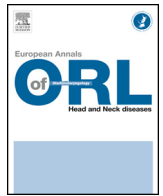




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## The development of new clinical instruments in laryngopharyngeal reflux disease: The international project of young otolaryngologists of the International Federation of Oto-rhino-laryngological Societies

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### ABSTRACT

**Introduction:** To analyze the epidemiological characteristics of placebo controlled randomized trials (RCTs) that evaluated the effectiveness of medical treatments over placebo in laryngopharyngeal reflux (LPR).

**Material and methods:** PubMed, Cochrane database, and Scopus were assessed for subject headings using the PRISMA recommendations. Placebo RCTs published between 1990 and 2018 describing clinical evolution throughout LPR treatment were extracted and analyzed for evidence-based level, number of patients, inclusion and exclusion criteria, gender, age, symptoms and signs used as therapeutic outcomes, and treatment schemes.

**Results:** The database search identified 15 placebo RCTs with a total of 763 patients. The mean age of patients was 48.59 years and 52.68% of patients were female. Among the 15 placebo RCTs, 9 have demonstrated a partial or total superiority of a medical treatment over placebo. Most of authors based the LPR diagnosis on symptoms and signs without additional examination. Our analysis reveals an important heterogeneity between studies with regard to the diagnosis criteria, treatment schemes and signs and symptoms used as therapeutic outcomes. Many commonly reported signs and symptoms related to LPR were not used as therapeutic outcomes. Half of the authors did not prescribe diet and behavioral changes along the treatment.

**Conclusion:** The controversy in the RCTs about the superiority of medical treatment over placebo in LPR disease is probably due to discrepancies in the diagnosis method, exclusion criteria, therapeutic schemes and the lack of comprehensive tools for the assessment of signs and symptoms. In this context, the LPR Study Group of Young-Otolaryngologists of the International Federations of Oto-Rhino-Laryngological Societies developed two new instruments to precisely assess signs and symptoms throughout the treatment. These two instruments could be used in future trials comparing medical treatment over placebo in LPR disease.

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## 1. Introduction

Laryngopharyngeal reflux (LPR, also called silent reflux, reflux laryngitis) is an inflammatory disease characterized by the back flow of gastric and/or duodenal content into the laryngopharynx where it comes in contact with mucosa of the upper aerodigestive tract. This disease affects 10% of patients being treated in otolaryngology, and more than 50% of patients suffering from voice disorders in the United States [1,2]. Today, the prevalence of LPR disease in Europe remains unknown. On the clinical plane, the acidic, bile or mixed acid/non-acid gaseous refluxes cause acute and/or chronic irritation to the mucosa of the upper digestive tract, manifesting as different complaints or clinical symptoms [3]. The main symptoms of LPR are globus, dysphonia, dry throat, cough, and throat clearing as well as an excess of viscous secretions in the throat [1,4,5]. Heartburn and acid reflux are not systematic, as they only affect 50 to 86% of patients [6–8]. Their absence does not rule out diagnosis. On a semiological plane, LPR is characterised by different endoscopic signs such as hypertrophy and erythema of the posterior commissure, ventricular bands, arytenoids, epiglottis, as well as the presence of thick and sticky mucus at the level of the endolarynx or the piriform sinuses [1,4,5].

The diagnostic and therapeutic approaches of LPR are currently the object of a double controversy. On one hand, impedance pH monitoring remains controversial because of non-negligible rates of false positives and false negatives, the absence of a clinical threshold considered as pathological, and the absence of correlation between the impedance pH monitoring results, and the signs and symptoms of LPR patients [8–11]. On the other hand, the efficiency of proton-pump inhibitors on LPR has not yet been demonstrated because of uncertain results in different randomized placebo-controlled studies, which have taken place over the last two decades [12,13]. The controversial results of placebo-controlled studies could be explained by three hypotheses. Firstly, the absence of a complete clinical tool allowing for the evaluation of all signs and symptoms during the course of treatment. Secondly, the administration of diet and lifestyle changes in the placebo group could alter the interpretation of results, given the demonstrated therapeutic impact of the plan. [5,14,15]. Finally, major interstudy differences in the inclusion and exclusion criteria of patients could also guide the selection of subgroups of patients, distinguishing some from others by their different therapeutic responses to proton-pump inhibitors (PPIs).

