The Journal of Laryngology & Otology (2007), ***121***, *1165–1169*.

doi:10.1017/S0022215107000680
Printed in the United Kingdom
First published online 12 October 2007

Main Article

Should patients with pH-documented laryngopharyngeal reflux routinely undergo oesophagogastroduodenoscopy? A retrospective analysis

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Abstract

Objectives: Patients with laryngopharyngeal reflux uncommonly suffer from conditions associated with gastroesophageal reflux disease. However, in some laryngopharyngeal reflux patients, oesophagitis and Barrett's metaplasia can be diagnosed by oesophagogastroduodenoscopy. However, it is unclear which patients with laryngopharyngeal reflux would benefit from routine oesophagogastroduodenoscopy.

Study design: Retrospective analysis.

Materials and methods: Analysis of the results of oesophagogastroduodenoscopy in 28 patients with pH-documented laryngopharyngeal reflux.

Results: Oesophagogastroduodenoscopy showed oesophagitis in five patients (four with grade A, one with grade B), hiatus hernia in 10 patients (36 per cent), Barrett's metaplasia in two patients, *Helicobacter pylori*-associated chronic gastritis in two patients and gastric mucosal erosions in seven patients (25 per cent). In 13 patients, no abnormalities were detected (46 per cent). Barrett's metaplasia or grade B oesophagitis was diagnosed only in patients with heartburn as their main presenting symptom.

Conclusions: Oesophagogastroduodenoscopy is indicated in at least those laryngopharyngeal reflux patients reporting heartburn as their main complaint.

Key words: Gastro-Oesophageal Reflux; Larynx; Barrett Oesophagus; Endoscopy

Introduction

Over the last 15 years, numerous clinical trials have gradually added evidence that duodenogastro-esophageal reflux reaching the laryngopharynx plays an important aetiological role in the pathogenesis of laryngeal, pharyngeal and pulmonary disorders. While patients suffering from gastroesophageal reflux disease usually complain of heartburn, chest pain and acid regurgitation, these symptoms are rarely found in patients with laryngopharyngeal reflux (LPR). The typical so-called supra-oesophageal reflux symptoms are globus pharyngeus, frequent throat-clearing, chronic cough, hoarseness, asthma, dysphagia and sore throat.[1]

Although oesophagogastroduodenoscopy with biopsy is not the method of choice for diagnosis of LPR, this diagnostic approach might be indicated in some patients with pH-documented LPR, in order to exclude Barrett's metaplasia, *Helicobacter pylori*-associated chronic gastritis, or other gastric or oesophageal abnormalities. *Helicobacter pylori*-associated chronic gastritis is involved in the development of duodenal and gastric ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue. 'Barrett's oesophagus' is a precancerous condition in the development of oesophageal adenocarcinoma. The incidence of oesophageal adenocarcinoma has increased steadily over the last decades at a faster rate than any other type of cancer.[2,3]

Another argument for routine oesophagogastroduodenoscopy in LPR patients could be provided by Reavis and colleagues' results demonstrating that LPR symptoms were better indicators of oesophageal adenocarcinoma than were gastroesophageal symptoms.[4]

Currently, few studies have analysed the prevalence of Barrett's oesophagus or *H pylori*-associated chronic gastritis in patients with LPR. Therefore, the goal of this retrospective study was to determine the rates of Barrett's metaplasia, *H pylori*-associated chronic gastritis, and other pathological gastric and oesophageal findings, in consecutive patients with pH-documented LPR diagnosed by oesophagogastroduodenoscopy and biopsy.

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Accepted for publication: 25 June 2007.

Patients and methods

Between January 2005 and December 2006, 28 consecutive patients (15 women, 13 men; mean age 50 years) had presented to the Department of Otorhinolaryngology, Head and Neck Surgery at Ludwig Maximilians University Munich, with nonspecific otolaryngological symptoms (Table I). All patients had been suspected of having LPR, based on their symptoms and laryngeal findings, using the reflux symptom index and the reflux finding score.[5,6] None of the patients had been treated with proton pump inhibitors (PPIs) or any other anti-reflux medication at the time of presentation.

