Original Article

J Nepal Health Res Counc 2020 Jul-Sep;18(48): 513-9

DOI: https://doi.org/10.33314/jnhrc.v18i3.2493

Comparison of Proton Pump Inhibitor and Triple Therapy Regimen for Laryngospharyngeal Reflux Disease

Apar Pokharel,[1] Jaya Prakash Mayya,[1] Hari Prasad Upadhyay[2]

[1]Department of Otorhinolaryngology and Head and Neck Surgery, College of Medical Sciences, Chitwan, Nepal, [2]Department of Community Medicine and Biostatistics, College of Medical sciences, Chitwan, Nepal.

ABSTRACT

Background: Laryngopharyngeal reflux is retrograde flow of contents of the stomach to the larynx and the pharynx. The study aims to compare two regimens (proton pump inhibitor monotherapy versus triple therapy) on the outcome of Helicobactor pylori positive laryngopharyngeal reflux disease.

Methods: The presence of laryngopharyngeal reflux was determined by reflux symptom index and reflux finding score. The presence of Helicobactor pylori in the tissue was confirmed by rapid urease test. All urease test negative laryngopharyngeal reflux patients were given a course of proton pump inhibitors and results were evaluated. All urease test positive patients were divided into two groups. One group was given a course of proton pump inhibitors and another group was given a course of triple therapy and the results were compared.

Results: A total number of 704 laryngopharyngeal reflux patients were screened for urease test. Among them 138 patients (19.6 %) were urease test negative and were given proton pump inhibitor therapy. Improvement in both reflux finding score (average score 11.75) and reflux symptom index (average score 5.25) score was observed after 3 months with p-value<0.05. In urease test positive patients, improvement in scores was observed in both proton pump inhibitors and triple therapy group, however marked improvement in the clinical features was observed in triple therapy group with p-value<0.05.

Conclusions: The study reveals association between laryngopharyngeal reflux and Helicobactor pylori. Proton pump inhibitor therapy is sufficient if no Helicobactor pylori is detected, however incase of presence of Helicobactor pylori, triple therapy gives better results.

Keywords: Helicobacter pylori; laryngopharyngeal reflux disease; rapid urease test

INTRODUCTION

Laryngopharyngeal reflux is the most common extra esophageal manifestations of gastroesophageal reflux disease (GERD).[1]

Helicobactor pylori (H.pylori) is primarily found in the gastric mucosa. However studies have shown the existence of this microorganism in paranasal sinuses, tonsils, adenoids, and middle ear mucosa.[2-4] The rapid urease test (RUT) helps to see the presence of *H. pylori* based on the presence of urease enzyme on the tissue mucosa. Its advantage over serology is that it only detects thepresence of an active infection. [5]

The usual practice for the treatment of *H. pylori* positive laryngopharyngeal reflux disease (LPRD) is to give proton pump inhibitors, twice daily for 8 weeks.[6] The first single optical isomer proton pump inhibitor, generally provides better acid control than current racemic proton pump inhibitors and has a favourable pharmacokinetic profile relative to omeprazole. The objectives of this study are to determine the incidence of *H. pylori* in patients with LPRD and to compare proton pump inhibitors monotherapy versus triple therapy (proton pump inhibitors plus two antibiotics)on the treatment outcome of *H. pylori* positive LPRD.

METHODS

This prospective study was carried out from August 2018 to August 2019 in the Department of Otolaryngology-Head and Neck Surgery at College of Medical Sciences Teaching Hospital in Chitwan, Nepal. Patients above 18

Correspondence: Dr Apar Pokharel, Department of Otorhinolaryngology and Head and Neck Surgery, College of Medical Sciences, Chitwan, Nepal. Email:aparpokharel@hotmail.com, Phone: +9779841558234.

years, diagnosed with features of laryngopharyngeal reflux as per RFS and/or RSI criteria and were consecutively enrolled for the study. Patients with recent history of gastrointestinal bleeding and patients currently on treatment with proton pump inhibitors or H2 antagonists or antibiotics within a period of last 4 weeks were excluded from the study.