Considering these three hypotheses, the aim of this study is to analyze the epidemiological, clinical and therapeutic characteristics of placebo-controlled randomized trials (RCTs) carried out in the context of LPR. Following an analysis of literature, we suggest improvement tips for the treatment of LPR, with the help of new clinical tools.

## 2. Material and methods

### 2.1. Research strategy

A literature review has been carried out to identify each scientific article published between 1990 and 2018 in English, or French on PubMed, Scopus, and the Cochrane Library. The key words used were 'laryngopharyngeal', 'reflux', 'laryngitis', 'gastroesophageal', 'placebo' and 'treatment'. For each study, we identified the team carrying out the study, the name, average age and gender of the patients to avoid multiple inclusions. [Supplementary Fig. 1](#) shows the charflow of the study carried out using PRISMA Statement [16].

### 2.2. Selection, extraction and analysis of data

In review, we focused on placebo RCTs studying the impact of a medical treatment on patients with suspected or confirmed LPR disease.

In terms of the existing controversy surrounding the diagnosis of LPR, we wished to remain as inclusive as possible in terms of the diagnostic methods used in placebo RCTs. The diagnosis could be based either on impedance pH monitoring (LPR patients) or on laryngoscopic signs and symptoms of LPR (patients suspected to have LPR). Moreover, each author must have carefully excluded patients who are already being treated for LPR, having undergone antireflux surgery or those suffering or being treated for cancer of the upper aerodigestive tract. We have not included studies that exclusively concern voice professionals or children. Two authors have evaluated the summaries of different publications identified by key words (JRL & MRB). Only those studies that met our inclusion and exclusion criteria have been analyzed with the full text of the publication.

For each of these studies, the characteristics of the patients (number, age, gender), of the study (type of study and level of evidence), the LPR diagnostic method, the inclusion and exclusion criteria, the treatment (type and duration) and the clinical scales have been identified. The level of EBM evidence of each study (going from Ia to V) has been determined using recommendations from the Oxford Evidence-Based Medicine Center [17].

### 2.3. Therapeutic interventions

LPR patients had to be treated either by placebo or by medication, which could include the exclusive or simultaneous use of PPIs, antihistamines, alginates or other nonsurgical treatment. We have identified the use of diet and behavioral changes.

### 2.4. Identification of clinical evaluations, inclusion and exclusion criteria

To be included, the studies must evaluate the impact of the treatment using clinical evaluations (symptoms and/or signs) supported or not by standardized instruments. Inclusion and exclusion criteria for the studies have been analyzed to study the profiles of the included patients. More precisely, we have analyzed whether the authors have excluded some conditions that could lead to complaints similar to those of LPR, such as the presence of an infectious pathology of the upper respiratory tract during the month preceding the consultation (group 1), frequent consumption of alcohol or tobacco, or the presence of an active allergy (group 2), use of antireflux medication at the time of inclusion in the study (group 3), history of pharyngolaryngeal trauma, cancer of the upper respiratory tract or otolaryngological surgery (group 4), the presence of benign vocal fold lesions (group 5) and the presence of a neurological or psychiatric pathology (group 6).

## 3. Results

### 3.1. Results of the research

Systematic research on our databases identified 72 studies carried out on LPR. Among these we have selected 15 placebo-controlled studies. The included placebo-RCTs are Ib evidence level, according to the recommendations of the Oxford Evidence-Based Medicine Center [17]. With the exception of two studies [18,19], all publications are available on PubMed. The epidemiological characteristics of these 15 placebo RCTs [18–32] are described in [Table 1](#). Eight studies were carried out in North America (7 in the United States and 1 in Canada), 3 in Asia (China, Taiwan, and India), 2 in

