



HAL
open science

Review of management of laryngopharyngeal reflux disease

J.-R. Lechien, F. Mouawad, F. Bobin, E. Bartaire, L. Crevier-Buchman, S. Saussez

► **To cite this version:**

J.-R. Lechien, F. Mouawad, F. Bobin, E. Bartaire, L. Crevier-Buchman, et al.. Review of management of laryngopharyngeal reflux disease. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, 2021, 138 (4), pp.257-267. 10.1016/j.anorl.2020.11.002 . halshs-03379964

HAL Id: halshs-03379964

<https://shs.hal.science/halshs-03379964>

Submitted on 22 Aug 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Review of Management of Laryngopharyngeal Reflux Disease.

Jerome R. Lechien^{1-4#}, Francois Mouawad^{4#}, Francois Bobin^{1,5}, Emmanuel Bartaire^{1,6}, Lise Crevier-Buchman^{1,7}, Sven Saussez^{1,2}.

1. Laryngopharyngeal Reflux Study Group of Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS).
2. Department of Anatomy and Experimental Oncology, Mons School of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium.
3. Laboratory of Phonetics, Faculty of Psychology, Research Institute for Language Sciences and Technology, University of Mons (UMons), Mons, Belgium.
4. Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Lille, Hôpital Claude Huriez, Lille, France.
5. Department of Otolaryngology-Head and Neck Surgery, Polyclinique de Poitiers, Poitiers, France.
6. Department of Otorhinolaryngology and Head and Neck Surgery, GHICL Saint-Vincent-de-Paul Hospital, Faculté Libre de Médecine de Lille, Lille, France.
7. Department of Otorhinolaryngology and Head and Neck Surgery, Foch Hospital, Paris, France.

#These authors have equally contributed to the publication and are proposed as co-first authors.

* Corresponding author:

E-mail: Jerome.Lechien@umons.ac.be (Jerome R. Lechien)

Laboratory of Anatomy and Cell Biology, Faculty of Medicine, University of Mons (UMONS), Avenue du Champ de Mars, 6, B7000 Mons, Belgium

Telephone: +32 65 37 35 84

Abstract

This review was conducted according to the Patient/problem Intervention Comparison Outcome (PICO) Statements.

Some studies reported that 10-30% of patients consulting in ENT come with presenting symptoms of laryngopharyngeal reflux (LPR), but the exact prevalence of LPR is still unknown. Management has not changed in 20 years despite a significant increase in the number of publications on epidemiology, clinical presentation, diagnosis and treatment. The development of hypopharyngeal-esophageal multichannel intraluminal impedance pH monitoring (HEMII-pH) and saliva pepsin detection now allow a new multidimensional diagnostic approach associating clinical scores to HEMII-pH and saliva pepsin detection. This new approach may enable personalized treatment according to LPR profile on HEMII-pH (acid, non-acid, mixed; upright, recumbent reflux episodes). Updated treatment of LPR could consist in a 3-month association of dietary measures, proton pump inhibitors, alginate and magaldrate, followed by treatment adaptation.

Keywords: Laryngopharyngeal; reflux; laryngitis; diagnosis; treatment.

1. Introduction

Laryngopharyngeal reflux (LPR) is an upper airway inflammatory pathology involving gas and/or liquid reflux of gastroduodenal contents at the upper airway mucosa [1]. The inflammatory reaction is above all induced by direct irritation by pepsin, trypsin and other enzymatic molecules, gastroduodenal contents may also irritate the lower esophagus, stimulate chemoreceptors and cause reflex cough, hemming and laryngopharyngeal mucosal hypersecretion [2,3]. The inflammatory reaction is thus due to both direct and indirect irritation.

Since the late 1990s, LPR has been the focus of an increasing number of studies (Figure 1 [4]), mostly highlighting differences with gastroesophageal reflux disease (GERD), leading some authors to consider them as two different entities [5,6]. Despite the abundant literature, assessment and treatment remain highly controversial. The present article is a systematic review of the literature on the epidemiology, clinical presentation, diagnosis and treatment of LPR, with a proposal for updated management.

2. Material and methods

Methodologically, the review used the Patient/problem Intervention Comparison Outcomes (PICO) criteria [7]. Studies were required to concern adult (≥ 18 years) LPR patients, diagnosed clinically (symptoms \pm signs), and could include complementary examinations (pH monitoring, pH impedance monitoring, pepsin detection) for confirmation. Patients with purely clinical diagnosis were considered as having suspicion of LPR; those with further complementary examination were considered as having definite LPR. Studies were not required to analyze treatment impact, but simply to provide new information on epidemiology, clinical presentation, diagnosis and/or treatment. Pediatric cohorts and case reports were excluded.

The study used the PubMed, Cochrane Library and Scopus databases, with search terms: *reflux; laryngopharyngeal; laryngitis; gastroesophageal; outcomes; epidemiology; diagnosis; and treatment*, over the period 1980-2018. Articles were required to be written in English, French or Spanish. Selection was first on Abstract, and articles meeting the inclusion criteria (epidemiology, clinical presentation, diagnosis and/or treatment) were downloaded then further selected on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [8], as shown in figure 2. Critical analysis of inclusion and exclusion criteria, diagnostic method and treatment was performed and is discussed below. Only clinical studies with >10 patients were included. Systematic reviews were also included.

3. Discussion

3.1. Epidemiology

The first epidemiological study dates from the 1990s. At the time, Koufman assessed incidence at 10% of ENT consultations [9]. Only 62% of the 225 patients underwent dual-probe pH monitoring (with a distal esophageal and a proximal sensor) and 30% had ≥ 1 reflux episode in the proximal esophagus. In 2002, the same authors reported that 69% of patients consulting in a voice clinic had signs and symptoms of reflux; 73% had positive dual-probe pH monitoring [9,10]. These two studies are, to date, the only ones to assess reflux incidence in two populations with pH-monitoring. Other studies were performed in the last 20 years to determine incidence of reflux complaints in various populations. Chen et al. reported 18.8% prevalence in a Chinese population on the Reflux Symptom Index (RSI) [11]. Using the same clinical instrument, two authors estimated that 5% and 30% of Greek and British populations respectively showed symptoms of LPR [12,13]. However, none of these diagnostic studies included confirmation on complementary examination, and reflux symptoms are very poorly specific, easily encountered in other frequent airway pathologies: chronic rhinosinusitis, allergy, smoking- or alcohol-related laryngopharyngitis, etc. [14-17], none of which were analyzed, seriously relativizing study conclusions.

Given these reports, we consider LPR incidence and prevalence currently unknown. Although diagnosis was confirmed on pH monitoring in some studies, we now know that this fails to detect non-acid or mixed reflux, found in 50% of patients with complaints and signs of reflux [18,19]. If shown to be highly sensitive and specific, new less invasive diagnostic techniques, such as pepsin and trypsin detection in airway mucosa, could enable new epidemiological studies determining real incidence and prevalence. Given the major impact of diet on the development of reflux [20-22], such studies will have to take account of specific population characteristics and will be difficult to extrapolate to the worldwide general population. GERD, which is better documented, affects 20-30% of the US population [23,24].

3.2. Diagnosis

3.2.1. Clinical presentation

A recent literature review reported that the most frequent reflux complaints concern sensation of foreign body in the throat, hemming, hoarseness and excessive mucus in the throat [4]. Prevalence of these symptoms varied between studies, but they generally affect more than

70% of patients [25,26]. However, they are not very specific and are found in other airway pathologies, making clinical diagnosis difficult and uncertain. Moreover, prevalence varies with gender and age: women more often show dysphonia, due to various anatomic, histologic and functional factors [27,28], while age-related sensorineural degeneration means that elderly subjects feel acid reflux less strongly [29,30].

The presenting symptoms of GERD are less frequent in LPR, as most episodes are gaseous rather than liquid: fewer than 50% of patients show acid reflux or pyrosis [25,31]. This underlies a controversy as to the link between LPR and GERD, some authors considering the two to be distinct [6], while others speak of “extradigestive manifestations of GERD” [32,33] and recent data point to shared pathophysiological mechanisms and to GERD patients being more liable to develop LPR [31,32]. Some authors reported 33-39% prevalence of laryngopharyngeal symptoms in GERD [31,34], and extra risk of esophagitis or Barret’s metaplasia in case of LPR [35]. The association can be insidious and concern elderly patients in particular, who are less sensitive to pyrosis and thus develop relatively asymptomatic esophagitis or Barret’s metaplasia. In contrast to received wisdom, LPR patients may also show digestive symptoms, improving significantly under treatment [18].

Concerning natural history, 25-50% of patients experience recurrent episodes throughout life [9]. In practice, we encounter some patients with chronic mild to moderate reflux which, like certain rhinosinusopathies, are exacerbated under certain conditions that also favor LPR: stress, or unhealthy lifestyle and diet. Oddly, the concept of chronic LPR is little reported and poorly defined in the literature.

