The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Empiric Treatment of Laryngopharyngeal Reflux with Proton Pump Inhibitors: A Systematic Review

Petros D. Karkos, AFRCSI; Janet A. Wilson, MD, FRCS

Objective: **The objective of this study was to define the outcome of empiric treatment of suspected laryngopharyngeal reflux (LPR) symptoms with proton pump inhibitors (PPIs).** ***Design:*** **The authors conducted a systematic review of the English and foreign literature. Studies that used PPIs as an empiric treatment modality for suspected LPR, whether alone or in combination with other acid suppressants and/or placebo, were included. Studies that did not include PPIs as a treatment option were excluded.** ***Main Outcome Measures:*** **A lack of common outcome measures was evident in the uncontrolled studies. In the randomized, controlled trials, outcome measures included symptom questionnaires and videolaryngoscopy. Only one study used computerized voice analysis.** ***Results:*** **Fourteen uncontrolled studies together with one unblinded, nonrandomized study with a control group of healthy volunteers and six double-blind, placebo-controlled randomized trials were identified from 1994 to 2004. Selection bias, blinding of the results, and lack of common outcome measures were some of the problems preventing a formal metaanalysis. Although uncontrolled series reported positive results, randomized, controlled trials demonstrated no statistically significant differences for changes in severity or frequency of symptoms associated with suspected reflux between PPIs and placebo.** ***Conclusions:*** **Recommendations for empiric treatment of suspected LPR with PPIs, by far the most common ear, nose and throat practice in the United Kingdom, are based on poor levels of evidence from uncontrolled studies. The few randomized, controlled trials have failed to demonstrate superiority of PPIs over placebo for treatment of suspected LPR.**

From the Department of Otolaryngology, The Freeman Hospital, Newcastle upon Tyne, U.K.

This study was presented in part at the Royal Society of Medicine, Section of Laryngology & Rhinology, London, March 2004.

Editor's Note: This Manuscript was accepted for publication September 21, 2005.

Send Correspondence to Prof. Janet A. Wilson, Department of Otolaryngology, University of Newcastle upon Tyne, The Freeman Hospital, Newcastle upon Tyne, NE7 7DN, U.K. E-mail: j.a.wilson@ncl.ac.uk

DOI: 10.1097/01.mlg.0000191463.67692.36

Key Words: **Laryngopharyngeal, reflux, larynx, gastroesophageal, proton pump inhibitors, treatment.**
Laryngoscope, **116:144–148, 2006**

INTRODUCTION

Laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the laryngopharynx.[1] Gastric juice contains not only acid, but also pepsin, particularly implicated by recent research in LPR and childhood otitis media. Pepsin may also play a role in rejection in patients undergoing lung transplantation.[2] LPR is increasingly cited as the cause of many symptoms such as globus pharyngeus, hoarseness, postnasal drip, chronic cough, dysphagia, and throat pain.[3] However, these common throat symptoms may be all caused by other triggers: voice abuse (excessive talking, screaming, extremes of voice use), smoking, asthma, allergy, associated infections, or alcohol abuse. Thus, the proportion of patients with laryngeal symptoms who have reflux as the primary etiology may be overestimated in some studies.[4]

The current gold standard diagnostic test for LPR is dual-probe 24-hour pH monitoring, a safe but invasive test with poor sensitivity; the proportion of false-negative results can be as high as 50%.[5] Normal pH values for the distal esophagus have been well established in the literature.[6] Any number of episodes of pharyngeal reflux is counted by some authors as positive evidence of LPR, but the normal pH values for the hypopharynx are much less well defined than the ones for the distal esophagus. Even in the lower esophagus, however, the response to proton pump inhibitor (PPI) therapy is usually so clearcut that a trial of PPIs has tended to supersede pH-metry over the last 5 to 10 years, except in refractory or research situations. Because there have now been several studies on the efficacy of PPIs in suspected LPR, and because the Cochrane methodology is much more refined for therapy than investigative studies, this study aimed to review the outcome of therapeutic PPI trials in LPR.