**Table 1**  
Placebo RCTs.

References	Design	EL	Characteristics	Inclusion/exclusion criterias	Symptoms	Signs	Outcomes	Results	Treatment
Havas, 1999	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 7) Gr2: suspected LPR (n = 8) Gender: 8F, 7 M Age: 54y	1. LPR symptoms & signs 2. Exclusion: 3	N.A.	N.A.	Composite symptoms score	t1 > t0; Gr1 = Gr2	Gr1: Lanzoprazole (30 mg 2/d) Gr2: Placebo  Diet: + Duration: 12w
EI-Serag, 2001	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 10) Gr2: suspected LPR (n = 10) Gender: 1F, 19 M Age: 62y	1. LPR symptoms & signs Since at least 3w 2. Exclusion: 1	PS, HB,GS, TC, CT, PC	LE, EH, GG, UC	GERD symptoms, Erosive esophagitis  Double probe pH-metry Comp. signs & symptoms Q Complete symptom response	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 > Gr2	Gr1: Lansoprazole (30 mg 2/d) Gr2: Placebo  Diet: - Duration: 12w
Noordzij, 2001	Monocentric Placebo RCT	Ib	Gr1: LPR (n = 15) Gr2: LPR (n = 15) Gender: 14F, 16 M Age: Gr1: 51.7y	1. LPR symptoms Since at least 3 m 2. Dual-probe pH metry 3. Exclusion: 1,2,4,5,7	VD, TC, ST, GS, HB, EM, DD, ST, OD	VE, EH, GG, LE, TM	Comp. Sympt. Q: Roughness Throat clearing Comp. Sign Q	Gr1 > Gr2 Gr1 > Gr2 Gr1 = Gr2	Gr1: Omeprazole (40 mg, 2/d) Gr2: Placebo (2/d) Diet: - Duration: 8w
Langevin, 2001	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 14) Gr2: suspected LPR (n = 16) Gender: 16F, 14 M Age: 53y	1. LPR symptoms Since at least 3 m 2. Exclusion: 4,5,7	VD, CT, ST, TC	N.A.	Global symptom score	Gr1 > Gr2	Gr1: Omeprazole (40 mg/d) Gr2: Placebo  Diet: - Duration: 12w
Eherer, 2003	Monocentric Placebo RCT	Ib	Gr1: LPR (n = 7) Gr2: LPR (n = 7) Gender: 5F, 16 M Age: 48y	1. Laryngeal symptoms Since at least 2 m 2. Dual-probe pH metry 3. Exclusion: 1,2,4	HB, DD, PS, ST, VD, GS, PC, CT, OD, RE	GG, EH, PY, VE, VR, PH, TM, SE, SP, SR, PP	Comp Sympt Q Comp Signs Q	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2	Gr1: Pantoprazole (40 mg, 2/d) Gr2: Placebo Diet: - Duration: 12w
Steward, 2004	Monocentric Placebo RCT	Ib	Gr1: LPR (n = 21) Gr2: LPR (n = 21) Gender: 30F, 12 M Age: 49.3y	1. LPR symptoms & signs Since at least 1 m 2. Dual-probe pH metry 3. Exclusion: 1,2,3,4,5,6,7	VD, TC, HB, GS, DD, EM, CT, ST, PS, RE	EH, VE, LE, PH, VR, GG, ND, UC, SE	Comp Sympt Q Comp Signs Q	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2	Gr1: Rabeprazole (20 mg 2/d) Gr2: Placebo Diet: + Duration: 8w
Vaezi, 2006	Multicentric Placebo RCT	Ib	Gr1: suspected LPR (n = 95) Gr2: suspected LPR (n = 50) Gender: 74F, 71 M Age: 51y	1. LPR symptoms Since at least 3 m 2. CPLI ≥ 5 3. Exclusion: 1,2,3,4,5,7	TC, CT, VD, ST, GS	EH, GG, LE, PW, PH, VR, VE,	Patient symptom resolution CPLI	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2	Gr1: Esomeprazole (40 mg, 2/d) Gr2: Placebo  Diet: - Duration: 16w
Wo, 2006	Monocentric Placebo RCT	Ib	Gr1: LPR (n = 19) Gr2: LPR (n = 20) Gender: 26F, 13 M Age: 39y	1. LPR symptoms (3/w) Since at least 2 m 2. Triple-probe pH metry 3. Exclusion: 3,7	GS, CT, ST, VD, TC, EM, PS	SE, VV, EH, VE, LE, PH, GG, TM	RFS Laryngeal visual analog scale	Gr1 & 2: t1 > t0 Gr1 = Gr2 Gr1 & 2: t1 > t0	Gr1: Pantoprazole (40 mg/d) Gr2: Placebo Diet: - Duration: 12w
Reichel, 2008	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 30) Gr2: suspected LPR (n = 28) Gender: 30F, 32 M	1. RSI > 13 & RFS > 7 2. Exclusion: 2,3,4,5,6,7	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	SE, VV, EH, VE, LE, PH, GG, TM	RSI 6w (Gr1 & 2) RFS 6w (Gr1 & 2) RSI 12w (Gr1 & 2)	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 > Gr2	Gr1: Esomeprazole (20 mg, 2/d) Gr 2: Placebo  Diet: -