The most frequent clinical signs are posterior commissure hypertrophy, interarytenoid and laryngeal erythema, and thick adhesive laryngeal mucus [4,25,26]. Like the symptomatology, these signs are relatively non-specific, found also in other airway disorders [1]. The laryngopharyngeal signs most frequently encountered in the asymptomatic population are posterior commissure hypertrophy and interarytenoid and laryngeal erythema [36,37], confirming their poor specificity.

To improve diagnosis and treatment assessment, in 2001 Belafsky et al. developed 2 clinical instruments: the Reflux Symptom Index (RSI) and the Reflux Finding Score (RFS) [38,39]. The RSI was translated and adapted and validated in French, Italian, Spanish and Chinese [40-43], but doubt has been cast on its internal validity and several key symptoms are overlooked [1,44]. 1) it combines some very different symptoms in a single item: acid reflux, chest pain, heartburn and poor digestion. 2) It assesses only symptom severity and not frequency. And 3) it overlooks some key symptoms: sore throat, odynophagia and halitosis.

Likewise, the RFS overlooks various signs: oro- and hypo-pharyngeal erythema, retrocricoid edema, lingual tonsil hypertrophy, saburrual tongue, anterior pillar erythema, etc. [17,45]. Moreover, its analogic assessment of reflux signs makes severity assessment highly subjective in some cases [17]. Various studies reported poor intra-observer reliability [46,47], vitiating comparison across studies [1,17]. These weaknesses of the RSI and RFS cast doubt on their content and presentation, and new more complete clinical instruments were developed, taking account of symptoms severity and frequency and precisely defining degrees of severity of reflux signs [1,45]. The Reflux Symptom Score (RSS) shows statistically better internal validity than the RSI (Figure 3) [18] and is under validation in Italian, English, Korean and Spanish [45]. RSS >13 shows 95% sensitivity for diagnosis of reflux and could be used for ENT screening; The Reflux Sign Assessment (RSA) was recently validated and showed superiority over the RFS [46]. It assesses laryngeal and extra-laryngeal signs, which significantly improve under treatment (Figure 4) [46].

3.2.2. Objective examinations

24-hour pH impedance monitoring is the complementary examination of choice to confirm diagnosis and has largely replaced traditional pH monitoring, which fails to detect non-acid reflux, and thus shows only 70-80% sensitivity, with 20-50% false-negative rates [33,49]. pH impedance monitoring provides a precise reflux profile: type of reflux (acid, non-acid, mixed; liquid and/or gaseous), number and duration of episodes, timing (day, night), and concomitant GER. It has, however, several weaknesses, and is not yet a gold standard. Given the natural history of LPR, patients may not experience any significant episode during the 24-hour test period. Diet, stress and lifestyle all influence episode onset [31,50]. Moreover, pH impedance monitoring does not correlate with objective signs and symptoms in consultation [4]. Absence of LPR on pH impedance monitoring thus does not rule out diagnosis [51,52]. To get around this and improve correlation between reflux episodes and symptoms, 48- or 96-hour studies have been advocated [53]. Also, probe positioning and diagnostic criteria are not yet standardized, hindering comparison across studies [1,4]. A rigorous survey is needed, screening for the various differential diagnoses detailed in Table 1.

Oropharyngeal pH monitoring in consultation is an alternative advocated by several teams. A pH monitoring probe is placed in the oropharynx for 24 hours to measure liquid or gaseous reflux episodes. Like in 24-hour pH impedance monitoring, there is no consensus on diagnostic criteria, although most teams using oropharyngeal pH monitoring consider diagnosis of LPR to be positive in case of Ryan >9.4 in upright stance or >6.8 lying [55-60].

The advantage of esophageal pH impedance monitoring over oropharyngeal pH monitoring lies in concomitant detection of LPR and GER. In GERD, this may indicate gastroscopy with esophago-gastric biopsy to rule out erosive pathology. Finally, there may be discordance between the 2 examinations in a given patient, as some episodes may be detected in the proximal esophagus but not in the hypopharynx [51,61-63]. Prospective studies are needed in patients undergoing concomitant classical pH impedance monitoring and oropharyngeal pH monitoring.

3.2.3. Empiric treatment

Considering the cost, discomfort and limitations of pH impedance monitoring, several authors advocated empiric treatment as a means of confirming diagnosis [64,65]. This involves clinical scores for diagnosis and empiric treatment based on diet and 20mg daily proton-pump inhibitor. Reassessment on clinical scores is performed at 3 months to adapt treatment [64]: according to clinical improvement, treatment may be decreased, increased or maintained for 3 more months [64]. There is at present no consensus on the definition of treatment “response” [66]: the various definitions tend to be based on improvement in symptoms or concomitant improvement in signs and symptoms [21,67-69]. Empiric treatments also vary between studies, and dietary prescription is not systematic [1].

At first sight, this approach appears straightforward and cost-saving, but cost and efficacy have in fact never been compared versus treatment personalized according to pH impedance monitoring. About 50% of patients seem to respond to empiric treatment [66,67,69,70], but a non-negligible proportion are poorly treated for several months without real confirmation of diagnosis. A recent study reported that a non-negligible proportion of ENT physicians prescribe long-course proton-pump inhibitors in case of lack of clinical improvement [71]. Finally, empiric treatment requires ruling out differential diagnoses mimicking LPR, whereas a recent systematic review found that this varied strongly between studies [1].

Generally, empiric treatment is recommended when 24h pH impedance monitoring is difficult to perform [66]. Treatment should involve ruling out confounding factors (Table 1), dietary prescription, lifestyle changes and dual anti-reflux treatment by proton-pump inhibitor (pantoprazole, 20mg 2/daily 30 minutes before midday and evening meals) and alginate (Gaviscon®, 3/daily 30 minutes after meals), the last point being especially important in light of the prevalence of non-acid and mixed reflux [18,19] (Figure 5). In case of GERD symptoms or age >50 years, digestive endoscopy is recommended [72].

3.2.4. Biochemical examinations

Pepsin detection is a new non-invasive diagnostic technique consisting in immunohistochemical analysis of pepsin in airway mucosa or secretions at different times of day: awakening, after meals, after episode [73]. A recent meta-analysis assessed sensitivity and specificity in saliva at 64% and 68% respectively [74]. In practice, reliability is not known and depends on the analysis technique (ELISA versus Western blot versus immunohistochemistry), diagnostic threshold (percentage positive immunofluorescence), and timing [75]. The Peptest (salivary pepsin detection) is specific to pepsin 3b (the most active), responsible for tissue lesions. Although there have been no studies, we think it probable that stress, physical activity and meal contents during the sampling period significantly impact results. Importantly, pepsin measurement is relevant to both acid and non-acid reflux [76]: activity is optimal at pH 2.0, but present in pH up to 7.0, liable to cause mucosal tissue lesions [77]. Moreover, pepsin can be internalized in epithelial cells lining the airway and reactivated in the Golgi apparatus where pH is generally <6.0, liable to cause intracellular lesions [78]. Pepsin is thus active down to neutral pH. A recent study found no correlation between number and duration of reflux episodes and saliva pepsin levels [76], reinforcing the hypothesis of intracellular toxicity but also suggesting that pepsin is not the only enzyme implicated in mucosal lesions. Although little studied, trypsin is a pancreatic enzyme active at more alkaline pH levels, and seeming to play a major role in the development of airway mucosal lesions [79]. Further studies are needed to elucidate the pathophysiological mechanisms underlying the activity of pepsin, trypsin, other gastroduodenal enzymes and biliary salts and acids liable to contribute to the development of mucosal lesions in LPR.

3.3. Treatment

3.3.1. Lifestyle and dietary rules

Pathophysiologically, several factors account for onset of LPR: esophageal dysfunction (transient or permanent sphincter relaxation, dysmotility), unhealthy lifestyle (stress, late meals, aerophagy, smoking, etc.) and low-protein high-fat diet [4,20,22,80]. Fatty foods are associated with longer gastric digestion and onset of reflux episodes [20]. Acid foods and some amino acids contribute to acidic reflux and hence to pepsin enzymatic activity in airway mucosa. Finally, smoking, alcohol, spices, coffee, tea and fizzy drinks impair esophageal sphincter tonus [81], inducing relaxation, in contrast to protein-rich foods. In the light of these various pathophysiological mechanisms, lifestyle and dietary measures should be systematically prescribed. A recent study classified the main foods consumed in Europe in 5

categories according to refluxogenic potential (Tables 2 and 3) [82], enabling authors to develop clinical scores assessing the refluxogenic potential of meals and overall diet [82]. The importance of diet was shown in a recent meta-analysis [1] and in several clinical studies, whether proton-pump inhibitors were associated [20], or not [21], and also in resistant patients [22]. In a recent retrospective study, Zalvan et al. [21] reported that an alkaline “Mediterranean” diet based on plant proteins, cooked vegetables, and low levels of animal fat was quite as effective as proton-pump inhibitors. Patients receiving proton-pump inhibitors who adhered to a Mediterranean diet showed greater clinical improvement than those who did not [20]. Most treatment decisions are related to more or less functional symptoms, and the trade-off between symptom intensity and the drawbacks of long-course medication needs to be assessed. As pointed out by Zalvan et al. [21], it should be borne in mind that diet alone is enough to deal with most mild to moderate LPR, saving health-care costs. Recent studies validated a European anti-reflux diet based on a mathematical score taking account of foodstuff pH, and content in fat, protein and quick sugar and substances liable to impair esophageal sphincter tonus (caffeine, spices, etc.) [82,83].