METHODS

A PubMed, Medline, Embase, Cinahl, and Cochrane search was performed using the terms: "laryngopharyngeal," "reflux,"

TABLE I.
Uncontrolled Studies (in Chronological Order) Investigating the Role of Empiric Treatment of Laryngopharyngeal Reflux with Proton Pump Inhibitors (PPIs).*

Study	No. of Patients	Duration of Treatment (wk)	Drug and Dose	Outcome Measures	Outcome and/or Response Rate
Kamel, 1994[7]	16	6–24	Omeprazole 40 mg od (increased to 40 mg twice a day in 4 patients for 6 wk)	SQ, VL	Both symptom indices and VL scores improved over baseline ($P < .05$)
Hanson, 1995[8]	182	4	Omeprazole 20 mg once daily (n = 41) or famotidine 20 mg once daily (n = 62)	SQ, VL	96% responded, 83% in the omeprazole group and 77% in the famotidine group
Jaspersen, 1996[9]	21	4	Omeprazole 40 mg once daily	SQ, OGD, VL	100%
Shaw, 1996[10]	68	12	Omeprazole 20 mg once daily	SQ, VL, AA	85%
Metz, 1997[11]	10	4	Omeprazole 20 mg twice a day	SQ, OGD, VL, MA, pH	75%
Shaw, 1997[12]	96	12	Omeprazole 20 mg once daily	SQ, VL, AA	Symptomatic improvement ($P < .05$)
Wo, 1997[13]	22	8	Omeprazole 40 mg once daily	SQ, VL	67%
Habermann, 1999[14]	29	6	Pantoprazole 40 mg once daily	SQ, VL	Both symptoms and VL scores improved over baseline ($P < .05$)
Fossati, 2000[15]	47	12	Pantoprazole 40 mg once daily	SQ, VL	89% (cured in 14%, improved in 75%)
Habermann, 2002[16]	24	6	Pantoprazole 40 mg once daily	SQ, VL, pH	100%
Rodriguez-Tellez, 2002[17]	21	12	Omeprazole 20 mg twice per day	SQ, VL	Decrease in symptom severity and frequency over baseline ($P < .05$)
Garigues, 2003[18]	91	12 or 24	Omeprazole 20 mg twice per day	SQ, OGD, VL, MA, pH	41% in 12 weeks, 65% in 24 weeks
DelGaudio, 2003[19]	30	8	Esomeprazole 40 mg once daily	SQ, VL, pH	63%
Siupsinskiene, 2003[20]	100	4	Omeprazole 20 mg once or twice per day or two or three times per day	SQ, VL, UO	65%
Bilgen, 2004[21]	59	24	Lansoprazole 30 mg twice per day for 8 weeks, then 15 mg twice per day for 16 weeks	SQ, RSI, RFS, pH	Both RSI and RFS improved over baseline ($P < .05$)

*There is also a controlled (nonrandomized, unblinded) study that includes a control group of 23 healthy adults.[21]
SQ = symptom questionnaire; VL = videolaryngoscopy; AA = computerized acoustic analysis; RSI = reflux symptom index; RFS = reflux finding score; OGD = esophagogastroduodenoscopy; MA = manometry; pH = 24-hour dual-probe pH monitoring; UO = upper esophagoscopy.

"larynx," "diagnosis," "gastroesophageal," "proton pump inhibitors," "treatment," and "empiric." References from the relevant articles were also searched.

We included studies that used PPIs as an empiric treatment modality for suspected LPR whether used alone or in combination with other acid suppressants and/or placebo. We excluded those studies that did not include PPIs as a treatment option. This is because there is evidence that PPIs are superior to other antacids such as H_2 receptor antagonists in achieving acid suppression.[3] Thus, a negative result from a non-PPI intervention may simply imply failure of adequate acid suppression rather than failure of attributable response of symptoms.

