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**Laryngopharyngeal reflux and *Helicobacter pylori***

Yılmaz T *et al*. Laryngopharyngeal reflux and *H. pylori*

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**Abstract**

Laryngopharyngeal reflux (LPR) happens when gastric contents pass the upper esophageal sphincter, therefore causing symptoms like hoarseness, sore throat, coughing, excess throat mucus and globus. The pattern of reflux is different in LPR and gastroesophageal reflux. LPR usually occurs during the daytime in the upright position whereas gastroesophageal reflux disease takes place more often in the supine position at nighttime or during a nap. Ambulatory 24-h double pH-probe monitoring is the gold standart diagnostic tool for LPR. Acid suppression with proton pump inhibitor on a long-term basis is the mainstay of treatment. *Helicobacter pylori* (*H. pylori*) is found in many sites including laryngeal mucosa and interarytenoid region. In this paper we aim to present the relationship between LPR and *H. pylori* and review the current literature.

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**Key words:** Laryngophrayngeal reflux; *Helicobacter pylori*; Gastroesophageal reflux disease; Proton pump inhibitors

**Core tip:** This paper reviews the literature regarding the relationship between laryngophrayngeal reflux and *Helicobacter pylori*. The otolaryngology perspective of laryngophrayngeal reflux and importance of endoscopic examination is emphasized.

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**INTRODUCTION**

Gastroesophageal reflux (GER) can be a normal physiologic phenomenon that occurs in most people, especially after meals. Gastroesophageal reflux disease (GERD) develops when the reflux causes symptoms like heartburn and acid regurgitation. Laryngopharyngeal reflux (LPR) happens when gastric contents pass the upper esophageal sphincter, therefore causing symptoms like hoarseness, sore throat, coughing, excess throat mucus and globus. The pattern of reflux is different in LPR and GER. LPR usually occurs during the daytime in the upright position whereas GERD takes place more often in the supine position at nighttime or during a nap[[1](#_ENREF_1)]. Interestingly the patients are different in terms of body type as well. There are reports suggesting a relationship between GERD and obesity[[2](#_ENREF_2),[3](#_ENREF_3)]. In contrast, in a group of patients with laryngeal and pharyngeal symptoms, those with abnormal pharyngeal reflux events did not have a higher mean body mass index (BMI) than those with normal studies[[4](#_ENREF_4)]. A significantly higher percentage of esophageal reflux events was seen in obese versus non-obese participants. The authors concluded that abnormal esophageal reflux (GERD) is associated with increasing BMI and obesity, although this was not true for patients with pharyngeal reflux.

*Helicobacter pylori* (*H. pylori*) was originally identified by Marshall and Warren[[5](#_ENREF_5)]. It was called a Campylobacter-like organism at first. It is a gram-negative bacterium with a spiral shape and four to six flagella. It is obligate microaerophilic, urease, catalase, and oxidase positive. Although it is susceptible to acid, it is protected from the harmful effects of acid by both its motility and its ability to convert urea to ammonium by urease and form a basic milieu around itself. Although it occurs less commonly in developed countries and in children and is more common in developing countries and adults, its prevalence varies between different regions and socioeconomic strata of the same country. Probable routes of contamination are fecal–oral, oral–oral, gastro–oral (reflux, vomiting), and iatrogenic (*e.g.*, insufficiently disinfected endoscopes)[[6](#_ENREF_6)]. The relationship of *H. pylori* with gastritis, peptic ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma has been demonstrated in many studies[[7](#_ENREF_7)]. Different noninvasive [urea breath test (UBT), serological tests, stool tests] and invasive [histological and microbiological examination of biopsy materials, rapid urease test, polymerase chain reaction (PCR)] tests with varying specificity and sensitivity may be performed for the diagnosis for *H. pylori* in tissue[[8](#_ENREF_8)]. *Helicobacter pylori* is localized primarily in the gastric mucosa. It is reported that the microorganism may exist in paranasal sinuses, tonsils, adenoids, and even middle ear mucosa[[9-12](#_ENREF_9)]. It may also exist in atypical locations like dental plaque and saliva[[13](#_ENREF_13),[14](#_ENREF_14)]. On the other hand, in many studies *H. pylori* could not be found in tonsils, adenoids, dental plaque, saliva, or the oral cavity, which may mean that these tissues are only temporary colonization sites for *H. pylori*[[15-18](#_ENREF_15)].