3.3.2. Anti-reflux drugs

For several decades now, standard treatment for LPR consisted in fasting proton-pump inhibitors before breakfast and lunch. However, evidence of superiority versus placebo is weak [1], due to 1) the small number of randomized studies versus placebo, 2) disparities between studies in inclusion and exclusion criteria, diagnostic method, dietary prescriptions or not and efficacy assessment instruments, and 3) failure to take account of patients with non-acid and mixed reflux (pH monitoring without impedance), who show less response to proton-pump inhibitors [1,19,84-86].

In the light of these various studies and the recent development of pH impedance monitoring, treatment approaches need to progress to take account of individual reflux profiles. Optimal treatment would associate diet \pm proton-pump inhibitors \pm alginate \pm magaldrate (Figure 6). Proton-pump inhibitors are important for acid and mixed reflux, as they alkalinize acid gaseous and liquid reflux, decreasing pepsin activity [4,87,88]; their interest in non-acid reflux is less great [88]. In acid or mixed reflux, adding an alginate after the meal reduces gaseous reflux. In a recent study, associated proton-pump inhibitors and Gaviscon advance® showed results comparable to those of Gaviscon advance® alone [87]. A European survey showed that non-acid reflux is thought by many ENT physicians to be resistant to all anti-reflux treatments [71]; yet clinical response to alginate or magaldrate is similar to that of acid

reflux treated by proton-pump inhibitor \pm alginate [89], confirming the interest of associating different drugs.

Whatever the type of treatment, it should be adapted after 3 months and drug treatments should be of limited duration, lifestyle and dietary measures being continued. In the long term, proton-pump inhibitors and other drugs may cause adverse bone, endocrine and renal effects [88]. Antihistamines currently have no contribution to make, due their short action time (4-8 hours) [4].

Whatever the treatment, resistance calls for thorough history taking. Pisegna et al. reported that 63% of non-responders (considered resistant) had in fact not adhered to treatment [90]. If the patient does seem to have adhered to treatment, confounding pathology should be screened for (Table 1); if none is found, other molecules may be added and lifestyle/dietary measures should be stepped up. After 6 months' trial treatment, complementary examinations may be performed (esophageal manometry, gastroscopy, etc.) to screen for mechanisms such as gastroparesis, hiatal hernia, ectopic esophageal gastric mucosa, etc.. Before indicating surgery, baclofen or other neuromodulators may be associated to treatment [66,91,92]: they reinforce esophageal sphincter function and are used in GERD, and could be useful in LPR resistant to conventional treatment. Serotonin reuptake inhibitors may also be useful in some cases of resistant reflux with chronic cough [66]; their action mechanism is not known, but they may act on the autonomic nervous system by decreasing sympathetic activity and thus reducing transient esophageal sphincter relaxation [66].

3.3.3. Surgery

Laparoscopic fundoplication is a valid option in case of drug and diet resistant reflux [93], but efficacy in LPR is controversial [93] as success rates range between 44% and 94% [93] compared to 85-90% in GERD [94-96]. Like for the randomized studies versus placebo for proton-pump inhibitors, clinical studies on laparoscopic fundoplication vary in inclusion and exclusion criteria, diagnostic method and efficacy assessment instruments, preventing any clear conclusions from being drawn as to efficacy and indications for fundoplication in LPR [93].

4. Conclusion

Laryngopharyngeal reflux is frequent, although incidence and prevalence are not known. There is at present no international consensus on diagnostic criteria for positive 24-hour pH impedance monitoring. A multiparameter score associating signs and symptoms assessed on

complete and reliable clinical instruments, plus ≥ 24 -hour pH impedance monitoring and airway pepsin/trypsin detection would significantly improve diagnostic and therapeutic management. With the recent development of pH impedance monitoring, anti-reflux treatment should become more personalized, based on diet with or without association to different drugs according to reflux type (acid, non-acid, mixed). Future multicenter studies are needed to assess the efficacy of this personalized management algorithm.

Acknowledgments: Pr Dominique Chevalier for advice and careful re-editing.

Disclosure of interest: The authors have no conflicts of interest to disclose.

Références

- [1] Lechien JR, Saussez S, Schindler A, Karkos P, et al. Symptoms and Signs Outcomes of Laryngopharyngeal reflux Treatment: A critical Systematic review and Meta-analysis. *Laryngoscope*. 2019 May;129(5):1174-1187. doi: 10.1002/lary.27591.
- [2] Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP. *Lancet*. Reflux of gastric juice and glue ear in children. 2002; 359(9305):493.
- [3] Arruda Henry MA, Martins RH, Lerco MM, et al. Gastroesophageal reflux disease and vocal disturbances. *Arq Gastroenterol*. 2011;48(2):98-103.
- [4] Lechien JR, Akst LM, Hamdan AL, et al. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. *Otolaryngol Head Neck Surg*. 2019;160(5):762-782. doi: 10.1177/0194599819827488.
- [5] Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg*. 2002; 127(1):32-5.
- [6] Koufman JA. Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease. *Ear Nose Throat J*. 2002; 81(9 Suppl 2):7-9.
- [7] Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007; 7:16.
- [8] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097.
- [9] Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991; 101(4 Pt 2 Suppl 53):1-78.
- [10] Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. *Otolaryngol Head Neck Surg*. 2000; 123(4):385-8.
- [11] Lam P, Wei WI, Hui Y, Ho WK. Prevalence of pH-documented laryngopharyngeal reflux in Chinese patients with clinically suspected reflux laryngitis. *Am J Otolaryngol*. 2006; 27(3):186-9.
- [12] Spantideas N, Drosou E, Bougea A, Assimakopoulos D. Laryngopharyngeal reflux disease in the Greek general population, prevalence and risk factors. *BMC Ear Nose Throat*

Disord. 2015; 15:7.

[13] Kamani T, Penney S, Mitra I, Pothula V. The prevalence of laryngopharyngeal reflux in the English population. *Eur Arch Otorhinolaryngol*. 2012; 269(10):2219-25.

[14] Habermann W, Schmid C, Neumann K, et al. Reflux symptom index and reflux finding score in otolaryngologic practice. *J Voice*. 2012; 26(3):e123-7.

[15] Lee YS, Choi SH, Son YI, Park YH, Kim SY, Nam SY. Prospective, observational study using rabeprazole in 455 patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol*. 2011; 268(6):863-9.

[16] Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol*. 1995; 104(7):550-5.

[17] Lechien JR, Schindler A, De Marrez LG, et al. Instruments Evaluating the Clinical Findings of Laryngopharyngeal Reflux: A Systematic Review. *Laryngoscope*. 2018; 129(3):720-736. doi: 10.1002/lary.27537.

[18] Lechien JR, Bobin F, Muls V, Thill MP, Horoi M, Ostermann K, Huet K, et al. Validity and reliability of the reflux symptom score. *Laryngoscope*. 2019. doi: 10.1002/lary.28017.

[19] Carroll TL, Fedore LW, Aldahlawi MM. pH Impedance and high-resolution manometry in laryngopharyngeal reflux disease high-dose proton pump inhibitor failures. *Laryngoscope*. 2012; 122(11):2473-81.

[20] Lechien JR, Huet K, Khalife M, et al. Alkaline, protein, low-fat and low-acid diet in laryngopharyngeal reflux disease: Our experience on 65 patients. *Clin Otolaryngol*. 2019; 44(3):379-384. doi: 10.1111/coa.13269.

[21] Zalvan CH, Hu S, Greenberg B, Geliebter J. A Comparison of Alkaline Water and Mediterranean Diet vs Proton Pump Inhibition for Treatment of Laryngopharyngeal Reflux. *JAMA Otolaryngol Head Neck Surg*. 2017; 143(10):1023-1029.

[22] Koufman JA. Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. *Ann Otol Rhinol Laryngol*. 2011; 120(5):281-7.

[23] Ciprandi G, Gelardi M. Gastric reflux: comparison between the gastroenterologist and the otorhinolaryngologist's approach. Pragmatic conclusive remarks. *J Biol Regul Homeost Agents*. 2018; 32(1 Suppl. 2):33-38.

[24] Truck GT. GERD by the numbers: Facts, Statistics & You. Newsletter Healthline 02.03.15

[25] Habermann W, Schmid C, Neumann K, et al. Reflux symptom index and reflux finding score in otolaryngologic practice. *J Voice*. 2012; 26(3):e123-7.