Complete symptomatic response was defined in most studies by the total resolution of all presenting symptoms of LPR. Nonresponse to therapy was defined by persistence of any of the initial laryngitis symptoms. Complete resolution of laryngeal signs was defined by the absence of all abnormal signs noted on pretreatment evaluation, whereas partial resolution denoted the resolution of some but not all of the abnormal findings.

RESULTS

Table I summarizes the prospective uncontrolled trials[7–20] together with one unblinded, nonrandomized study with a control group of 23 healthy volunteers.[21] In all these uncontrolled studies, there is a statistically significant improvement of symptoms and laryngoscopic signs after empiric antireflux treatment.

We could identify only six double-blind, placebo-controlled, randomized trials in the international literature (Tables II and III).[22–27] There was significant heterogeneity among studies with regard to patient selection, outcome measures, and study design.

Five of the randomized, controlled trials (Table II) had a parallel-group design; the sixth was a crossover study. Duration of treatment ranged from 8 to 16 weeks. Two studies used 30 mg lansoprazole twice per day; the remaining four used 40 mg omeprazole twice per day, 40 mg pantoprazole twice per day, 40 mg esomeprazole twice

TABLE II.
Double-blind, Placebo-controlled, Randomized Trials (in Chronological Order) on Empiric Treatment of Laryngopharyngeal Reflux with Proton Pump Inhibitors.

Study	PPI (n)	Placebo (n)	Duration of Treatment (wk)	Drug and Dose	Outcome Measures
Havas[22]	8	7	12	Lansoprazole 30 mg twice per day or placebo	OGD, MA, pH, SQ, VL
El-serag[23]	12	10	12	Lansoprazole 30 mg twice per day or placebo	pH, SQ, VL
Noordzij[24]	15	15	8	Omeprazole 40 mg twice per day or placebo	pH, SQ, VL
Eherer[25]	14	14	12	Pantoprazole 40 mg twice per day or placebo	pH, SQ, VL
Steward[26]	17	19	8	Rabeprazole 20 mg twice per day or placebo	SQ, VL
Vaezi[27]	95	50	16	Esomeprazole 40 mg twice per day or placebo	pH, SQ, VL

PPI = proton pump inhibitor; SQ = symptom questionnaire; VL = videolaryngoscopy; pH = 24-hour dual-probe pH monitoring; OGD = esophagogastroduodenoscopy; MA = manometry.

TABLE III.
Double-blind, Randomized, Controlled Trials Comparing Proton Pump Inhibitor Treatment with Placebo.*

	Symptom Score (Mean ± SEM)†				Laryngoscopic Score (Mean ± SEM)†			
	PPI		Placebo		PPI		Placebo	
Study	Baseline	End of Rx	Baseline	End of Rx	Baseline	End of Rx	Baseline	End of Rx
Havas[22]	11.25 ± 2.7	7.376 ± 2.7	11.70 ± 1.4	7.850 ± 2.5	2.88 ± 0.23	1.625 ± 0.53	2.80 ± 0.25	1.625 ± 0.53
Noordzij‡[24]	2055.0 ± 402.6	1078.6 ± 371.7	2399.3 ± 288.4	1944.9 ± 376.4	0.00 ± 0.00	0.08 ± 0.08	0.071 ± 0.07	0.07 ± 0.07
Eherer[25]	14.6 ± 3.1	Change of 8.3 ± 3.6	17.4 ± 3.1	Change of 10.3 ± 3.9	NA	Change of 8.0 ± 1.4	NA	Change of 5.6 ± 2.6
Steward[26]	41.2 ± 12.0	Change of 9.7 ± 11.1	35.6 ± 11.53	Change of 6.6 ± 12.5	8.6 ± 2.9	Change of 0.6 ± 1.8	9.8 ± 3.4	Change of 0.5 ± 2.3
El-serag[23]	NA	NA	NA	NA	NA	NA	NA	NA
Vaezi[27]	NA	NA	NA	NA	NA	NA	NA	NA