Table 1 (Continued)

References	Design	EL	Characteristics	Inclusion/exclusion criterias	Symptoms	Signs	Outcomes	Results	Treatment
Vashani, 2010	Monocentric Placebo RCT	Ib	Age: 48.7y Gr1: suspected LPR (n = 16) Gr2: suspected LPR (n = 16) Gender: 18F, 14 M  Age: >18y	1. LPR symptoms & signs 2. Hoarseness 3. Esophagitis 4. Exclusion: 2,3,5,7	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK, RE	VE, LE, EH, PW, PO	RFS 12w (Gr1 & 2) Throat clearing, mucous, sore throat Vocal folds erythema & edema Pharyngeal erythema & edema Hypopharyngeal erythema Hypopharyngeal edema RSI (8w)	t1 > t0; Gr1 > Gr2 t1 > t0, Gr2 > Gr1 t1 > t0, Gr2 > Gr1 t1 > t0, Gr2 > Gr1 t1 > t0, Gr2 > Gr1 t1 > t0; Gr1 > Gr2	Duration: 12w Gr1: voice therapy (2/w)+ Omeprazole (20 mg, 2/d) Gr 2: Placebo (2/d)  Diet: -  Duration: 6w  Gr1: Gaviscon (4/d) Gr2: Placebo
McGlashan, 2009	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 24) Gr2: suspected LPR (n = 25) Gender: 21F, 28 M Age: 54.5y	1. RSI > 10 & RSF > 5 2. Exclusion: 1,3,6,7	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	SE, VV, EH, VE, LE, PH, GG, TM	RFS (8w)  RSI (24w) RFS (24w)	t1 > t0; Gr1 = Gr2  t2 > t0; Gr1 > Gr2 t2 > t0; Gr1 = Gr2	Gr1: Gaviscon (4/d) Gr2: Placebo  Diet: + Duration: 24w Gr1: Esomeprazole (20 mg, 2/d) Gr2: Placebo
Fass, 2010	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 24) Gr1: suspected LPR (n = 17) Gender: 17F, 24 M Age: 65y	1. LPR symptoms & signs 2. Exclusion: 3,4	HB, PS, VD, TC, CT, DD, RE	SE, VV, EH, VE, LE, PH, GG, TM	Heartburn symptoms scores RFS	t1 > t0; Gr1 > Gr2 t1 > t0; Gr1 = Gr2	Gr1: Esomeprazole (20 mg, 2/d) Gr2: Placebo  Diet: + Duration: 12w
Lam, 2010	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 42) Gr2: suspected LPR (n = 40) Gender: 59F, 23 M Age: 46.8y	1. LPR symptoms Since at least 1 m 2. RFS > 7 3. Exclusion: 1,2,3,4,7	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	SE, VV, EH, VE, LE, PH, GG, TM	RSI (6 & 12w) RSI (18w) RFS (6, 12 & 18w)	t1, 2 > t0; Gr1 > Gr2 t3 > t0; Gr1 = Gr2 t3,2,1 > t0; Gr1 = Gr2	Gr1: Rabeprazole (20 mg, 2/d) Gr2: Placebo  Diet: + Duration: 18w Gr1: Pantoprazole (40 mg/d) & Itopride (50 mg, 3/d)
Ezzat, 2011	Monocentric Placebo RCT	Ib	Gr1: suspected LPR (n = 42) Gr2: suspected LPR (n = 45) Gender: 34F, 53 M  Age: 33.5y	1. LPR symptoms & signs Since at least 1 m 2. Exclusion: 3,4,5,6,7	VD, TC, CT, ST, HB, RE, OD, DD RE	SE, VV, EH, VE, LE, PH, GG, TM	Comp Sympt Q Esophageal Symptoms Score RFS	t1 > t0; Gr1 > Gr2 t1 > t0; Gr1 > Gr2 t1 > t0; Gr1 > Gr2	Gr1: Pantoprazole (40 mg/d) & Placebo Diet: + - Duration: 8w Gr1: Alginate  Gr2: Pantoprazole (40 mg/d) & Placebo Diet: + - Duration: 8w
Tseng, 2018	Monocentric Placebo RCT	Ib	Gr1: LPR (n = 39) Gr2: LPR (n = 40) Gender: 49F, 30 M Age: 47.9y	1. LPR symptoms & signs Since at least 1 m 2. RSI > 10 & RFS > 5 3. pH impedance metry 4. Exclusion: 1,3,4	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	SE, VV, EH, VE, LE, PH, GG, TM	RSI RFS	t1 > t0; Gr1 = Gr2 t1 > t0; Gr1 = Gr2	Gr1: Alginate  Gr2: Placebo Diet: + Duration: 8w