In order to confirm the diagnosis of LPR, all patients had undergone 24-hour pH-monitoring, using a pH device consisting of one proximal and one distal probe with a fixed distance of approximately 10 cm between the probes. After application of a local, decongestant anaesthetic spray, the recording probe of the device had been placed transnasally. The proximal probe had been positioned immediately above the upper oesophageal sphincter, under the guidance of flexible or rigid laryngoscopy. Patients had kept a diary, recording times and durations of meals. No oesophageal manometry had been performed.

To record the data, we used the pH response reflux diagnostic system (Medtronic Xomed, Jacksonville, Florida, USA). All meal intervals and the first two minutes of the immediate postprandial period had been eliminated from analysis. In order to exclude artefacts from analysis, upper probe events with pH $<$ 4 had only been accepted as proximal reflux episodes when an association with a lower probe event could be clearly identified. Such pH-monitoring enabled determination of the reflux area index, currently the most useful parameter for measuring laryngopharyngeal reflux severity.[7] This parameter not only incorporates the number and duration of proximal reflux events, but also the degree to which these episodes drop below pH 4. The reflux area index is a measure of the area subjected to pH $<$ 4, corrected for the duration of the study for each patient.[7] Laryngopharyngeal reflux had been diagnosed when the reflux area index was $>$6.3 for the total pH study duration.

In 10 patients, oesophagogastroduodenoscopy with biopsy had been performed by gastroenterologists in private practice, within a maximum period of six weeks before presentation to our department. Four patients had been referred to our department by the gastrointestinal function laboratory of the department of surgery of Ludwig Maximilians University, due to abnormal laryngeal findings diagnosed during oesophagogastroduodenoscopy (Figure 1). Due to suspected LPR, 14 patients had first undergone 24-hour pH-monitoring in our department and had then been referred to the gastrointestinal function laboratory of our University's surgical department, in order to exclude additional gastroesophageal reflux disease, conditions associated with gastroesophageal reflux disease, or *H pylori*-associated chronic gastritis. All oesophagogastroduodenoscopy biopsies had been examined by either pathologists of the Ludwig Maximilians University pathology department or by pathologists in private practice ($n = 10$).

TABLE I

PATIENTS PRESENTING SYMPTOMS

Main symptom	Patients	
	n	%
Heartburn	5	18
Globus sensation	5	18
Frequent throat-clearing	2	7
Dysphagia	6	21
Hoarseness	8	29
Sore throat	1	3.5
Chronic cough	1	3.5

Results

The reflux symptom index had been greater than 13 and the reflux finding score greater than seven in all 28 patients, strongly indicating LPR.[5,6] Additional 24-hour pH-monitoring had also revealed a reflux area index of $>$6.3 in all 28 patients, reflecting abnormal proximal reflux.[7]

No oesophagogastroduodenoscopy abnormalities had been detected in 13 patients (46 per cent). Oesophagitis, classified according to the Los Angeles classification, had been diagnosed in five patients (grade A in four patients, grade B in one patient). Hiatus hernia had been detected in 10 patients (36 per cent) and gastric mucosal erosions in seven patients (25 per cent).

Histological examination of biopsies had revealed *H pylori*-associated chronic gastritis in two patients (7 per cent) and Barrett's metaplasia in two patients. In one patient, both Barrett's metaplasia and *H pylori*-associated chronic gastritis had been diagnosed (patient two, Table II). Oesophagitis grade B