*Mean ± standard error of mean (SEM) for symptom scoring and laryngoscopic scoring for the PPI and placebo groups at baseline and at the end of the treatment (end of Rx) or changes from pretreatment baseline for the two groups. A positive change indicates improvement in the scores.
†*P* values for differences in mean change in symptom and laryngoscopic scores during treatment between groups were all nonsignificant.
‡In this study, PPI treatment significantly improved symptoms of hoarseness and throat clearing compared with placebo, but no statistical difference was found for the rest of the symptoms.
PPI = proton pump inhibitor; NA = information not available.

per day, or 20 mg rabeprazole twice per day. Outcome measures used in the trials included symptom questionnaires and videolaryngoscopy, whereas only one study used computerized voice analysis.[10] In all, 161 patients (including 14 in the crossover trial) completed PPI treatment; 115 completed placebo treatment. Baseline characteristics were similar between PPI and placebo groups in most of the studies in which this information was available. In the study by Noordzij et al., however, there were large differences in initial symptom severity between the two groups for certain symptoms.[24]

None of the six randomized, controlled trials demonstrated any statistically significant postintervention difference in the severity or frequency of reflux symptoms between PPI- and placebo-treated patients (Table III). No significant differences were noted between treatment groups for change in health status or change in videolaryngeal grading scores and appearances. In the study by Noordzij et al.,[24] most symptoms improved over time in both treatment groups, signifying the possibility of a placebo effect or a self-limiting natural history. The observed improvement in symptoms of hoarseness and throat-clearing was significantly greater in the omeprazole-treated patients when compared with the placebo group, but this may have simply reflected baseline differences.[24]

DISCUSSION

It is obvious from our review of six available randomized, controlled studies that the majority of symptoms in a reflux laryngitis cohort (throat pain, globus, mucus, dysphagia, and painful swallowing) improved similarly in the PPI and control arms, although, at least in one study, throat-clearing and hoarseness appeared more responsive to omeprazole.[24] Empiric antireflux treatment has been widely used over recent years as an alternative diagnostic modality for LPR detection instead of dual-probe 24-hour pH monitoring. Because the signs of reflux are at best nonspecific, and at worst absent, response is based largely on reported improvement in symptoms. Therapeutic response to empiric therapy allows for both diagnosis and treatment of LPR and involves lifestyle modifications and the use of acid-suppressing medications, most recently,

PPIs.[8] In head and neck symptoms, most reports have been empiric, uncontrolled therapeutic trials of treatment with PPI reporting a positive effect (Table I), but often in selected patients and in conjunction with other much more general lifestyle interventions such as smoking cessation and even voice therapy.

The evaluation of a medical or surgical outcome relies on accurate diagnostic methods. Unfortunately, to date, there are no validated tools that can accurately document symptoms or signs of reflux laryngitis and, more generally, of LPR. The North Carolina Group came close to achieving this by introducing a Reflux Symptom Index, and also a Reflux Finding Score.[28,29] The Reflux Symptom Index is a self-administered, nine-item outcomes instrument for LPR and includes symptoms such as globus pharyngeus, hoarseness, throat-clearing, chronic cough, postnasal drip, dysphagia, choking episodes, dysphagia, and heartburn. It is easily administered, but like every symptom questionnaire, it is entirely subjective. The use of the Reflux Symptom Index as a primary outcome measure in randomized, controlled trials may be problematic; the scale does not include throat pain. Also, one of the items incorporates heartburn, which might induce a bias in favor of the nonplacebo limb, because some authorities now define heartburn as "that which responds to PPI therapy."[30]