It has been estimated that half of otolaryngology patients (ORL) with laryngeal and voice disorders have LPR[[19](#_ENREF_19)]. LPR is considered one of the most important and common factors causing inflammation in the upper airways. The tissue damage is demonstrated in both animals and human beings. It may be caused by direct exposure to acid, pepsin and bile, by vagally mediated reflexes[[20](#_ENREF_20),[21](#_ENREF_21)]. Besides acid and pepsin, the presence of *H. pylori* may be related to the symptoms and findings of LPR.

The variance between esophageal symptoms and upper aerodigestive tract disease may reflect the relative susceptibility of the epithelium of the larynx and pharynx to reflux-related injury. LPR may also occur in healthy individuals without symptoms or laryngeal pathology. LPR related laryngeal disease and findings tend to resolve in a longer time and more often need higher levels of medication and therapy. LPR has an impact on various laryngeal pathologies including stenosis, malignancy, benign lesions, dysphagia and functional disorders.

**DIAGNOSIS**

Laryngeal and voice disorders may present with diverse clinical manifestations. Many voice clinicians recommend that LPR be routinely assessed in patients with laryngeal and voice disorders; however, even among otolaryngologists who have a relatively high index of suspicion for LPR, it appears that this disorder is still often underdiagnosed and undertreated[[22](#_ENREF_22)]. The symptoms, manifestations, patterns, and mechanisms of LPR and GERD are different. Patients with LPR usually deny symptoms of heartburn and/or regurgitation[[21](#_ENREF_21)]. Less than half of ORL patients with LPR documented by pH monitoring complain of heartburn or regurgitation[[23](#_ENREF_23)].

As with majority of the diseases, the diagnosis of LPR begins with the history. It is then confirmed by laryngoscopy and subsequently validated by response to a trial of proton pump inhibitor therapy. Although some institutions do perform routine pH testing, for the majority of cases this testing is reserved for refractory or complicated cases. The most common symptoms associated with LPR are cough, throat clearing, sore throat, globus, excess throat mucus, choking, and asthma. However, these entities have a multifactorial etiology and may be caused by recent sinusitis or other respiratory infections, smoking, voice abuse, and allergy, in addition to that those symptoms may be lacking. Therefore accurate diagnosis based on history is a challenge. Belafsky *et al*[[24](#_ENREF_24)] developed the Reflux Symptom Index (RSI), a self-administered nine-item questionnaire to help categorize the severity of LPR (Table 1). An RSI of greater than 13 is considered abnormal. Symptoms of GERD, which include heartburn, chest pain, indigestion or a regurgitation of acid, are important, but it should be noted that more than half of the patients with LPR do not have these classic GERD symptoms[[25](#_ENREF_25)]. Laryngeal examination is the second step in the diagnostic evaluation. The findings of LPR on laryngeal examination vary considerably. According to Koufmann laryngeal edema is the hallmark finding of LPR[[25-27](#_ENREF_25)]. However most otolaryngologists rely solely on the findings of erythema or of posterior laryngitis (PL) (Figure 1A). Unfortunately, those findings are not present in many LPR patients. In our experience, edema (Figure 1B) is the principal, and most common, finding of LPR along with PL. PL is characterized by edema or hypertrophy, and sometimes erythema and hyperemia on the posterior wall of the glottis. Inflammation may reach the medial surface of the arytenoid cartilages and aryepiglottic folds. Furthermore, diffuse vocal fold edema and infraglottic edema reaching from the anterior commissure to the posterior wall may create an illusion of sulcus vocalis[[27](#_ENREF_27)]. The nature of endolaryngeal mucus if it is thick and tenacious will also point to PL (Figure 1C). LPR patients may present with one or all of these findings[[21](#_ENREF_21)]. The difficulty in making a LPR diagnosis is that the findings are sometimes quite subtle; signs of inflammation and irritation are absent and patients may display a quite normal looking larynx (Figure 1D). Therefore a high index of suspicion is needed. Reflux finding score (RFS) may be quite useful in categorizing the severity of the mucosal injury on laryngoscopy[[26](#_ENREF_26)] (Table 2). Laryngoscopy should be done by both flexible and rigid endoscopes. There are also controversial studies on this matter. Branski *et al*[[28](#_ENREF_28)] reported on a series of patients in whom reflux findings were scrutinized by five observers reviewing videotaped examinations. The conclusions of the paper were that significant variability exists in describing reflux related findings. In another important study by Hicks *et al*[[29](#_ENREF_29)], 100 normal subjects underwent laryngoscopy; their examinations were then reviewed by otolaryngologists and speech-language pathologists to estimate the presence of "reflux related" lesions in these healthy volunteers. The key finding in this study was nearly 80% of the normal volunteers had an interarytenoid bar or posterior commissure hypertrophy. Unfortunately, this finding has been taken by many to be an indication that laryngoscopy in general is not useful in the clinical evaluation of reflux disease. However it’s important to realize that physician’s own perception during a laryngoscopy strongly effects the diagnosis. That is only a mild laryngeal edema might be the sole finding of LPR.