In all patients with classic symptoms of laryngopharyngeal reflux disease (LPRD), a reflux symptom index (RSI) was determined on the basis of their answers in the RSI questionnaire (Table 1).[7] After that all patients underwent a physical examination, including a flexible nasal endoscopic assessment of the larynx to determine the reflux finding score (RFS) (Table 2).[8] Patients with an RSI of 14 or more and/or an RFS of 8 or more were considered to have LPRD as defined in the literature.[9] For all patients screened in the LPRD, samples were collected from interarytenoid area using flexible nasal endoscope containing 1.8 mm biopsy forceps under topical local anesthesia, and tested for *H.pylori* with the rapid urease test (RUT).

The sterilely taken biopsy (minimum 2*2 mm pieces) was placed in a medium with urea and pH indicator. If the biopsy material contained *H. pylori*, urease enzyme present in the bacteria acted on urea to change it into ammonia and carbon dioxide.pH was changed by the released ammonia, and the indicator changed its color from yellow to orange, red, or purple. CLO (Kimberly-Clark, USA) test was used. The color changes were evaluated after 20 min, as well as 1, 3, and 24 hours.[10] A positive RUT requires approximately 100,000 H. pylori in the biopsy sample to change the color using an agar-based test such as the CLO test.[11]The time for the test to turn positive depended on the concentration of bacteria and the temperature. Most turned positive within 120 to 180 minutes but it was best to wait for atleast 24 hours.[12,13] After 24 hours the test might turn positive from the presence non-H. pylori urease containing organisms.[13] Positive results after24 hours were considered false positive and were not used for treatment decisions.

Patients with negative RUT results received once daily esomeprazole magnesium, 40mg, for 4 weeks.[14] 566 patients with positive RUT test results were divided into 2 equal randomly assigned groups, 283 each: one group received only esomeprazole magnesium, 40 mg, for 4 weeks, and the other group that received triple therapy comprising esomeprazole magnesium, 40 mg, plus amoxicillin sodium, 1g, and clarithromycin, 500 mg, for the same period.

Principal investigator who was blinded to the treatment protocol performed follow-up evaluation for all patients after the end of medical treatment. The patients were followed up after one months and three months. Reflux symptom index and reflux finding score was again determined in all patients. Patients with an RSI of less than 14 and/or an RFS of less than 8 were considered to be fully recovered from LPR.

A proforma was filled by the principal investigator which contained initial RFS and RSI scores, result of RUT test and subsequent RFS and RSI scores after one and three months. The three month post treatment RSI and RFS scores were taken to monitor treatment outcome. The study protocol was approved by the local ethics committee and written and informed consent was obtained from all patients.

Table 1. Reflux Symptiom Index.[7]

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
3. Excess throat mucous 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 or a lump in your throat	0 1 2 3 4 5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0 1 2 3 4 5
Total	

Table 2. Reflux Finfing Score.[8]

Subglottic Edema	2 = present 0 = absent	
Ventricular Obliteration	2 = partial 4 = complete	
Erythema/Hyperemia	2 = arytenoids only 4 = diffuse	
Vocal Fold Edema	1 = mild 2 = moderate 3 = severe 4 = polypoid	
Diffuse Laryngeal Edema	1 = mild 2 = moderate 3 = severe 4 = obstructing	
Posterior Commissure Hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing	
Granuloma/Granulation	2 = present 0 = absent	
Thick Endolaryngeal Mucus	2 = present 0 = absent	
	Total:	

RESULTS

The mean age of the 704 patients in the study was 32.4 years and male to female ratio was 1.9. Descriptive statistics categorized based on *H.pylori* status are shown in Table 3. The main symptom was globus sensation seen in 90.05% of patients, followed by frequent throat clearing (58.52%) and voice problems (51.84%) (Table 4). Erythema of the supraglottic region was the most common laryngoscopic finding seen in 89.91% of cases, followed by posterior commissure hypertrophy (76.14%) and ventricular obliteration (64.91%) (Table 5).