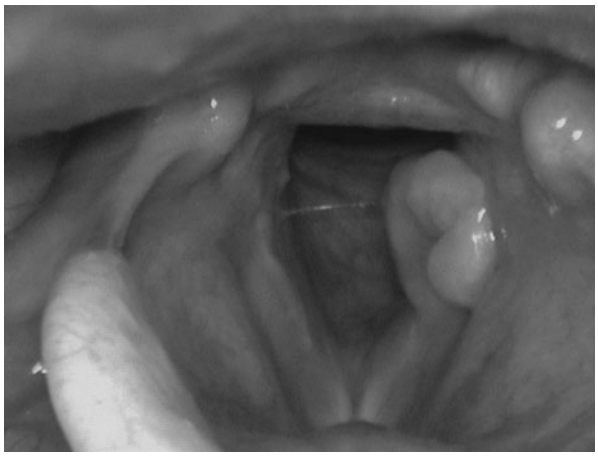

FIG. 1

Larynx of patient 10 (see Table II), suffering from combined pH-documented laryngopharyngeal reflux (reflux area index $>$6.3) and gastroesophageal reflux disease. Oesophagogastroduodenoscopy revealed grade B oesophagitis and a large, reflux-induced granuloma of the larynx.

https://doi.org/10.1017/S0022215107000680 Published online by Cambridge University Press

or Barrett's metaplasia had only been found in patients with heartburn as their main presenting symptom. Data for each patient are summarised in Table II.

Discussion

Gastroesophageal reflux disease is considered the most prevalent gastrointestinal disease in Western countries. It is estimated that in central and northern Europe, between 18 and 40 per cent of the population suffer from gastroesophageal reflux disease. This frequent condition is characterised by various clinical manifestations of abnormal reflux of gastric contents from the stomach into the oesophagus.[8,9] The most common clinical manifestations of gastroesophageal reflux disease are heartburn and acid regurgitation. When stomach content flows back up to the larynx or even to higher regions of the head and neck, it can cause a wide range of symptoms, commonly termed laryngopharyngeal reflux.

The incidence of heartburn in Laryngopharyngeal reflux patients, however, is less than 40 per cent.[1] In our study, only five patients (18 per cent) had been reported as suffering from heartburn. Nevertheless, in approximately 50 per cent of LPR patients, abnormal gastroesophageal reflux can be identified by pH study, potentially causing such complications as oesophagitis, strictures, Barrett's oesophagus and oesophageal adenocarcinoma.[10]

TABLE II
PATIENT DATA

Pt	Main symptom	OGD result
1	Globus sensation	NA
2	Heartburn	HPG, O1, HH, BM
3	Frequent throat-clearing	GME
4	Globus sensation	HH
5	Globus sensation	NA
6	Hoarseness	NA
7	Hoarseness	HH
8	Heartburn	O1, HH, BM
9	Hoarseness	NA
10	Heartburn	O2, HH
11	Dysphagia	HH
12	Globus sensation	GME, HH
13	Heartburn	NA
14	Dysphagia	NA
15	Heartburn	GME
16	Dysphagia	NA
17	Dysphagia	NA
18	Globus sensation	GME, O1, HH
19	Hoarseness	NA
20	Hoarseness	NA
21	Throat pain	HPG, O1
22	Hoarseness	GME
23	Dysphagia	HH
24	Frequent throat-clearing	NA
25	Hoarseness	NA
26	Dysphagia	GME
27	Chronic cough	NA
28	Hoarseness	GME, HH

Pt = patient; OGD = oesophagogastroduodenoscopy; NA = no abnormality; HPG = *Helicobacter pylori*-associated chronic gastritis; O1 = oesophagitis grade A; HH = hiatus hernia; BM = Barrett's metaplasia; GME = gastric mucosal erosions; O2 = oesophagitis grade B

Since the 1980s, the incidence of oesophageal adenocarcinoma has been rising by 4–10 per cent annually, and this increasing trend is still continuing.[3] Barrett's oesophagus is the most recognised risk factor for oesophageal adenocarcinoma, and the main risk factor for Barrett's oesophagus is gastroesophageal reflux disease.[3] The prevalence of Barrett's oesophagus among gastroesophageal reflux disease patients is estimated to range between 5 and 20 per cent.[11] The incidence of oesophageal adenocarcinoma in patients with Barrett's metaplasia is estimated to be 0.5 per cent per year.[12]