Traditional diagnostic tests for GERD lack both sensitivity and specificity for LPR. As mentioned before these two patient groups is different in terms of sypmtoms and diagnosis. Barium esophagography, radionuclide scanning, the Bernstein acid-perfusion test and esophagoscopy with biopsy are all often negative in LPR patients[[21](#_ENREF_21)]. The reason for that is probably most LPR patients do not develop esophagitis, because esophageal mucosa is more resistant to acid and pepsin related injury than laryngeal and pharyngeal mucosa[[21](#_ENREF_21),[23](#_ENREF_23)]. Therefore evaluating a patient depending on GERD patient protocols may lead the otolaryngologist to a misdiagnosis. At the present time ambulatory 24-h double pH probe (simultaneous esophageal and pharyngeal) monitoring has become the diagnostic gold standard for LPR[[30-32](#_ENREF_30)]. The upper probe must be placed in a consistent zone at or above (2 cm) the functional upper esophageal sphincter. This allows the lower probe to be placed approximately 5 cm above the lower esophageal sphincter. However, it is expensive and it is not widely available. Nevertheless, pH monitoring effectively documents LPR with a high degree of specificity and sensitivity. Esophageal manometry is also important for accurate placement of the pH electrodes and also particularly useful in patients with chronic cough.

Endoscopic examinaton of the esophagus (TNE) is performed in the clinic setting with or without sedation. It is generally used to check GERD related complications and exclude other diseases. TNE has allowed the otolaryngologist to screen the esophagus. In a large series, Postma *et al*[[33](#_ENREF_33)] reported that 50% of the patients had positive findings on TNE, including, esophagitis 17%, hiatal hernia 8%, Barrett's metaplasia 5%, Candida esophagitis 5%, and stricture 4%. Despite that esophagoscopy alone does not diagnose LPR. Only a small percentage of LPR patients have abnormal esophagoscopy.

*H. pylori* infects your stomach, usually during childhood. The most common cause of peptic ulcers, *H. pylori* infection is present in about half the people in the world. There are several different methods to test for *H. pylori* infection.

***Breath test (called the carbon isotope-urea breath test or UBT)***

Up to 2 wk before the test, the patient must stop taking any antibiotics, bismuth-containing medications such as Pepto-Bismol, and proton pump inhibitors (PPIs). The patient swallows a special substance containing urea (a waste product the body produces as it breaks down protein) that has been made harmlessly radioactive. If *H. pylori* is present, the bacteria convert the urea into carbon dioxide, which is detected and recorded in the patient's exhaled breath after 10 minutes. This test can identify almost all people who have *H. pylori* and confirm that the *H. pylori* infection has been fully treated.

***Blood tests***

Blood tests are used to measure *H. pylori* IgG, and *H. pylori* CagA IgG antibodies. This test is not quite as accurate as the other tests. These blood tests can be used to diagnose whether an *H. pylori* infection is present. However, the test cannot determine whether you have an infection at the time of the test or how long you have had it because the test remains positive for years even if the infection is cured. As a result, it cannot be used to see if the infection has been eradicated.

***Stool test***

A test to detect the genetic traces of *H. pylori* in the feces appears to be as accurate as the breath test for initially detecting the bacteria, and for detecting recurrences after antibiotic therapy. This test can also be used to diagnose the infection and confirm that the *H. pylori* infection has been eradicated.