Table 3. Comparison of the demographics and unhealthy habits between the patients positive and negative for *H. pylori* in the biopsy material from the larynx.

Variables	Rapid Urease Test Result		p-Value
	Positive (566) patients	Negative (138) patients	
Male/Female ratio	2.04	1.76	
Age (years)	37.8 years	33.6 years	
Body mass index	27.8	28.2	
Smoker (%)	212 (37.5%)	57 (41.3%)	0.46*
Drinkers (%)	168 (29.7%)	36 (26.2%)	0.47*
History of GERD (%)	440 (77.8%)	112(81.1%)	0.45*

**Chi square test done showing p-value>0.05*

Table 4. Relationship Between Laryngopharyngeal Reflux Disease (LPRD) Symptoms With Rapid Urease Test Results.

Laryngopharyngeal Reflux Disease Symptoms	Rapid Urease Test Result		p-Value
	Positive (566) patients	Negative (138) patients	
Hoarseness or voice problems	297(52.47%)	68(49.27%)	0.50*
Throat clearing	333(58.83%)	79(57.24%)	0.73*
Excess mucus or postnasal drip	141(24.91%)	31(22.46%)	0.64*
Difficulty in swallowing	81(14.31%)	19(13.76%)	0.87*
Coughing after eating or lying down	37(6.58%)	10(7.25%)	0.76*
Breathing difficulties or choking episodes	31(5.48%)	9(6.52%)	0.63*
Annoying cough	197(34.8%)	43(31.16%)	0.42*
Sensation of a lump or foreign body in the throat	513(90.6%)	121(87.69%)	0.30*
Burning, heartburn, chest pain, indigestion, or stomach acid coming up (reflux)	255(45.05%)	61(44.20%)	0.86*

**Chi square test done showing p-value>0.05*

Table 5. Relationship Between Laryngopharyngeal Reflux Disease (LPRD) Signs With Rapid Urease Test Results.

Laryngopharyngeal Reflux Disease signs (Flexible Nasopharyngolaryngoscopic Findings)	Rapid Urease Test Result		p-Value
	Positive (566) patients	Negative (138) patients	
Subglottic oedema	113 (19.96%)	29 (21.01%)	0.78*
Ventricular obliteration	375 (66.25%)	82 (59.42%)	0.13*
Erythema/hyperemia	512 (90.45%)	121 (87.68%)	0.33*
Vocal fold oedema	99 (17.49%)	27 (19.56%)	0.57*
Diffuse laryngeal oedema	41 (7.24%)	11 (7.97%)	0.77*
Posterior commissure hypertrophy	425 (75.08%)	111 (80.43%)	0.18*
Granuloma/Granulation tissue	41 (7.24%)	9 (6.52%)	0.08*
Thick endolaryngeal mucus	323 (57.06%)	91 (65.94%)	0.06*

**Chi square test done showing p-value>0.05*

The patients were divided into two groups based on the results of RUT. Patients who's RUT were negative were given once daily dose of esomeprazole magnesium, 40 mg, for 4 weeks. On follow up after three months marked improvement in both the RSI and RFS was observed (Table 6). The P value in both the RSI and RFS was statistically significant (p-value<0.0001).

The 566 patients with positive RUT test results were randomized into 2 equal groups (283 patients each). Esomeprazole magnesium, 40 mg, for 4 weeks was given to control group (283 patients); 120 patients (42.4%) showed marked improvement in symptoms, while 151 patients (53.71%) reported no improvement. Twelve patients discontinued follow-up.

The second study group (283 patients) received triple therapy comprising esomeprazole magnesium, 40 mg once a day, amoxicillin sodium, 1 g two times a day, and clarithromycin, 500 mg two times a day, for the same period. 214 patients (75.62%) showed marked improvement in symptoms and 60 patients (21.2%) showed no improvement. Nine patients discontinued follow-up.