Therefore, one could argue that oesophagogastroduodenoscopy should be performed as a routine procedure in patients with pH-documented LPR, in order to rule out additional Barrett's metaplasia. However, little is known about the prevalence of Barrett's oesophagus or oesophagitis in LPR patients. In a recently published study by Halum *et al.*, the prevalence of Barrett's metaplasia in LPR patients was 3 per cent.[11] One study by Koufman *et al.* found oesophagitis in 12 per cent and Barrett's metaplasia in 7 per cent of patients with LPR.[13] These findings are similar to our results, with a prevalence of oesophagitis in 18 per cent and Barrett's metaplasia in 7 per cent of patients with pH-documented LPR. As Barrett's metaplasia might only be prevalent in 3 to 7 per cent of LPR patients, it does not, in our opinion, represent an indication to perform routine oesophagogastroduodenoscopy in such patients. However, in those LPR patients with heartburn as their main symptom, oesophagogastroduodenoscopy might be indicated; in our study, Barrett's metaplasia or oesophagitis grade B had only been found in patients complaining mainly of heartburn (i.e. patients 2, 8 and 10; Table II).

A second reason for performing oesophagogastroduodenoscopy as a routine diagnostic procedure in patients with pH-documented LPR could be to rule out *H pylori* colonisation, this being a strong risk factor for peptic ulceration and distal gastric cancer.[14] Moreover, long-term PPI therapy for LPR in the presence of *H pylori*-associated chronic gastritis may accelerate the loss of specialised glands, leading to atrophic gastritis and potentially to gastric cancer.[15,16]

Laryngopharyngeal reflux management recommendations call for initial treatment with twice-daily PPIs for a minimum period of six months, with many patients requiring prolonged chronic treatment; *H pylori* eradication might therefore be especially indicated in many LPR patients.[1,17]

To our knowledge, there is only one published study investigating the role of gastric *H pylori* infection in LPR disease. The results of this study, by Ercan *et al.*, demonstrated no relationship between *H pylori*-associated chronic gastritis and LPR.[18] However, according to Oridate *et al.*, *H pylori* seropositivity predicts the outcomes of PPI therapy for LPR symptoms.[19] Little is known about the prevalence of *H pylori*-associated chronic gastritis in LPR patients. In our study, we found *H pylori*-associated chronic gastritis in two patients (7 per cent) from

https://doi.org/10.1017/S0022215107000680 Published online by Cambridge University Press

Munich, Germany, whereas Ercan *et al.* reported *H pylori*-associated chronic gastritis to be present in 22 of 32 LPR patients (69 per cent) living in Turkey.[18] These different results could be explained by the fact that certain ethnic groups are more prone to develop *H pylori*-associated chronic gastritis than others. In a study by Loffeld *et al.*, *H pylori* was present in 60.6 per cent of Turkish patients living in the Netherlands but in only 18.5 per cent of Dutch patients.[20]

As mentioned above, *H pylori* testing should be considered in LPR patients who anticipate requiring long-term maintenance therapy with PPIs. However, oesophagogastroduodenoscopy is not the method of choice for the diagnosis of *H pylori*-associated chronic gastritis, as non-invasive tests with a very high degree of diagnostic accuracy exist (such as the C-urea breath test, stool antigen tests and various immunological tests).[16] Therefore, oesophagogastroduodenoscopy is not indicated as a routine diagnostic procedure in LPR patients to exclude *H pylori*-associated chronic gastritis. It remains unclear which LPR patients would benefit from routine *H pylori* testing before initiation of PPI therapy.

In our study patients, we found a relatively high prevalence of hiatus hernia (36 per cent), a protrusion of the upper part of the stomach into the thorax through a tear or weakness in the diaphragm. Older trials have found hiatus hernia in between 14 and 22 per cent of subjects undergoing upper endoscopy.[21,22] As these trials, with large study populations ranging from 293 to 1000 subjects, did not specifically focus on LPR patients, the different prevalence data are difficult to interpret. The frequency of hiatus hernia in asymptomatic individuals would be of great interest, but reliable data are unavailable as most studies relate to patients suffering from gastroesophageal reflux disease symptoms undergoing investigation.