- [26] Lee JS, Lee YC, Kim SW, Kwon KH, Eun YG. Changes in the quality of life of patients with laryngopharyngeal reflux after treatment. *J Voice*. 2014;28(4):487-91.
- [27] Gao CK, Li YF, Wang L, et al. Different cutoffs of the reflux finding score for diagnosing laryngopharyngeal reflux disease should be used for different genders. *Acta Otolaryngol*. 2018; 1-7.
- [28] Lechien JR, Huet K, Khalife M, et al. Gender differences in the presentation of dysphonia related to laryngopharyngeal reflux disease: a case-control study. *Eur Arch Otorhinolaryngol*. 2018; 275(6):1513-1524.
- [29] Lechien JR, Finck C, Huet K, et al. Impact of age on laryngopharyngeal reflux disease presentation: a multi-center prospective study. *Eur Arch Otorhinolaryngol*. 2017; 274(10):3687-3696.
- [30] Mendelsohn AH. The Effects of Reflux on the Elderly: The Problems with Medications and Interventions. *Otolaryngol Clin North Am*. 2018; 51(4):779-787.
- [31] Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. *Aliment Pharmacol Ther*. 2003; 17(12):1515-20.
- [32] Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol*. 2003;1(5): 333–44.
- [33] Patel D, Vaezi MF. Normal esophageal physiology and laryngopharyngeal reflux. *Otolaryngol Clin N Am*. 2013;46(6): 1023–41.
- [34] Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci*. 2007; 52(2):463-8.
- [35] Lai YC, Wang PC, Lin JC. Laryngopharyngeal reflux in patients with reflux esophagitis. *World J Gastroenterol*. 2008 Jul 28;14(28):4523-8.
- [36] Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice*. 2002; 16(4):564-79.
- [37] Chen M, Hou C, Chen T, Lin Z, et al. Reflux symptom index and reflux finding score in 91 asymptomatic volunteers. *Acta Otolaryngol*. 2018; 138(7): 659-663.
- [38] Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002; 16(2):274-7.
- [39] Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope*. 2001; 111(8):1313-7.

- [40] Lechien JR, Huet K, Finck C, et al. Validity and Reliability of a French Version of Reflux Symptom Index. *J Voice*. 2017; 31(4):512.e1-512.e7.
- [41] Schindler A, Mozzanica F, Ginocchio D, Peri A, Bottero A, Ottaviani F. Reliability and clinical validity of the Italian Reflux Symptom Index. *J Voice*. 2010; 24(3):354-8.
- [42] Calvo-Henríquez C, Ruano-Ravina A, Vaamonde P, et al. Translation and Validation of the Reflux Symptom Index to Spanish. *J Voice*. 2018.
- [43] Li J, Zhang L, Zhang C, Cheng JY, Li J, Jeff Cheng CF. Linguistic Adaptation, Reliability, Validation, and Responsivity of the Chinese Version of Reflux Symptom Index. *J Voice*. 2016; 30(1):104-8.
- [44] Karkos PD, Wilson JA. Empiric treatment of laryngopharyngeal reflux with proton pump inhibitors: a systematic review. *Laryngoscope*. 2006; 116(1):144-8.
- [45] Lechien JR, Schindler A, Hamdan AL, et al. 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. *Eur Ann Otorhinolaryngol*. 2018;135(5S):S85-S91. doi: 10.1016/j.anorl.2018.05.013.
- [46] Lechien JR, Rodriguez Ruiz A, Dequanter D, et al. Validity and Reliability of the Reflux Sign Assessment. *Ann Otol Rhinol Laryngol*. 2019;3489419888947. doi: 10.1177/0003489419888947.
- [47] Musser J, Kelchner L, Neils-Strunjas J, Montrose M. A comparison of rating scales used in the diagnosis of extraesophageal reflux. *J Voice*. 2011; 25(3):293-300.
- [48] Chang BA, MacNeil SD, Morrison MD, Lee PK. The Reliability of the Reflux Finding Score Among General Otolaryngologists. *J Voice*. 2015; 29(5):572-7.
- [49] Borges LF, Chan WW, Carroll TL. Dual pH Probes Without Proximal Esophageal and Pharyngeal Impedance May Be Deficient in Diagnosing LPR. *J Voice*. 2018.
- [50] Chang BA, MacNeil SD, Morrison MD, Lee PK. The Reliability of the Reflux Finding Score Among General Otolaryngologists. *J Voice*. 2015; 29(5):572-7.
- [51] Becker V, Graf S, Schlag C, et al. First agreement analysis and day-to-day comparison of pharyngeal pH monitoring with pH/impedance monitoring in patients with suspected laryngopharyngeal reflux. *J Gastrointest Surg*. 2012; 16(6):1096-101.
- [52] Gupta R, Sataloff RT. Laryngopharyngeal reflux: current concepts and questions. *Curr Opin Otolaryngol Head Neck Surg*. 2009; 17(3):143-8.
- [53] Chander B, Hanley-Williams N, Deng Y, Sheth A. 24 Versus 48-hour bravo pH monitoring. *J Clin Gastroenterol*. 2012; 46(3):197-200.
- [54] Ayazi S, Lipham JC, Hagen JA, et al. A new technique for measurement of pharyngeal

- pH: normal values and discriminating pH threshold. *J Gastrointest Surg.* 2009;13(8):1422–9.
- [55] Wiener GJ, Tsukashima R, Kelly C, et al. Oropharyngeal pH monitoring for the detection of liquid and aerosolized supraesophageal gastric reflux. *J Voice.* 2009;23(4):498–504.
- [56] Vailati C, Mazzoleni G, Bondi S, Bussi M, Testoni PA, Passaretti S. Oropharyngeal pH monitoring for laryngopharyngeal reflux: is it a reliable test before therapy? *J Voice.* 2013; 27(1):84-9.
- [57] Feng G, Wang J, Zhang L, Liu Y. A Study to Draw a Normative Database of Laryngopharynx pH Profile in Chinese. *J Neurogastroenterol Motil.* 2014; 20(3):347-51.
- [58] Yuksel ES, Slaughter JC, Mukhtar N, et al. An oropharyngeal pH monitoring device to evaluate patients with chronic laryngitis. *Neurogastroenterol Motil.* 2013;25(5):e315–23.
- [59] Chheda NN, Seybt MW, Schade RR, Postma GN. Normal values for pharyngeal pH monitoring. *Ann Otol Rhinol Laryngol.* 2009;118(3):166–71. ^{[[L]]}_{SEP}
- [60] Sun G, Muddana S, Slaughter JC, et al. A new pH catheter for laryngopharyngeal reflux: normal values. *Laryngoscope.* 2009;119(8):1639–43.
- [61] Chiou E, Rosen R, Jiang H, Nurko S. Diagnosis of supra-esophageal gastric reflux: correlation of oropharyngeal pH with esophageal impedance monitoring for gastroesophageal reflux. *Neurogastroenterol Motil.* 2011;23(8):717–e326. ^{[[L]]}_{SEP}
- [62] Ummarino D, Vandermeulen L, Roosens B, Urbain D, Hauser B, Vandenplas Y. Gastroesophageal reflux evaluation in patients affected by chronic cough: restech versus multichannel intraluminal impedance/pH metry. *Laryngoscope.* 2013;123(4):980–4. ^{[[L]]}_{SEP}
- [63] Fuchs HF, Müller DT, Berlth F, et al. Simultaneous laryngopharyngeal pH monitoring (Restech) and conventional esophageal pH monitoring-correlation using a large patient cohort of more than 100 patients with suspected gastroesophageal reflux disease. *Dis Esophagus.*
- [64] Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA.* 2005; 294(12):1534-40.
- [65] Gupta N, Green RW, Megwalu UC. Evaluation of a laryngopharyngeal reflux management protocol. *Am J Otolaryngol.* 2016; 37(3):245-50.
- [66] Lechien JR, Muls V, Dapri G, Mouawad F, Eisendrath P, Schindler A, Nacci A, Barillari MR, Finck C, Saussez S, Akst LM, Sataloff RT. Management of Patients with recalcitrant Laryngopharyngeal Reflux: Contemporary Review. *Clin Otolaryngol,* 2019; 44(5):784-800. doi: 10.1111/coa.13395.
- [67] Lechien JR, Finck C, Huet K, et al. Voice Quality as Therapeutic Outcome in Laryngopharyngeal Reflux Disease: A Prospective Cohort Study. *J Voice.* 2018. pii: S0892-1997(18)30291-1.