In RUT-negative laryngopharyngeal reflux disease, the

mean of difference between pre- and post-therapy RFS score was 8.41 with CI 95% (7.89, 8.94) and p-value<0.05. Similarly, it was found that the mean of difference between pre- and post-therapy RFS score was 7.32 with CI 95% (6.86, 7.78) and p-value<0.05. (Table 6).

Pre- and post-therapy RSI and RFS scores were compared using two sample t- test in RUT-positive LPRD patients. The mean of difference between pre- and post-therapy RSI score was 1.11 with CI 95% (0.93, 1.28) and p-value<0.001 when only proton pump inhibitors were given for 1 month. Similarly the mean of difference between pre- and post-therapy RSI score was 10.06 with CI 95% (9.83, 10.29) and p-value<0.001 when triple therapy was given (Table 7). However, when the efficacy of both forms of treatment were compared, there was a significant improvement in RSI score in the triple therapy group compared to proton pump inhibitors group. The mean difference between the two groups' RSI score was 8.95 with CI 95% (8.66, 9.24) and p-value<0.001 (Table 8).

The mean of difference between pre- and post-therapy RFS score was 1.40 with CI 95% (1.23, 1.56) and p-value<0.001 when only proton pump inhibitors were given for 1 month. Similarly, it was found that the mean of difference between pre- and post-therapy RFS score was 7.44 with CI 95% (7.15, 7.73) and p-value<0.001 when triple therapy was given. (Table 7) However when the efficacy of both forms of treatment were compared, there was a significant improvement in RFS score in the triple therapy group compared to proton pump inhibitors group. The mean difference between the two groups' RFS score was 6.04 with CI 95% (5.7, 6.38) and p-value<0.001 (Table 8).

Table 6. Changes in the RUT-negative Laryngopharyngeal Reflux Disease Clinical Features after Anti-Reflux therapy (n=138).

	RSI score		RFS Score	
	Before treatment	After Treatment	Before treatment	After Treatment
Mean	20.16	11.75	12.57	5.25
Standard Deviation	3.5	1.56	3.67	2.06
Mean Difference	8.41		7.32	
Confidence Interval	7.89 to 8.94		6.86 to 7.78	
p-value	<0.05		<0.05	

Table 7. Changes in the RUT-positive Laryngopharyngeal Reflux Disease Clinical Features after Therapy.

	RSI Score				RFS Score			
	Only Anti-Reflux therapy(n=271)		Triple Therapy (n=274)		Only Anti-Reflux therapy (n=271)		Triple Therapy (n=274)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Mean	19.91	18.80	22.52	12.46	12.36	10.96	12.28	4.84
Standard Deviation	3.38	2.76	2.12	1.47	3.27	2.70	2.45	1.69
Mean Difference		1.11		10.06		1.40		7.44
Confidence Interval		0.93 to 1.28		9.83 to 10.29		1.23 to 1.56		7.15 to 7.73
p-value		<0.001		<0.001		<0.001		<0.001

Table 8. Comparative Data in the Improvement of RUT-positive Laryngopharyngeal Reflux Disease Clinical Features after Therapy.

	RSI Score		RFS Score	
	Only Anti-Reflux therapy(n=271)	Triple Therapy(n=274)	Only Anti-Reflux therapy(n=271)	Triple Therapy(n=274)
Mean	1.11	10.06	1.40	7.44
Standard Deviation	1.47	1.94	1.39	2.45
Mean Difference		8.95		6.04
Confidence Interval		8.66 to 9.24		5.7 to 6.38
p-value		<0.001		<0.001

DISCUSSION

In otolaryngology daily practice, LPRD is one of the most common diseases we encounter. Our study explored two questions. In the first part of the study, we tested the efficacy of long term treatment by proton pump inhibitors in H.pylori negative LPRD. The results showed both the symptoms and signs of LPRD improved post anti-reflux therapy with p-value<0.05. In the second part of the study, a test was done to see the association of H.pylori infection with the degree or severity of symptoms and laryngoscopic findings. The study showed that the severity of symptoms and signs do not correlate with *H.pylori* infection in the larynx. The study also compared the efficacy of proton pump inhibitor monotherapy versus triple therapy in RUT positive H.pylori infection of the larynx. The study showed better results with triple therapy.