***Biopsy***

The most accurate way to identify the presence of *H. pylori* is by taking a tissue biopsy. *H. pylori* DNA was screened using a nested PCR amplification method for a portion of the 23S ribosomal RNA (rRNA) gene. Tissue samples can also be cultured on homogenized brain heart infusion agar. Suspected colonies were tested and catalase-, oxidase-, and urease-positive, curved gram-negative rods were defined as *H. pylori*.

Another important diagnostic tool is an empiric trial of PPI therapy over a prolonged period has been proposed as a valid diagnostic test for LPR. The typical regime is twice-a-day PPI therapy for a duration of 1 to 6 mo. This recommendation is based on the fact that we have not identified the specific symptom combination, or combination of symptoms and laryngeal signs, pathognomonic to LPR. Besides, ambulatory 24-hour double-probe pH measurement is not available in all clinics. The principal disadvantage of PPI therapy trial is its high cost, patient unwillingness and placebo effect. Nevertheless it’s a useful diagnostic tool in many cases.

**TREATMENT**

The treatment for LPR include lifestyle modifications, acid suppressive medications and surgical therapy. Lifestyle modifications include elevation of the head of the bed, decreased intake of fat, citrus, tomato, chocolate, caffeine, and alcohol, cessation of smoking, and avoiding recumbency and further eating 3 hours before bedtime. These measures are helpful if there is associated abnormal esophageal acid exposure[[1](#_ENREF_1)]. If only LPR is present these measures may be less meaningful because pharyngeal reflux occurs most often in upright position during the daytime. Although Hanson described a 50% response rate to these measures alone in patients with chronic laryngitis[[34](#_ENREF_34)], there is minimal supportive data on the efficacy of these measures in LPR. Medical acid suppression is the most important and common method of treatment. The treatment of LPR has dramatically changed since the introduction of PPI. PPIs are the most widely used drugs for the treatment of reflux. They maintain a potent and consistent effect on gastric acid secretion with few adverse effects. Comparisons between the five available compounds (omeprazole, rabeprazole, lansoprazole, esomeprazole, and pantoprazole) show that they have a similar antisecretory potency on a milligram basis. Treatment recommendation at present is twice-daily dosing of PPIs for at least 3 to 4 mo. Most authors suggests a longer duration at least 6 mo up to a year[[22](#_ENREF_22),[25](#_ENREF_25)]. Symptoms frequently improve before the laryngoscopic findings resolve[[25](#_ENREF_25)]. Although PPIs effectively reduce the acid secretion, reflux still continues meaning that larynx and pharynx are still exposed to pepsin and bile.

Surgical therapy or antireflux surgery has been shown to be effective for patients with aggressive or life-threatening LPR[[35](#_ENREF_35)]. Main procedure for antireflux surgery is Nissen fundoplication. The fundus of the stomach is wrapped around the lower esophageal sphincter to provide an antireflux barrier. Patients who have a good control of GER and LPR symptoms with the acid suppression may not need a surgical intervention. However in patients who do not respond to medical therapy the symptoms can be attributed to pepsin and bile reflux. This patient group considered as the best candidates for Nissen fundoplication[[36](#_ENREF_36)]. However it is not a widely accepted treatment choice.

No single drug cures *H. pylori* infection. Treatment involves taking several medications for 14 d. The recommended first-line therapy is PPI-clarithromycin-amoxicillin– or metronidazole. The consensus was that a 14-d rather than a seven-day treatment had a slight advantage in terms of treatment success. With regard to second-line therapies, bismuth-based quadruple therapies remain the best option. If unavailable, PPI-amoxicillin or tetracycline and metronidazole are recommended. There are increasing numbers of patients with *H. pylori* infection that is resistant to antibiotics so it is important to take all the medications prescribed and to have a test that confirms that the infection has been cleared. Antimicrobial susceptibility testing is required in the resistant cases or treatment failures[[37](#_ENREF_37)].