CK: breathing disorder/chocking; CP: chest pain; CT: troublesome cough; Comp. Signs Q: Composite sign questionnaire; Comp. Sympt. Q: Composite symptom questionnaire; CPLI: Chronic Posterior Laryngitis Index; DD: dysphagia; EH: laryngeal/arytenoids erythema; EM: excess throat mucous/postnasal drip; GG: granuloma/granulations (posterior commissure); GS: globus sensation; HB: heartburn; LE: laryngeal edema; m: month(s); OD: odynophagia; PC: Coughing after you ate/lying down; PH: posterior commissure hypertrophy; PO: posterior oropharyngeal wall erythema; PS: pyrosis/stomach acid coming up; ST: throat pain; PW: posterior pharyngeal wall erythema; RE: regurgitations; SE: subglottic edema; SP: supraglottic edema; SR: supraglottic erythema; TC: throat clearing; TM: thick endolaryngeal mucus; UC: laryngeal ulcerations; VD: voice disorders; VE: vocal folds edema; VR: vocal folds erythema; VV: ventricular obliteration; w: week(s). Authors have excluded some conditions that could lead to complaints similar to those of LPR (column 4), such as (1) the presence of an infectious pathology of the upper respiratory tract during the month preceding the consultation; (2) frequent consumption of alcohol or tobacco, or the presence of an active allergy; (3) use of anti-reflux medication at the time of inclusion in the study; (4) history of pharyngo-laryngeal trauma, cancer of the upper respiratory tract or otolaryngological surgery; (5) the presence of benign vocal fold lesions; and (6) the presence of a neurological or psychiatric pathology.

**Table 2**  
Signs and symptoms used for the assessment of treatment effectiveness.

Symptoms	AB	N	Signs	AB	N
Laryngopharyngeal			Laryngopharyngeal		
Throat clearing	TC	13	Diffuse laryngeal edema	LE	14
Dysphonia	VD	13	arytenoid/laryngeal erythema	EH	13
Cough	CT	13	Vocal fold edema	VE	11
Globus	GS	11	Posterior commissure hypertrophy	PH	9
Dysphagia	DD	10	Endolaryngeal mucus	TM	8
Pyrosis	PS	10	Subglottic edema	SE	8
Mucus excess, postnasal drip	EM	8	Granulation and/or granuloma	GG	7
Throat pain	ST	8	Ventricular obliteration	VV	7
Cough after meals/lying down	PC	7	Supraglottis edema	SP	3
Chest pain	CP	5	Vocal fold erythema	VR	1
Breathing disorders (Chocking)	CK	5	Laryngeal ulcerations	UC	1
Odynophagia	OD	3	Hypopharyngeal posterior wall erythema	PW	1
			Supraglottis erythema	SR	1
Gastro-esophageal			Extralaryngeal		
Heartburn	HB	11	Oropharyngeal erythema	PO	1
Regurgitations	RE	6			

The abbreviations (AB) of symptoms and signs are available in the table; n: number.

Europe (Germany and Austria), 1 in Australia and 1 in Egypt. All the studies were published in English.

### 3.2. Inclusion and diagnosis criteria and treatments

A total of 763 patients were included when adding the patients from the 15 selected studies. The size of cohorts ranged from between 14 and 145 patients. The average age of the subjects was 48,59 years old; and 52,68% of the patients were female ( $n=402$ ). With regard to the diagnosis, 9 teams gave a diagnosis based on signs and symptoms of LPR [19,20,24,26–31] and one single study [18] based on the presence of LPR symptoms (Table 1). Five studies based the inclusion of patients on their signs/symptoms of LPR, in association with a complementary examination supporting the diagnosis (pH metry and/or pH impedance metry) [21–23,25,32]. One team integrated patients based on the presence of a peptic oesophagitis [27]. In terms of exclusion criteria, several authors did not exclude some co-factors that could bias their clinical evaluations [19,20,22,25,29,32], while other did not state their exclusion criteria [18–20,22,25,28,29,32] (Table 1). One author did not exclude patients who smoked from their study [20].