Study shows more than 70 bacterial species were identified as commensal of larynx. Among them, 36 species were confined to the subglottis and 24 confined to the supraglottis and the remainder were common to both sites. The majority of the bacterial species were same as oral cavity commensals; however potential pathogens including *Streptococcus pneumoniae*, *Haemophilus* and *Neisseria* were also present. *H.pylori* was not identified as normal laryngeal flora.[15] However, other studies have suggested that in the presence of *H pylori* infection of the stomach, if there is a pharyngeal acid reflux, it would expose the pharynx to the *H pylori* bacterium.[16,17]There are also studies which shows no relationship between gastric H pylori infection and LPR.[18] *H pylori* has been also shown in dental plaques and pharyngeal tonsils.[19,20]

There are only a few studies that explore the association between H.pylori infection of larynx and LPR symptoms.[17,21,22]There is no definite test for LPR. Empirical therapy with PPIs has been widely accepted as the treatment of choice for LPR. Other treatment options include lifestyle and dietary changes like quitting smoking and drinking, weight loss, and avoiding caffeine.[23]

In our study, 704 patients had clinical features suggestive of LPRD. Among these 566 (80.05%) patients had a positive RUT. In a similar study done by Youssef et al, the prevalence was found to be 57.5% and *H.pylori* was detected by stool antigen test. [21] In another study done by Haruma et al in Japan, a relationship was shown between *H.pylori* and LPRD with incidence of 31-41%.[24] In both RUT positive and negative groups, the most common symptoms were sensation of lump or foreign body in throat followed by repeated throat clearing and voice problems. The prevalence of symptoms in both the groups was almost similar and the difference was not statistically significant. The most common laryngoscopic findings were erythema of the supraglottic region followed by posterior commissure hypertrophy and ventricular obliteration in both the RUT positive and negative groups and the difference was not statistically significant. Similar findings were seen in other studies. [21]

In RUT negative group, long term proton pump inhibitors showed positive results in terms of improvement of RSI and RFS score. Mattoo et al also quoted similar findings.[25] RUT positive patients were divided into two groups in our study. The first group received only proton pump inhibitors where as the second group received triple therapy. Both groups showed positive results in term of improvement of RSI and RFS score, however the improvement was more significant in triple therapy group. Youssef et al showed similar findings.[21]A meta-analysis, done by Guo et al found PPI therapy had a higher response rate than placebo (risk difference, 0.15; 95% CI, 0.01-0.30), but it did not show any significant improvement in the Reflux Finding Score compared to placebo.[26]

There are certain limitations of this study. It is a single center study. The presence of *H.pylori* in the gastric mucosa was not assessed even when *H.pylori* was detected in laryngeal mucosa. In most of the studies, proton pump inhibitors therapy is given for atleast three months.[27-29] In this study it was given only for one month. Our study does not aim to point to a specific treatment regimen for LPRD, a task left better for randomized controlled trials, but our data showed that patients with RUT negative LPRD benefit from long term treatment with esomeprazole magnesium, with marked symptom improvement in most cases. While the patients with RUT positive LPRD benefit more from triple therapy treatment. Reports of triple therapy success in the treatment of GERD are in agreement with our results, but still, no available clear guidelines are there for the treatment of LPRD.[30]

CONCLUSIONS

Our study reveals most of the cases of laryngophatyngeal reflux have associated *H.pylori* infection as confirmed by rapid urease test. Proton pump inhibitors can give better results if *H.pylori* infection is not seen by rapid urease test. However, if rapid uraese test is positive for *H.pylori*, then triple therapy give better results than proton pump inhibitors. However, the use of triple therapy in the management of *H.pylori*

positive laryngopharyngeal reflux should be confirmed by larger scale, well designed, multicentre research studies that would examine the relationship between laryngopharyngeal reflux disease and *H. pylori* infection in the upper airway, and would assess the effect of *H. pylori* eradication medical management on the course of *H. pylori*-associated laryngeal diseases.