- [68] Lechien JR, Finck C, Khalife M, et al. Change of signs, symptoms and voice quality evaluations throughout a 3- to 6-month empirical treatment for laryngopharyngeal reflux disease. *Clin Otolaryngol*. 2018; 43(5):1273-1282..
- [69] Lechien JR, Huet K, Khalife M, et al. Impact of laryngopharyngeal reflux on subjective and objective voice assessments: a prospective study. *J Otolaryngol Head Neck Surg*. 2016; 45(1):59.
- [70] Lien HC, Wang CC, Lee SW, et al. Responder Definition of a Patient-Reported Outcome Instrument for Laryngopharyngeal Reflux Based on the US FDA Guidance. *Value Health*. 2015; 18(4):396-403.
- [71] Lechien JR, Mouawad F, Mortuaire G, et al. Awareness of European Otolaryngologists and General Practitioners Toward Laryngopharyngeal Reflux. *Ann Otol Rhinol Laryngol*. 2019:3489419858090.
- [72] Lei WY, Yu HC, Wen SH, et al. Predictive factors of silent reflux in subjects with erosive esophagitis. *Dig Liver Dis*. 2015; 47(1):24-9.
- [73] Saritas Yuksel E, Hong SK, Strugala V, et al. Rapid salivary pepsin test: blinded assessment of test performance in gastroesophageal reflux disease. *Laryngoscope*. 2012;122(6):1312–6.
- [74] Wang J, Zhao Y, Ren J, Xu Y. Pepsin in saliva as a diagnostic biomarker in laryngopharyngeal reflux: a meta-analysis. *Eur Arch Otorhinolaryngol*. 2018; 275(3):671-678.
- [75] Calvo-Henríquez C, Ruano-Ravina A, Vaamonde P, et al. Is Pepsin a Reliable Marker of Laryngopharyngeal Reflux? A Systematic Review. *Otolaryngol Head Neck Surg*. 2017; 157(3):385-391.
- [76] Bobin F, Journe F, Lechien JR. Saliva Pepsin Level of Laryngopharyngeal Reflux Patients is not correlated with Reflux Episodes. *Laryngoscope*, 2019. doi: 10.1002/lary.28260.
- [77] Johnston N, Ondrey F, Rosen R, Hurley BP, et al. Airway reflux. *Ann N Y Acad Sci*. 2016; 1381(1):5-13.
- [78] Johnston N, Wells CW, Samuels TL, Blumin JH. Pepsin in nonacidic refluxate can damage hypopharyngeal epithelial cells. *Ann Otol Rhinol Laryngol*. 2009; 118(9):677-85.
- [79] El-Serag HB, Lee P, Buchner A, Inadomi JM, Gavin M, McCarthy DM. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. *Am J Gastroenterol*. 2001; 96(4):979-83.
- [80] Wang AM, Wang G, Huang N, Zheng YY, Yang F, Qiu X, Chen XM. Association between laryngopharyngeal reflux disease and autonomic nerve dysfunction. *Eur Arch*

Otorhinolaryngol. 2019. doi: 10.1007/s00405-019-05482-w.

[81] Ducrotté P, Chaput U. Pathophysiology of gastro-oesophageal reflux. *EMC-Hepato-gastroenterol.* 2005 ; 362-369.

[82] Lechien JR, Bobin F, Mouawad F, et al. Development of Scores Assessing the Refluxogenic Potential of Diet of Patients with Laryngopharyngeal Reflux. *Eur Arch Otorhinolaryngol*, 2019; 276(12):3389-3404. doi: 10.1007/s00405-019-05631-1.

[83] Lechien JR, Bobin F, Muls V, Horoi M, Thill MP, Dequanter D, Rodriguez A, Saussez S. Patients with acid, high-fat and low-protein diet have higher laryngopharyngeal reflux episodes at the impedance-pH monitoring. *Eur Arch Otorhinolaryngol.* 2020; 277(2):511-520. doi: 10.1007/s00405-019-05711-2.

[84] Lee JS, Jung AR, Park JM, Park MJ, Lee YC, Eun YG. Comparison of Characteristics According to Reflux Type in Patients With Laryngopharyngeal Reflux. *Clin Exp Otorhinolaryngol.* 2018; 11(2):141-145.

[85] Galli J, Cammarota G, De Corso E, et al. Biliary laryngopharyngeal reflux: a new pathological entity. *Curr Opin Otolaryngol Head Neck Surg.* 2006; 14(3):128-32.

[86] Sereg-Bahar M, Jerin A, Jansa R, Stabuc B, Hocevar-Boltezar I. Pepsin and bile acids in saliva in patients with laryngopharyngeal reflux - a prospective comparative study. *Clin Otolaryngol.* 2015; 40(3):234-9.

[87] Wilkie MD, Fraser HM, Raja H. Gaviscon® Advance alone versus co-prescription of Gaviscon® Advance and proton pump inhibitors in the treatment of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol.* 2018; 275(10):2515-2521.

[88] Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD An overview of their pharmacology, efficacy and safety. *Pharmacol Res.* 2009; 59(3):135-53.

[89] Lechien JR, Bobin F, Muls V, et al. Gastroesophageal reflux in laryngopharyngeal reflux patients: Clinical features and therapeutic response. *Laryngoscope.* 2019. doi: 10.1002/lary.28482.

[90] Pisegna JM, Yang S, Purcell A, Rubio A. A Mixed-Methods Study of Patient Views on Reflux Symptoms and Medication Routines. *J Voice.* 2017; 31(3):381.e15-381.e25.

[91] Scarpellini E, Ang D, Pauwels A, De Santis A, Vanuytsel T, Tack J. Management of refractory typical GERD symptoms. *Nat Rev Gastroenterol Hepatol.* 2016; 13(5):281-94.

[92] Sataloff RT, Hawkshaw MJ, Gupta R. Laryngopharyngeal reflux and voice disorders: an overview on disease mechanisms, treatments, and research advances. *Discov Med.* 2010; 10(52):213-24.

- [93] Lechien JR, Dapri G, Dequanter D, et al. Surgical treatment for laryngopharyngeal reflux disease: A systematic review of 2,190 patients. *JAMA Otolaryngol Head Neck Surg*, 2019; 145(7):655-666. doi: 10.1001/jamaoto.2019.0315.
- [94] Farrell TM, Richardson WS, Trus TL, Smith CD, Hunter JG. Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery. *Br J Surg*. 2001; 88(12):1649-52.
- [95] Ciovica R, Gadenstätter M, Klingler A, Neumayer C, Schwab GP. Laparoscopic antireflux surgery provides excellent results and quality of life in gastroesophageal reflux disease patients with respiratory symptoms. *J Gastrointest Surg*. 2005; 9(5):633-7.
- [96] Frazzoni M, Piccoli M, Conigliaro R, Frazzoni L, Melotti G. Laparoscopic fundoplication for gastroesophageal reflux disease. *World J Gastroenterol*. 2014; 20(39):14272-9.

Table 1: Main differential diagnoses for laryngopharyngeal reflux symptoms.

Differential diagnoses for laryngopharyngeal reflux symptoms		
Esophageal and gastric pathologies	Upper airway pathologies	Non-upper airway pathologies
Eosinophile esophagitis	<i>Infection</i>	<i>Pulmonary pathologies</i>
Zenker diverticulum	Chronic rhinosinusitis	COPD
Scleroderma	Mycosis	Asthma
Mycotic esophagitis	Iterative pharyngitis	<i>Neuropsychiatric/psychological pathologies</i>
Esophageal ectopic gastric mucosa	Tuberculosis	Stress & anxiety
Neoplasia	<i>Rheumatologic & auto-immune pathologies</i>	Depression
Cricopharyngeal muscle spasm	Rheumatoid arthritis	Drugs
Esophageal spasm	Sjögren syndrome	
Inferior esophageal sphincter spasm	Pharyngo/laryngeal sarcoidosis	
Achalasia cardia	Pharyngo/laryngeal amyloidosis	
Absence of peristaltism	Pharyngo/laryngeal granulomatosis	
Gastroparesis	Fibromyalgia	
	Allergy	
	<i>Benign and malignant tumor</i>	
	<i>Anatomic abnormalities</i>	
	Epiglottic abnormalities	
	Lingual tonsil hypertrophy	
	Uvular hypertrophy	
	Epiglottic retroversion (in contact with pharyngeal wall)	
	<i>Traumatic pathologies</i>	
	Laryngeal fracture and trauma	
	Traumatic airway mucosa lesion	
	<i>Miscellaneous</i>	
	Spasmodic dysphonia	
	Laryngeal neuropathy	
	Cervical osteophytosis	
	Drug-induced and toxic pharyngolaryngitis	
	Presbyphonia	

Thyroid pathology (goiter, nodules, etc.)
Xerostomia reaction to anti-cholinergics

Table 1: These entities are to be assessed in case of diagnostic doubt.

Table 2: Refluxogenic potential of foods.