**DISCUSSION**

Regarding the relationship between LPR and *H. pylori* the literature is limited. Rouev *et al*[[38](#_ENREF_38)] compared 46 patients with GERD and LPR symptoms and found that there is an increasing tendency in GERD patients that develop LPR symptoms. They found 11 patients *H. pylori* infection but the treatment did not effect the overall outcome. One of the first studies investigating the relationship between *H. pylori* positivity and LPR Oridate *et al*[[39](#_ENREF_39)] compared *H. pylori* antibody positivity, laryngopharyngeal reflux symptoms, objective laryngopharyngeal findings, and rate of response to acid-suppression therapy in 42 subjects who were diagnosed with GERD. They found that the laryngopharyngeal, not esophageal, symptom relief by acid-suppression therapy was significantly lower among *H. pylori* antibody-negative cases than among antibody-positive cases. This was a rather surprising finding. Kountouras *et al*[[40](#_ENREF_40)] suggested that the increasing incidence of GERD complications after *H. pylori* eradication may be explained not just by the diminishing prevalence of *H. pylori* infection, but rather by healing of *H. pylori*–associated peptic ulcer disease, which coexists with GERD. The appearance of GERD depends on the esophageal acid exposure, and its symptomatology is related to acid hypersecretion, condition that predisposes to peptic ulcer disease. Given that the vast majority of peptic ulcer cases are caused by *H. pylori* infection, the bacterium could therefore dynamically also promote GERD development by inducing esophageal acidity but this doesn’t necessarily promote LPR. Çekin *et al*[[41](#_ENREF_41)] found no association between H pylori status and LPR status; in addition they analyzed two subgroups based on whether their lesions were benign or malignant/premalignant and found a significant relationship between LPR positivity and the presence of malignant/ premalignant laryngeal lesions. Again they found no association between H pylori status and either of the two subgroup categories.

LPR in pediatric population is believed to contribute to failure to thrive, laryngomalacia, recurrent respiratory papillomatosis, chronic cough, hoarseness, esophagitis, and aspiration among other pathologies. Thus, LPR should be considered as a chronic disease with a variety of presentations. High clinical suspicion along with consultation with an otolaryngologist, who can evaluate for laryngeal findings, is necessary to accurately diagnose LPR[[42](#_ENREF_42)]. The majority of infected persons acquire the bacteria during early childhood and one of the risk factors may be immunological. These factors are possibly the cause of divergent manifestations of *H. pylori* infection in children compared with adults.

Tezer *et al*[[43](#_ENREF_43)] concluded that the expression of *H. pylori* positivity and degree of GERD correlate with LPR in forty-five patients. *H. pylori* positivity and degree of GERD were more adverse in patients with a RFS of 7 or more. However their findings relied only on RFS, ambulatory 24-h double pH probe monitoring was not used. Toros *et al*[[44](#_ENREF_44)] investigated forty-five patients. In their stduy although the percentage of *H. pylori* positivity was high, there was no significant relationship between the symptoms and *H. pylori* positivity. All patients underwent medical therapy mostly for gastroenterological indications rather than laryngopharyngeal symptoms. In a recent article by Youssef and Ahmed[[45](#_ENREF_45)] *H. pylori* treatment and LPR symptom resolution was investigated. *H. pylori* stool antigen (HPSA) test were positive in 57% of the study group. Patients with negative HPSA were treated with esomeprazole as single modality with a reported improvement score of 96.6%. Patients with positive HPSA test results were divided into 2 groups: 1 received only esomeprazole, with reported improvement in 40%, whereas the second group was treated with esomeprazole, plus amoxicillin sodium and clarithromycin (triple therapy) and reported a 90% incidence of symptom improvement. The incidence of *H. pylori* infection in patients with LPR was 57%. They concluded that *H. pylori* infection should be considered when treatment is prescribed to patients with LPR because the standard therapy for GERD might be insufficient. Also the use of triple therapy in the treatment of LPR with *H. pylori* infection might result in a higher cure rate. But in a study by Ercan *et al*[[46](#_ENREF_46)] thirty-two LPR patients were investigated regarding the presence of *H. pylori* and sex, age, degree of gastritis and esophagitis, and also the number of reflux, fractional acid exposure time regarding proximal probe readings. They found that there was no relationship between the presence of *H. pylori* and LPR. Islam *et al*[[47](#_ENREF_47)] took biopsies from vocal fold and the interarytenoid region of fifty patients. They found that *H. pylori* was not found in the histological specimens of vocal fold pathologies and the interarytenoid region. The presence of *H. pylori* in the gastric mucosa, determined by urea breathe test and *H. pylori* antibodies, does not have an effect on the RFS and RSI. In their prospective study Siupsinskiene *et al*[[48](#_ENREF_48)] found *H. pylori* in the biopsy material from the larynx in more than one-third of the patients, equally suffering from benign laryngeal disease and laryngeal cancer, but significantly more often than in the control group subjects. Patients with chronic laryngitis and laryngeal cancer showed the highest rate of *H. pylori* infection in the larynx. However the relationship was not clearly identified and they concluded that further research studies were needed that would justify or deny the importance of *H. pylori* infection for the development of different laryngeal diseases, as well as the effect of *H. pylori* eradication on the course of laryngeal diseases.