REFERENCES

1. Hawkshaw MJ, Pebdani P, Sataloff RT. Reflux laryngitis: an update, 2009-2012. J Voice Off J Voice Found. 2013;27(4):486–94. DOI https://doi.org/10.1016/j.jvoice.2013.03.001
2. Morinaka S, Ichimiya M, Nakamura H. Detection of Helicobacter pylori in nasal and maxillary sinus specimens from patients with chronic sinusitis. Laryngoscope. 2003;113(9):1557–1563. DOI https://doi.org/10.1097/00005537-200309000-00027
3. Cirak MY, Ozdek A, Yilmaz D, Bayiz U, Samim E, Turet S. Detection of Helicobacter pylori and its CagA gene in tonsil and adenoid tissues by PCR. Arch Otolaryngol Neck Surg. 2003;129(11):1225–1229.[GoogleScholar]
4. Yilmaz T, Ceylan M, Akyün Y, Özçakỳr O, Gürsel B. Helicobacter pylori: a possible association with otitis media with effusion. Otolaryngol Neck Surg. 2006;134(5):772–777. DOI https://doi.org/10.1016/j.otohns.2006.02.002
5. Hazell SL, Borody TJ, Gal A, Lee A. Campylobacter pyloridis gastritis I: Detection of urease as a marker of bacterial colonization and gastritis. Am J Gastroenterol. 1987;82(4).[GoogleScholar]
6. Scott LJ, Dunn CJ, Mallarkey G, Sharpe M. Esomeprazole: a review of its use in the management of acid-related disorders. Drugs. 2002;62(10):1503–38.
7. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice Off J Voice Found. 2002;16(2):274–7.DOI https://doi.org/10.1016/S0892-1997(02)00097-8
8. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope. 2001;111(8):1313–7. DOI https://doi.org/10.1097/00005537-200108000-00001
9. Belafsky PC, Postma GN, Amin MR, Koufman JA. Symptoms and findings of laryngopharyngeal reflux. Ear Nose Throat J. 2002;81(9 Suppl 2):10–3.
10. Tseng C-A, Wang W-M, Wu D-C. Comparison of the clinical feasibility of three rapid urease tests in the diagnosis of Helicobacter pylori infection. Dig Dis Sci. 2005;50(3):449–452.[Springer]
11. Osaki T, Mabe K, Hanawa T, Kamiya S. Urease-positive bacteria in the stomach induce a false-positive reaction in a urea breath test for diagnosis of Helicobacter pylori infection. J Med Microbiol. 2008;57(7):814–819. DOI https://doi.org/10.1099/jmm.0.47768-0
12. Vaira D, Holton J, Cairns S, Polydorou A, Falzon M, Dowsett J, et al. Urease tests for Campylobacter pylori: care in interpretation. J Clin Pathol. 1988;41(7):812. DOI http://dx.doi.org/10.1136/jcp.41.7.812
13. Perna F, Ricci C, Gatta L, Bernabucci V, Cavina M, Miglioli M, et al. Diagnostic accuracy of a new rapid urease test (Pronto Dry), before and after treatment of Helicobacter pylori infection. Minerva Gastroenterol Dietol. 2005;51(3):247–254. PMID: 16280966
14. Ylitalo R, Lindestad P-A, Ramel S. Symptoms, laryngeal findings, and 24-hour pH monitoring in patients with suspected gastroesophago-pharyngeal reflux. Laryngoscope. 2001;111(10):1735–1741. DOI https://doi.org/10.1097/00005537-200110000-00013
15. Gillett SDS, Birchall MA, Cogan T, Rees L. Diversity of the bacterial flora of the larynx. Otolaryngol Neck Surg. 2009 Sep 1;141(2_suppl):P63–P63.
16. Rubin JS, Benjamin E, Prior A, Lavy J, Ratcliffe P. The prevalence of Helicobacter pylori infection in benign laryngeal disorders. J Voice. 2002;16(1):87–91.DOI https://doi.org/10.1016/S0892-1997(02)00076-0
17. Fellmann J, Weisert JU, Soltermann A, Morand G, Morra L, Moch H, et al. Helicobacter pylori detected in pharyngeal and laryngeal pathologies in patients with proven gastric colonization. Head Neck. 2014;36(11):1562–6. DOI https://doi.org/10.1002/hed.23492
18. Ercan İi, Çakir BÖ, Uzel TÇ, Sakiz D, Karaca Ç, Turgut S. The role of gastric Helicobacter pylori infection in laryngopharyngeal reflux disease. Otolaryngol Neck Surg. 2006;135(1):52–55. DOI https://doi.org/10.1016/j.otohns.2006.03.020
19. Umeda M, Kobayashi H, Takeuchi Y, Hayashi J, Morotome-Hayashi Y, Yano K, et al. High prevalence of Helicobacter pylori detected by PCR in the oral cavities of periodontitis patients. J Periodontol. 2003;74(1):129–134. DOI https://doi.org/10.1902/jop.2003.74.1.129
20. Unver S, Kubilay U, Sezen OS, Coskuner T. Investigation of Helicobacter pylori colonization in adenotonsillectomy specimens by means of the CLO test. Laryngoscope. 2001;111(12):2183–2186. DOI https://doi.org/10.1097/00005537-200112000-00021
21. Youssef TF, Ahmed MR. Treatment of clinically diagnosed laryngopharyngeal reflux disease. Arch Otolaryngol Neck Surg. 2010;136(11):1089–1092.[FullText]