The Reflux Finding Score is an eight-item grading scale that was developed to standardize the laryngoscopic findings of LPR so that laryngologists may better diagnose, evaluate clinical improvement, and assess therapeutic efficacy of patients with LPR. Although it is easily administered, it is also subjective because it depends on the experience of the laryngologist who grades it. A polling of a select group of otolaryngologists demonstrated variability in the criteria used to diagnose reflux laryngitis.[31] Also, the scale uses differential weightings whose basis is not entirely clear. Therefore, so far, there are no objective diagnostic tools for LPR detection, which explains why treatment is also controversial. The development of objective guidelines for the diagnosis of LPR is necessary to evaluate the manifestations and therapeutic interventions for this disease process.

The H+/K+-ATPase (proton) pump has been found in serous cells and ducts of submucosal glands in the human larynx, representing a potential site of PPI pharmacotherapy with possible relevance for patients treated for chronic laryngitis with or without laryngopharyngeal reflux disease.[32] However, the relevance of this observation remains unclear given the negative therapeutic response from the randomized, controlled trials identified.

The popularity of gastroesophagopharyngeal reflux as a causative factor for ear, nose and throat symptoms has increased steadily over the past 3 decades. Given the cost implications of empiric therapy with PPIs and the substantial knowledge gap, much work remains to be done. Once the reliability and discriminant validity of measures, such as the Reflux Symptom Index for LPR can be established, the unanswered questions such as the accessory role of bile and pepsin and the optimum therapy, whether medical or surgical, can be addressed.

CONCLUSIONS

Recommendations for the empiric treatment of suspected LPR with PPIs—by far the most common ear, nose, and throat practice in the United Kingdom—are based on poor levels of evidence from uncontrolled studies. The small volume of level I evidence has failed to demonstrate superiority of PPIs over placebo for treatment of suspected LPR. There are a lot of unanswered questions regarding LPR. The initial enthusiasm of the otolaryngology "believer" in reflux was replaced by a wave of skepticism following the recent negative randomized, controlled trials. At the same time, studies like those highlighting the potential role of pepsin[2] suggest that trial by PPI may not be sufficient finally to answer the question.

Our systemic review of empiric treatment of LPR with PPIs has shown no benefit of placebo over PPIs. Of course, this does not imply that LPR does not respond to antireflux therapy; what it perhaps suggests is that a more detailed diagnosis and selection of patients with LPR should take place before the beginning of any PPI treatment. Selecting patients based on symptoms and signs alone, without dual-probe pH-metry, will quite possibly lead to more negative trials creating more confusion on a topic that is already quite controversial.

BIBLIOGRAPHY

1. Koufman JA, Aviv JE, Casiano RR, et al. Laryngopharyngeal reflux: Position Statement of the Committee on Speech, Voice, and Swallowing Disorders of the American Academy of Otolaryngology–Head Neck Surgery. *Otolaryngol Head Neck Surg* 2002;127: 32–35.
2. Tasker A, Dettmar PW, Panetti M, et al. Is gastric reflux a cause of otitis media with effusion in children? *Laryngoscope* 2002;112:1930–1934.
3. 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(suppl 53):1–78.
4. Ylitalo R, Lindestad P, Ramel S. Symptoms, laryngeal findings, and 24-hour pH monitoring in patients with suspected gastroesophago-pharyngeal reflux. *Laryngoscope* 2001;111:1735–1741.
5. Weiner GJ, Koufman JA, Wu WC, et al. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-hour pH monitoring. *Am J Gastroenterol* 1989; 84:1053–1058.
6. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992;87:1102–1111.
7. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med* 1994;96:321–326.
8. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995;104:550–555.
9. Jaspersen D, Weber R, Hammar CH, et al Effect of omeprazole on the course of associated esophagitis and laryngitis. *J Gastroenterol* 1996;31:765–767.
10. Shaw GY, Searl JP, Young JL, et al. Subjective, laryngoscopic, and acoustic measurements of laryngeal reflux before and after treatment with omeprazole. *J Voice* 1996;10: 410–418.
11. Metz DC, Childs ML, Ruiz C, Weinstein GS. Pilot study of the oral omeprazole test for reflux laryngitis. *Otolaryngol Head Neck Surg* 1997;116:41–46.
12. Shaw GY, Searl JP. Laryngeal manifestations of gastro-