**CONCLUSION**

Detailed history and laryngoscopic examination constitute the basis for diagnosis of LPR. Most LPR patients have only mild symptoms. Unlike GERD patients they seldom have heart burn or regurgitation. Laryngoscopic examination will most commonly demonstrate findings in the posterior glottis and vocal folds. Laryngeal edema is an important indicator for LPR that is most often neglected. Ambulatory 24-h double pH-probe monitoring is the gold standart diagnostic tool for LPR. Acid suppression with PPI on a long-term basis is the mainstay of treatment; a trial of PPIs may also be useful as a diagnostic maneuver but it should be at least 4 mo. Laryngeal acid and pepsin sensitivity is greater than esophageal mucosa and this constitutes the main difference of LPR and GERD pathophysiology. *H. pylori* is found in many sites including laryngeal mucosa and interarytenoid region; however, the importance of this colonization and its effects on disease progress and treatment outcome is yet to be identified with prospective clinical studies.

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A

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**B**

**** C

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D

**Figure 1 Diagnosis.** A: Posterior laryngitis and erythema of the arytenoids; B: Laryngeal edema secondary to laryngopharyngeal reflux (LPR);C: Excessive posterior laryngitis. Note the thick mucus over the interarytenoid area and vocal cords; D: Normal larynx with only a mild posterior laryngitis treated by proton pump inhibitors with documented LPR by ambulatory double probe pH-metry.

**Table 1 Reflux symptom index**

|  |  |  |
| --- | --- | --- |
| **Within the last month, how did the following****problems affect you?** | **0 = No problem** | **5 = Severe problem** |
| 1. Hoarseness or a problem with your voice  | 0 1 2 3 4 5 |
| 2. Clearing your throat | 0 1 2 3 4 5  |
| Excess throat mucus or postnasal drip | 0 1 2 3 4 5 |
| 4. Difficulty swallowing food, liquids, or pills | 0 1 2 3 4 5 |
| 5. Coughing after you ate or after lying down | 0 1 2 3 4 5 |
| 6. Breathing difficulties or choking episodes | 0 1 2 3 4 5 |
| 7. Troublesome or annoying cough | 0 1 2 3 4 5 |
| 8. Sensations of something sticking in your throat | 0 1 2 3 4 5 |
| or a lump in your throat |  |
| 9. Heartburn, chest pain, indigestion, or stomach | 0 1 2 3 4 5 |
| acid coming up |  |

A total score of 13 is thought to be clinically significant.

**Table 2 Reflux finding score**

|  |  |
| --- | --- |
| 1. Subglottic edema  | 2 = Present |
| 0 = Absent | 　 |
| 2. Ventricular obliteration  | 2 = Partial |
| 4 = Complete | 　 |
| 3. Erythema/hyperemia  | 2 = Arytenoids only |
| 4 = Diffuse | 　 |
| 4. Vocal cord edema  | 1 = Mild |
| 2 = Moderate | 　 |
| 3 = Severe | 　 |
| 4 = Polypoid | 　 |
| 5. Diffuse laryngeal edema  | 1 = Mild |
| 2 = Moderate | 　 |
| 3 = Severe | 　 |
| 4 = Obstructing | 　 |
| 6. Posterior commissure hypertrophy  | 1 = Mild |
| 2 = Moderate | 　 |
| 3 = Severe | 　 |
| 4 = Obstructing | 　 |
| 　 | 　 |
| 7. Granuloma/granulation  | 0 = Absent |
| 2 = Present | 　 |
| 　 | 　 |
| 8. Thick endolaryngeal mucus/other  | 0 = Absent |
| 2 = Present | 　 |
| Total | 　 |

A total score of 7 is thought to be clinically significant.