22. Gillett SDS, Birchall MA, Cogan T, Birchenall K, Rees L. Laryngopharyngeal Reflux and the Flora of the Larynx. Otolaryngol Neck Surg. 2009;141(2_suppl):P66–P66. DOI https://doi.org/10.1016/j.otohns.2009.06.199

23. Campagnolo AM, Priston J, Thoen RH, Medeiros T, Assunção AR. Laryngopharyngeal reflux: diagnosis, treatment, and latest research. Int Arch Otorhinolaryngol. 2014;18(02):184–191.

24. Haruma K, Hamada H, Mihara M, Kamada T, Yoshihara M, Sumii K, et al. Negative association between Helicobacter pylori infection and reflux esophagitis in older patients: case-control study in Japan. Helicobacter. 2000;5(1):24–29. DOI https://doi.org/10.1046/j.1523-5378.2000.00003.x

25. Mattoo O, Muzaffar R, Mir A, Yousuf A, Charag AH, Ahmad R. laryngopharyngeal reflux: prospective study analyzing various nonsurgical treatment modalities for LPR. Int J Phonosurg Laryngol. 2012;2(1):5–8.[FullText]

26. Guo H, Ma H, Wang J. Proton Pump Inhibitor Therapy for the Treatment of Laryngopharyngeal Reflux: A Meta-Analysis of Randomized Controlled Trials. J Clin Gastroenterol. 2016 Apr;50(4):295–300. DOI https://doi.org/10.1097/MCG.0000000000000324

27. Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA. 2005;294(12):1534–40.[FullText]

28. Bove MJ, Rosen C. Diagnosis and management of laryngopharyngeal reflux disease. Curr Opin Otolaryngol Head Neck Surg. 2006 Jun;14(3):116–23.[Link]

29. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135(4):1392–1413. [Link]

30. Ching SS, Sabanathan S, Jenkinson LR. Treatment of Helicobacter pylori in surgical practice: a randomised trial of triple versus quadruple therapy in a rural district general hospital. World J Gastroenterol. 2008;14(24):3855. [PMC2721442]