Very low RP	Cat.	Low RP	Cat.	Moderate RP	Cat.	High RP	Cat.	Very high RP	Cat.
				Pear	3	Grapes	4		
Fish, fresh not-fatty	1			Nectarine	3	Blackberry	4	Carbonara sauce	5
Pork, lean	1			Egg (white + yolk)	3	Walnut	4	Pesto sauce	5
Rice, non-fat	1			Onion, raw*	3	Noodles	4	Candies	5
Rice, white	1			Orange	3	Marmalade	4		
Spaghetti, cooked	1			Bread, wholemeal	3	Parmesan	4		
Tuna, non-fat	1			Grapefruit	3	Pâté	4		
Veal	1			Peach	3	Apple	4		
Beetroot	1	Banana	2	Duck, lean	3	Chocolate cookies	4	Dark chocolate	5
Celery	1	Beef chops	2	Lamb chops	3	Strawberry jam	4	Croissant	5
Cheese, low-fat	1	Bread, rye	2	Fish oil	3	Gruyère cheese	4	Macadamia nut	5
Spinach	1	Bread, white	2	Guava	3	Pomegranate	4	Mayonnaise	5
Wheat	1	Carrot	2	Zucchini	3	Crackers	4	White chocolate	5
Broccoli	1	Cereals	2	Cucumber	3	Feta cheese	4	Choucroute	5
Brussel sprout	1	Cherries	2	Gherkin	3	Fontina cheese	4	Ice-cream	5
Egg white	1	Chicken, breast	2	Cornflakes	3	Cookies	4	Milk chocolate	5
Artichoke	1	Eggplant	2	Offal*	3	Cauliflower	4	Butter	5
Horse meat	1	Fennel	2	Shallot, raw*	3	Blue cheese	4	Chocolate eclairs	5
Cabbage, red	1	Ham, cooked, lean	2	Strawberry	3	Fat or hard cheese	4	Fries	5
Honey	1	Kidney, cooked	2	Milk, cow, semi-skimmed	3	Mango	4	Pesto	5
Garlic	1	Lamb, lean	2	Apricot	3	Cake	4	Avocado	5
Cooked greens*	1	Leak	2	Milk, goat, semi-skimmed	3	Milk, full-cream	4	Green olives	5
Crab	1	Melon	2	Raspberry	3	Red currant jelly	4	Coconut water	5
Asparagus*	1	Oats	2	Camembert cheese	3	Cheddar cheese	4	Chips	5
Milk, skimmed	1	Parsley	2	Ketchup*	3	Egg yolk	4	Black olive	5
Lentils	1	Pepper	2	Milk, soy	3	Litchi	4	Pain au chocolat	5
Chicory/endive	1	Pork, fillet	2	Fig	3	Goat and Brie cheese.	4	Spices	5
Mollusks	1	Rice, brown	2	Mandarin	3	Mustard	4	Béarnaise sauce	5
Sweet potato	1	Steak, lean	2	Mint	3	Mozzarella cheese	4	Pepper sauce	5
Peas	1	Tofu	2	Blueberry	3	Munster cheese	4	Roquefort sauce	5
Turkey, lean	1	Turnip	2	Ginger	3	Gouda cheese	4	Lard	5
Mushrooms, cooked	1	Veal chops	2	Pork chops	3	Strawberry jam	4	Curry	5
Green beans	1	Water melon	2	Olive oil	3	Mince	4	Cashew nuts, peanuts	5
				Fish, fatty	3	Ricotta cheese	4		
				Potato	3	Roquefort cheese	4		

	Plum	3	Mushroom sauce (meat)	4
	Prune	3	Tomato/Bolognaise sauce	4
	Rhubarb	3	Salami	4
	Fish sauce	3	Sausage	4
	Salmon	3	Sorbet	4
	Sardine	3	Vinaigrette	4
	Tomato	3	Full-cream yoghurt	4

Table 2: Refluxogenic potential (very low to very high) of foods commonly consumed in Europe according to pH and fat and protein concentration. Cooking (especially for vegetables) can affect ranking: e.g., onion or shallot would be in category 2 when cooked. Foods liable to be recategorized are shown with an asterisk. Details can be found in [82]. Abbreviations: Cat. = categories; RP= refluxogenic potential.

Table 3: Refluxogenic potential of drinks.

Drinks	pH	GI>40	Cat.
Spirits	4	+	5
Aloe vera	6.1	0	2
Apple juice	3.65	+	5
Beer	4	+	5
Hot chocolate	6.3	+	3
Chamomile	6.5	0	2
Chicory	5.95	0	3
Coffee	5	0	4
Grapefruit juice	3.05	+	5
Lemon juice	2.3	+	5
Multifruit juice	3.8	+	5
Orange juice	3.5	+	5
Soda, zero sugar	2.5	0	5
Soda with sugar	2.5	+	5
Syrup (grenadine, lemon, etc.)	2.15	+	5
Tea	5	0	4
Red fruit infusion	2.5	0	5
Black tea	5.3	0	4
Green tea	7	0	3
Lemon tea	2.9	0	5
Tomato juice	4.35	0	3
Sparkling water	7	0	3
Still water	7	0	2
Alkaline still water	8	0	1
Red wine	4	0	5
Rosé wine	4	0	5
White wine	4	0	5

Table 3: Refluxogenic potential of drinks commonly consumed in Europe according to pH and glycemic index (carbohydrate concentration associate with reflux risk), alcohol content and caffen content. Details can be found in [82]. Abbreviations: Cat. = categories; GI= glycemic index.

Figure 1: Progression of publications on laryngopharyngeal reflux in recent decades.

Figure 1: Figure based on the present literature search.

Figure 2: Flowchart.

Figure 2: Review was performed by 3 authors on PubMed, Cochrane Library and Scopus. Articles were selected on Abstract if presenting new information on epidemiology, clinical presentation, diagnosis or treatment of reflux. 608 of the 1,048 identified articles met eligibility criteria; 585 were included.

Figure 3: French-language version of the Reflux Symptom Score.

Figure 3: The Reflux Symptom Score (RSS) has been validated in French and is under validation in Korean, Spanish, English and Italian. Symptoms are assessed over the previous month: frequency (0-5: 0 = absent; 1 = once a week; 2 = 2 or 3 times a week; 3 = 4 or 5 times a week; 4 = 6 or 7 times a week; 5 = several times a day), severity (0 = absent, to 5 = very severe). Impact on quality of life is assessed, from 0 = absent to 5 = very disabling. Total clinical score is the sum of frequency and severity scores on each item. Maximum ENT symptom score is 100, digestive score 90 and respiratory score 40. Quality of life is assessed apart: maximum, 115. Patients are asked whether the questionnaire covers all complaints, to assess completeness; if not, the patient adds other complaints he/she attributes to LPR. The physician can validate a complaint not covered in the questionnaire.

Figure 4: French-language version of the Reflux Sign Assessment (RSA).

Figure 4: The RSA comprises 3 scores assessing signs in the oral cavity, pharynx and larynx. Total score is the sum of scores for each sign. Signs are weighted according to prevalence in an initial cohort of 102 patients [46]. The simplified RSA is shown here.

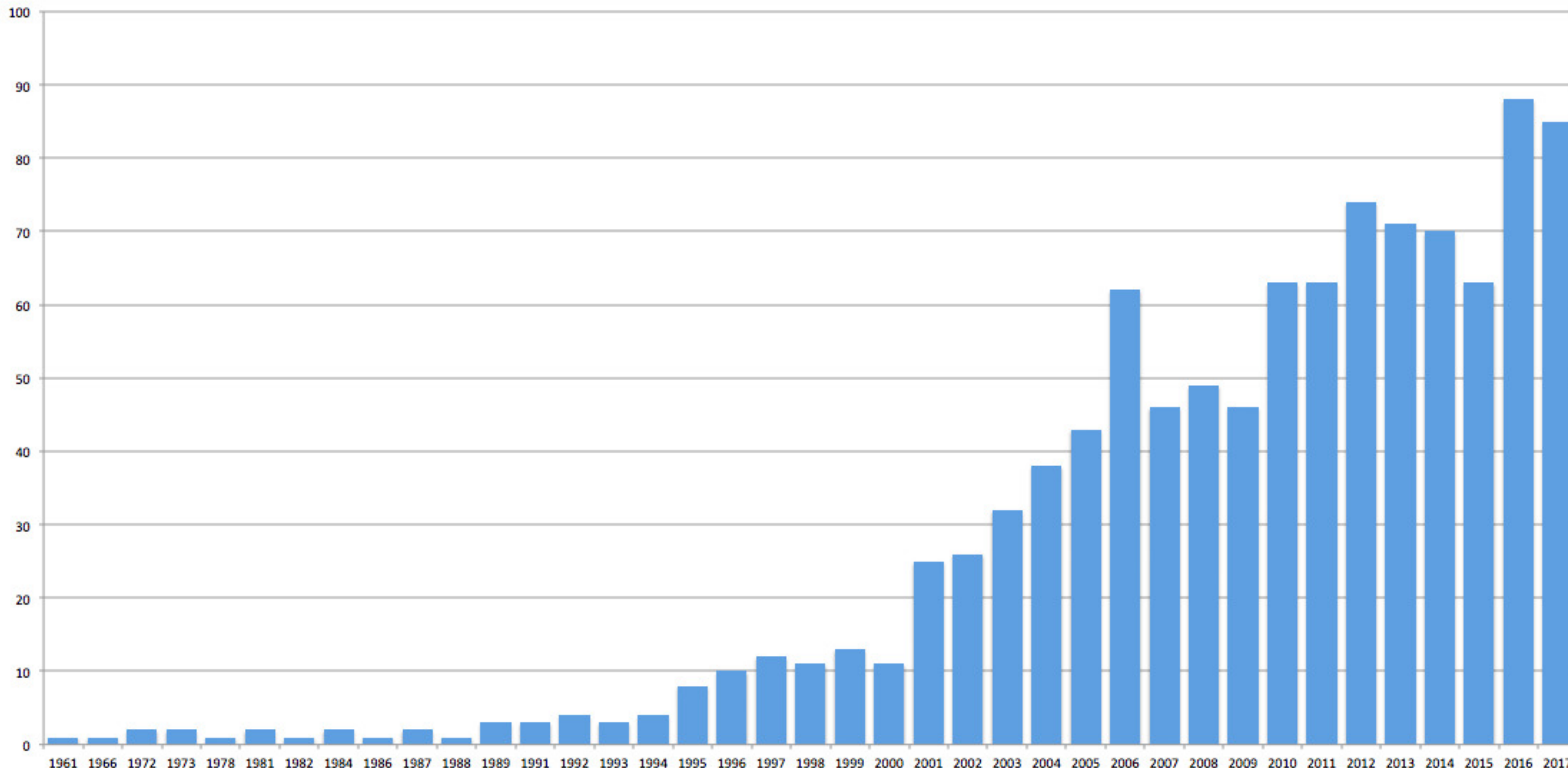
Figure 5: Algorithm of empiric treatment of suspected laryngopharyngeal reflux.