esophageal reflux before and after treatment with omeprazole. *South Med J* 1997;90:1115–1122.
13. Wo JM, Grist WJ, Gussack G, et al. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. *Am J Gastroenterol* 1997;92:2160–2165.
14. Habermann W, Eherer A, Lindbichler F, et al. Ex juvantibus approach for chronic posterior laryngitis results of short-term pantoprazole therapy. *J Laryngol Otol* 1999;113: 734–739.
15. Fossati D, Passaretti S, Strada E, et al ENT disorders caused by GERD: efficacy of treatment with pantoprazole. *Gastroenterology* 2000;118(suppl 2):5650–5651.
16. Habermann W, Kiesler K, Eherer A, et al. Short-term therapeutic trial of proton pump inhibitors in suspected extraesophageal reflux. *J Voice* 2002;16:425–432.
17. Rodriguez-Tellez M, Galera-Ruiz H, Arguelles-Arias F, et al. Posterior laryngitis: effects of treatment with omeprazole alone. *Rev Esp Enferm Dig* 2002;94:123–130.
18. Garrigues V, Gisbert L, Bastida G, et al. Manifestations of gastroesophageal reflux and response to omeprazole therapy in patients with chronic posterior laryngitis: an evaluation based clinical practice. *Dig Dis Sci* 2003;48: 2117–2123.
19. DelGaudio JM, Waring JP. Empiric esomeprazole in the treatment of laryngopharyngeal reflux. *Laryngoscope* 2003;113:598–601.
20. Siupsinskiene N, Adamonis K. Diagnostic test with omeprazole in patients with posterior laryngitis. *Medicina* 2003; 39:47–55.
21. Bilgen C, Ogut F, Kesimli-Dinc H, et al. The comparison of an empiric proton pump inhibitor trial vs 24-hour double-probe pH monitoring in laryngopharyngeal reflux. *J Laryngol Otol* 2003;117:386–390.
22. Havas T, Huang S, Levy M, et al. Posterior pharyngolaryngitis: double-blind randomised placebo-controlled trial of proton pump inhibitor therapy. *Aust J Otolaryngol* 1999;3: 243–246.
23. El-Serag HB, Lee P, Buchner A, et al. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. *Am J Gastroenterol* 2001;96: 979–983.
24. Noordzij JP, Khidr A, Desper E, et al. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. *Laryngoscope* 2002;112: 2192–2195.
25. Eherer AJ, Habermann HF, Klesler K, et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. *Scand J Gastroenterol* 2003;38:462–467.
26. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. *Otolaryngol Head Neck Surg* 2004;131:342–350.
27. Vaezi M, Richter J, Stasney SR, et al. A randomized, double blind, placebo-controlled study of acid suppression for the treatment of suspected laryngopharyngeal reflux [Abstract]. *Gastroenterology* 2004;126(suppl 2):A22.
28. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the Reflux Finding Score (RFS). *Laryngoscope* 2001;111:1313–1317.
29. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the Reflux Symptom Index (RSI). *J Voice* 2002;16: 274–277.
30. Carlsson R, Dent J, Bolling-Sternevald E, et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 2003;33:1023–1029.
31. Book DT, Rhee JS, Toohill RJ, et al. Perspectives in laryngopharyngeal reflux: an international survey. *Laryngoscope* 2002;112:1399–1406.
32. Altman KW, Haines GK 3rd, Hammer ND, et al. The H+/K+-ATPase (proton) pump is expressed in human laryngeal submucosal glands. *Laryngoscope* 2003;113:1927.