In terms of treatment, the authors treated the pharmacological group using just PPIs in 12 studies; with PPIs in association with a gastroprokinetic agent in one study [31]; with PPIs in association with speech therapy in one study [27]; and a single alginate in two studies (Table 1). No study evaluated a treatment based on the simultaneous use of PPIs and alginate to treat LPR disease. Seven authors prescribed diet and lifestyle changes at the same time as PPIs or placebo [19,23,28–32], others did not advise this. The duration of medical treatment varied between 6 and 24 weeks.

### 3.3. Clinical evaluations of treatment efficiency

Of the 15 trials included in the study, 9 clinically demonstrated, partially or totally, that the medication treatment was superior to the placebo [18,20,21,26–31].

The studies were distinguished from each other by the use of a combination of different instruments to evaluate LPR signs and symptoms. One study did not list signs and symptoms evaluated at the time of diagnosis and during the course of treatment [19]. Among the different instruments used to evaluate the symptoms of LPR, as described in Table 1, 5 studies used the Reflux Symptom Index (RSI), 2 used the original or modified score of gastroesophageal reflux (GERD) of Locke et al. [33], and 6 used a composite score created for the realization of the study. Finally, 2 studies [18,20] did

not use the score and evaluated the presence of symptoms during the course of the treatment.

Reflux Finding Score (RFS) was used as an instrument of reference for the evaluation of signs of LPR in 7 studies, the Chronic Posterior Laryngitis Index (CPLI) in one study, and alternative composite scores in 3 studies. Two studies were based on the presence or absence of some signs during the course of treatment without using instrument. Among the different scores used in these 15 clinical trials, the RFS and the CPLI were validated.

No author evaluated in a blind manner the signs of patients with regard to the complaints and the status of the patients (cured, versus not cured).

Table 2 transversally shows the symptoms and signs used to evaluate the efficiency of treatment. The most commonly evaluated pharyngo-laryngeal symptoms are those described in the RSI. The French versions of the RSI and RFS are shown in Supplementary Figs. 2 and 3. Certain symptoms such as odynophagia, sore throat, otalgia and burning tongue were rarely evaluated or not at all. Finally, the majority of signs used to evaluate the efficiency of treatment concerned the larynx. The signs related to hypopharyngeal or oropharyngeal irritation (erythema, oedema, granulations) or oral signs (coated tongue) were also a little evaluated, or not at all.

## 4. Discussion

Our review of literature included 15 placebo RCTs conducted between 1990 and 2018. These placebo RCTs seem to be heterogeneous in terms of inclusion and exclusion criteria, the symptoms and signs evaluated during the course of treatment and the administration or not of diet and behavioural changes.

The clinical diagnosis of LPR remains difficult, given the non-specific nature of its signs and symptoms and the absence of a gold standard diagnostic tool [3,8,13]. It is therefore essential to rigorously select patients included in each placebo-controlled study. Effectively, different co-factors affecting the upper respiratory tract could bias the evaluation of the signs and symptoms at the moment of diagnosis and post-treatment. Several authors [18,19,25,31] do not seem to have rigorously excluded patients suffering from many affectations able to bias the clinical evaluations of LPR, including active allergy, acute infections of the upper respiratory tract during the month preceding the initial examination, or chronic rhinosinusitis [34,35]. The inclusion of patients who smoked at the time of diagnosis [20] equally represents a major bias of clinical evaluation. In fact, even low tobacco consumption can lead to the development of chronic pharyngo-laryngitis, which can mimic the signs and symptoms of LPR [13]. In the context

of the lack of a gold standard for the LPR diagnosis, it could be relevant to exclude smokers from the future trials studying the LPR diagnosis. Finally, other authors [27] included their patients on the basis of the presence of esophagitis at the time of diagnosis, thus creating a selection bias. In fact, if it is known that more than 50% of patients with LPR do not have esophagitis [7], it has also equally been demonstrated that the subjects suffering from both GERD and LPR at the same time responded generally better to medication treatment [7,36]. The exclusion of different co-factors that affect the response to treatment plays a greater role in the study than a pathology known to be very controversial to diagnosis.