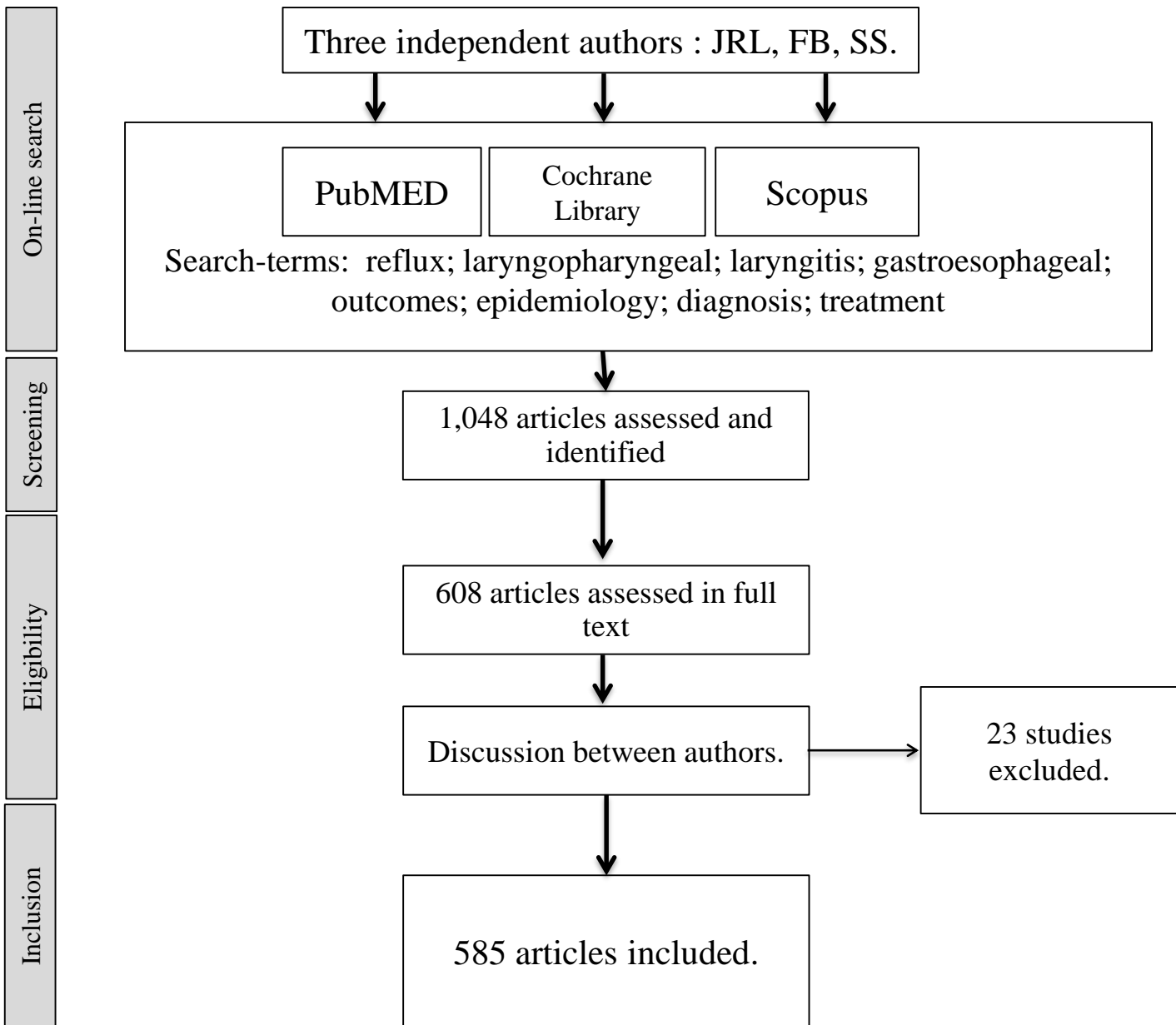
Figure 5: The Reflux Symptom Score (RSS) provides quick assessment of digestive (associated gastroesophageal reflux) and respiratory symptoms (bronchial hypersensitivity) at diagnosis and precise assessment of treatment efficacy at the end of the first course. In case of major digestive and respiratory symptoms, pneumology and gastroenterology consultations and examinations may be performed. In case of mild reflux symptoms, lifestyle/diet counseling may be performed, with drugs in case of lack of significant improvement. In the light of clinical progression, treatment may be modified at 3 months. Some patients may need adjustment (change of drug, dietary reinforcement) and more time for reflux to resolve. Drug treatment should not exceed 9 months, and early recurrence suggests esophageal anatomic or functional abnormality (hiatal hernia, gastroparesis, etc.) to be explored on complementary examination. At end of empiric treatment, lifestyle/diet measures are continued to reduce risk of recurrence. Abbreviations: LPR = laryngopharyngeal reflux; GER = gastroesophageal reflux; RSA= reflux sign score; RSS= reflux symptom score; SRI = serotonin reuptake inhibitor.

Figure 6: Algorithm of treatment of laryngopharyngeal reflux with pH impedance monitoring.

Figure 6: In practice, in first line, diagnosis is highly probable in case of signs, symptoms and positive pH impedance monitoring. Peptest can be concomitant to pH impedance monitoring or if the latter is negative and diagnosis is strongly suspected. In case of negative pH impedance monitoring and Peptest if diagnosis is strongly suspected, 48 or 96h pH impedance monitoring may be performed after ruling out differential diagnoses. In over-50 year-olds, gastroscopy is recommended, to rule out asymptomatic erosive esophagitis.

Abbreviations: LPR = laryngopharyngeal reflux; GER = gastroesophageal reflux; RSA= reflux sign score; RSS= reflux symptom score; PPI = proton pump inhibitor; SRI = serotonin reuptake inhibitor.





Reflux Symptom Score

Within the last month, I suffered from one/several followed symptoms

Severity: 0= problem is not severe, 5 = problem very troublesome when it occurs

Frequency: 0= I don't have this complaint over the past month, 1;2;3;4 = I had 1-2;2-3;3-4;4-5 weekly over the past month; 5= complaint occurs daily

	Disorder Frequency	Disorder Severity		Quality of Life impact	
			Total score		Total score
Ear Nose and Throat Disorders					
1. Hoarseness or a voice problem	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Throat pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Pain during swallowing time	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Difficulty swallowing (pills, liquids or solid foods)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Clearing your throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Sensation of something sticking in the throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Excess mucous in the throat or post nasal drip sensation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Ear pressure/pain (daytime or nigh-time)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Tongue burning	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
10. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Abdominal Disorders					
1. Heartburn, stomach acid coming up	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Regurgitations of liquids, solid foods or burps	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Abdominal pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Diarrheas	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Constipation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Indigestion	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Abdominal distension and/or flatus	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Halitosis	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Nausea	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
10. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Chest/respiratory Disorders					
1. Cough after eating or lying down	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Cough (daytime)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Breathing difficulties, breathlessness, or wheezing	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Chest pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5

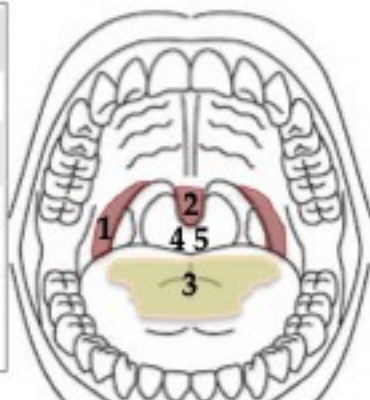
Do you think that this questionnaire well assesses your current complaints ? YES - NO **RSS total score:**..... **Quality of Life score:**.....

