/titration. **Patients without oesophageal cofactors and identified cause of resistance could benefit from a second impedance-pH monitoring under treatment to confirm the initial diagnosis, to detect and to characterise residual LPR episodes (acid, non-acid, mixed). A 96-h impedance-pH monitoring could be interesting to get better correlation between symptoms and reflux episodes and to assess some treatments under monitoring. Abbreviations: GI, gastrointestinal; LPR, laryngopharyngeal reflux; RAST, radioallergosorbent test; VLS, videolaryngostroboscopy

treatment might include prokinetic drugs, baclofen or selective serotonin reuptake inhibitors. For voice professionals as well as patients with muscle tension dysphonia and LPR, the addition of voice therapy could also be considered in the second therapeutic line—understand that this may not impact LPR directly, but that improved vocal hygiene and reduced phonotrauma may lessen laryngeal inflammation through other mechanisms. Fundoplication could be considered for LPR patients who are resistant to all medical treatments[81] or in patients with grade III or IV hiatal hernia according to the Hill classification but physicians would keep in mind that fundoplication may be associated with uncertain efficacy.[84]

In order to encourage discussions leading to international consensus, our LPR study group proposes a management algorithm for non-responder patients based on findings of the current literature (Figure 2)—we hope that this might be a starting point for on-going debate as to optimal approaches for patients with LPR, and that it might serve to inform future studies of patients with refractory LPR. This algorithm involves a definition of non-responder patients that takes into consideration precise evaluation of persistent symptoms. For those patients with <20% response to initial LPR treatment, it is incumbent upon treating physicians to evaluate for possible non-reflux causes of the patient's laryngopharyngeal complaints, and then manage these as appropriate. Beyond allergy, rhinosinusitis, and other otolaryngologic diagnoses, reasons for initial treatment failure can include motility disorders—the algorithm therefore suggests that testing at this point include both oesophageal manometry and also pH-impedance testing with or without pepsin. Once additional confounding diagnoses or oesophageal pathologies are addressed and managed in multidisciplinary fashion as needed, patients who truly fail into the "refractory LPR" group can be managed with first-line, second-line and third-line treatments suggested in Figure 2, moving from strict diet, PPI, alginate and magaldrate to addition of baclofen, selective serotonin re-uptake inhibitor or neuromodulator and then even to fundoplication as needed.

Naturally, this algorithm needs to be evaluated through clinical study, both in its definition of refractory LPR patients and in the treatment recommendations that it suggests. A potential strength of this is the way in which it invites collaborative multidisciplinary care that might include gastroenterologists, allergists, speech language pathologists, internists and abdominal surgeons in addition to otolaryngologists. This algorithm is put forward not as a finished product, but rather as a structure to invite criticism, improvement and research leading to evidence-based consensus. Future studies are needed to assess the validity and reliability of this algorithm in large cohorts of non-responder LPR patients, and to refine it.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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