We noticed that the majority of studies used signs and symptoms traditionally described in RSI [37] and RFS [38] scores for the assessment of treatment effectiveness. Even if RSI is a validated instrument, it presents several weaknesses that could affect the clinical evaluation of patients suffering from LPR. On one hand, many prevalent symptoms of LPR including sore throat [12], odynophagia [21], otalgia [39], or halitosis [40] are not or less described in RSI or in other scores. On the other hand, certain symptoms that slightly vary from each other are grouped in one single item of the RSI (i.e. regurgitations, heartburn, chest pain, indigestion) making clinical evaluation rather unspecific. Finally, each score evaluates each symptom in terms of its severity over the last month, using an analogical scale ranging from 0 to 5. This does not consider the frequency of symptoms, as well as the absence of clear reference in terms of the value of each score attributed to each item affecting the evaluation equally. Effectively, with similar severity and frequency, two patients suffering from the same complaint could rate it differently, which could considerably affect the reproducibility of the scale in a target population. It is mainly for these reasons that other authors prefer to use clinical scales, evaluating the severity and frequency of complaints, respecting a clear reference for the attribution of scores [22,23,31].

Like the symptoms, RFS seems to be the scale of reference to evaluate the signs of LPR. Though this scale was psychometrically validated [38], and easy to use, it only focuses on laryngeal signs. However, it has been demonstrated that LPR disease is also characterized by extralaryngeal signs such as hypertrophy of the lingual tonsils [5,41], hypo- or oropharyngeal erythema and edema [5,42], coated tongue [43], and erythema of the anterior pillars. Other laryngeal signs of reflux, namely leucoplakia, keratosis, etc. have not been described in RFS and/or other different instruments [44,45]. Also, no author evaluated patients' signs in a blind manner in terms of their clinical state (cured or not) or patients' complaints. This point is particularly important, and the knowledge of patients' complaints significantly influences the score attributed to the fibroscopical examination [46,47]. If it is demonstrated that the use of standardized and validated clinical scales significantly improves the treatment of the pathology [3,48,49], we can deduce that there is currently no standardized and validated scale that take into account all LPR symptoms and signs.

Finally, from a therapeutic point of view, our study highlights the existence of different placebo RCTs, associating the placebo with diet and lifestyle changes that can cause confusion about the impact of placebo versus diet [14,15]. Future studies aiming at comparing the real impact of PPIs will consider this point and carefully evaluate their real impact on curing patients. It has since been demonstrated that the patients respecting diet improved more despite their complaints, compared with the subjects who did not respect it much [5]. It is therefore likely that the majority of light cases of LPR can be treated simply, with the administration of a lifestyle plan.

## 5. Conclusion and perspectives

In the light of numerous controversies existing in this domain of research, future studies are needed to improve the diagnosis of LPR, evaluate impact of medication treatment, diet, and behavioral changes, and to develop new useful clinical instruments for the diagnosis and treatment of the condition. At the time of an international symposium organized at the last World Ear Nose, and Throat (ENT) Congress in Paris (Symposium: Hoarseness and Laryngopharyngeal reflux, Paris, June, 27, 2017), and in the context of the development of young otolaryngologists of the International Federation of Oto-Rhino-Laryngological Societies (YO-IFOS), a group of experts developed two new clinical questionnaires for the evaluation of both signs and symptoms related to LPR. The French and English versions of the Reflux Symptom Score (RSS) and the Reflux Signs Assessment (RSA) are shown in [Supplementary Figs. 4, 5, 6 and 7](#). These two instruments are in the process of being psychometrically validated in different French, Belgian, Italian and Lebanese hospitals. Their validation will allow us to promote new clinical studies, first allowing us to develop a gold standard for the diagnosis of LPR associating signs (RSA), symptoms (RSS), pH impedanceometry, and oral/oropharyngeal immunohistochemical detection of pepsine, and secondly, using these tools, to specify the superiority of adequate medication (IPP ± alginate) over the placebo, all the while taking into account diet and lifestyle changes. These future studies will also take into consideration the differences between acid, biliary, and mixed acid/non-acid LPR. Indeed, a few studies examined the clinical and therapeutic discrepancies between these three clinical entities. Considering the high incidence of LPR and its impact on the quality of life, the results of this study will significantly foster a multidisciplinary approach in attempt to improve knowledge and clinical practice related to this pathology.

### Disclosure of interest

The authors declared that they have no conflict of interest.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.anorl.2018.05.013>.

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