1 Erythema of anterior pillar
0 = absent 4 = present

2 Uvula edema ± erythema
0 = absent 3 = present

3 Coated tongue
0 = absent 2 = present

Oral Cavity RSA: .../9



4 Oro- hypopharyngeal erythema
0 = absent 4 = present

5 Oro- hypopharyngeal granulation
0 = absent 3 = present

6 Tongue tonsil hypertrophy
0= absent 3= mild/moderate 4= severe
Apparent vallecula *Apparent vallecula when tongue sticked* *Unapparent vallecula*

Pharyngeal RSA: .../19

7 Pharyngeal sticky mucus
0 = absent 4 = present

8 Contact between epiglottis & base of tongue
0 = absent 4 = present

9 Erythema/edema of the epiglottis
0 = absent
3 = present

10 Erythema/edema of the ventricular band
0 = absent
2 = present

11 Laryngeal erythema
0 = absent
4 = located to arytenoids
5 = diffuse

12 Inter-arytenoid inflammatory granulations
0 = absent
2 = present

13 Posterior commissure hypertrophy
0 = absent
5 = present

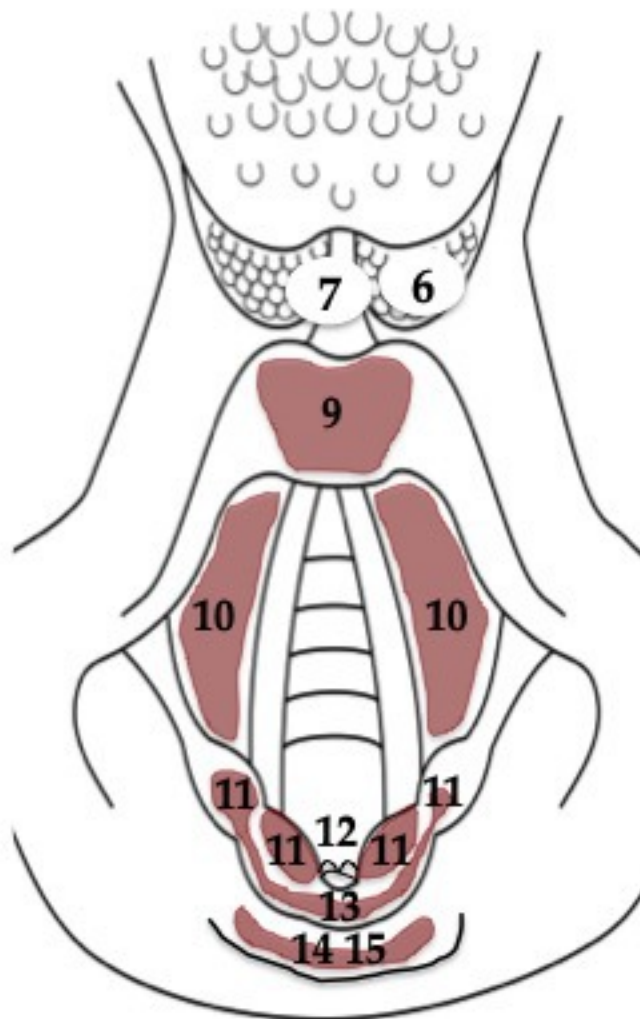
14 Retrocricoid erythema
0 = absent
3 = present

15 Retrocricoid edema
0 = no contact with hypopharyngeal wall (open glottis)
4 = contact with hypopharyngeal wall (open glottis)

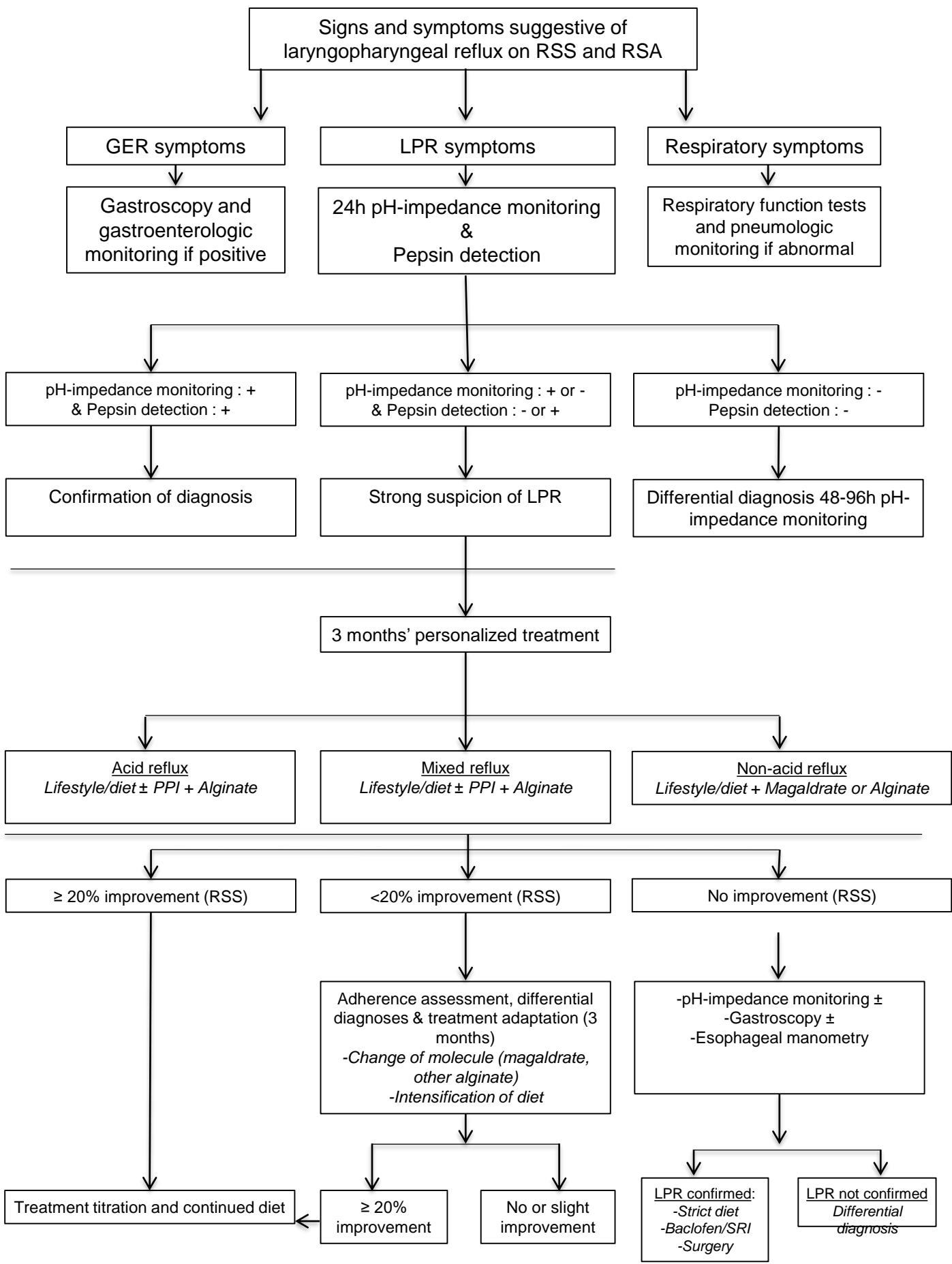
16 Endolaryngeal sticky mucus
0 = absent
3 = present

17 Vocal fold granuloma 0 = absent 2 = present
Laryngeal keratosis 0 = absent 2 = present
Vocal fold ulceration 0 = absent 2 = present

Laryngeal RSA: .../33



RSA total score: .../61



Signs and symptoms suggestive of laryngopharyngeal reflux on RSS and RSA

GER symptoms

LPR symptoms

Respiratory symptoms

Gastroscopy and gastroenterologic monitoring if positive

Exclusion of main differential diagnoses

Respiratory function tests and pneumologic monitoring if abnormal

3 months' empiric treatment
-Diet and lifestyle (sufficient in mild LPR)
-Proton-pump inhibitor (20mg 2/d before midday and evening meals)
-Alginate (3/d after meals)

Assessment at 3 months

≥ 20% symptom improvement (RSS)

<20% improvement or worsening (RSS)

Adherence assessment, differential diagnoses & treatment adaptation (3 months)
-Change of molecule (magaldrate, other alginate)
-Intensification of diet

No or slight improvement

-pH-impedance monitoring ±
-Gastroscopy ±
-Esophageal manometry

LPR confirmed:
-Strict diet
-Baclofen/SRI
-Surgery

LPR not confirmed
Differential diagnosis

≥ 20% improvement

Treatment titration and continued diet