As hiatus hernia impairs the lower oesophageal sphincter function by reducing its length and pressure, oesophagitis or Barrett's oesophagus are common sequels of reflux in subjects with hiatus hernia.[23] Cameron found hiatus hernia in 71 per cent of patients with oesophagitis and in 72 per cent of patients with short segment (<2 cm) Barrett's oesophagus.[24] Currently, there is no adequate, published evaluation of the frequency of hiatus hernia in LPR patients. Should future trials confirm a high prevalence of hiatus hernia in LPR patients, routine oesophagogastroduodenoscopy might be discussed in these patients in order to rule out this predisposing factor for Barrett's oesophagus. Alternative diagnostic procedures would comprise barium studies or oesophageal manometry.[23] However, the role of hiatus hernia in the pathogenesis and progression of gastroesophageal reflux disease and its complications remains unclear.[23] Therefore, at present, there is no indication for hiatus hernia screening of LPR patients by routine oesophagogastroduodenoscopy.

Gastric mucosal erosions were another frequent finding in our study population, with a prevalence of 25 per cent. These are common in both dyspeptic patients and asymptomatic volunteers.[25] A long-term study by Toljamo *et al.*, with a 17-year follow up, showed that a significant proportion of gastric mucosal erosions were chronic or recurrent but were generally without major systemic or local consequences.[26] Therefore, oesophagogastroduodenoscopy is not generally indicated in LPR patients to rule out gastric mucosal erosions, except in *H pylori* positive patients, as the latter are at a significantly greater risk of developing peptic ulcers.[26]

- **Recently, numerous clinical trials have added evidence that duodenogastroesophageal reflux reaching the laryngopharynx plays an important role in the pathogenesis of laryngeal, pharyngeal and pulmonary disorders**
- **Patients with laryngopharyngeal reflux (LPR) uncommonly suffer from conditions associated with gastroesophageal reflux disease, such as oesophagitis or oesophageal neoplasms; however, in a small number of such patients, oesophagitis and Barrett's metaplasia occur**
- **Symptoms such as heartburn or chest pain are indicators of additional gastroesophageal reflux disease in patients with pH-documented LPR; in these patients, endoscopy is indicated**
- ***Helicobacter pylori* testing, by non-invasive tests such as the C-urea breath test, should be considered in LPR patients requiring long-term proton pump inhibitor treatment**

The results of our study confirm the findings of other trials reporting a prevalence of oesophagitis in LPR patients of less than 20 per cent.[1,13] We found only mild forms of oesophagitis (grades A and B, Los Angeles classification), in 18 per cent of the study population. Hence, there is no indication for routine oesophagogastroduodenoscopy in LPR patients in order to rule out oesophagitis as a potential risk factor for oesophageal adenocarcinoma. Moreover, the generally recommended PPI dosage for LPR treatment (i.e. twice daily for three to six months) is much higher than that for mild oesophagitis. In consequence, oesophagitis in LPR patients should be cured by the long-term PPI therapy in most cases. An exception would be patients in whom PPIs were partially or entirely ineffective. In gastroesophageal reflux disease patients, the prevalence of so-called PPI non-responders ranges from 10 to 30 per cent; however, a PPI failure rate of up to 40 per cent has been found in LPR patients.[27,28]

Conclusions

From our findings, we conclude that not all patients with pH-documented LPR should routinely undergo oesophagogastroduodenoscopy. However, in patients with heartburn as their main symptom,

https://doi.org/10.1017/S0022215107000680 Published online by Cambridge University Press

Barrett's metaplasia or severe forms of oesophagitis should be excluded by oesophagogastroduodenoscopy. Non-invasive *H pylori* testing (e.g. the C-urea breath test) should be considered in LPR patients requiring long-term PPI treatment. In these patients, *H pylori* eradication might be indicated before PPI therapy. If future studies clearly demonstrate a strong influence of hiatus hernia on the pathogenesis and progression of gastroesophageal reflux disease and its complications, then the currently recommended diagnostic and management strategies of LPR may need to be reviewed.

References

1 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**:32–5
2 Labenz J. Consequences of *Helicobacter pylori* cure in ulcer patients. *Baillieres Best Pract Res Clin Gastroenterol* 2000;**14**:133–45
3 Van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MCJM, Kuipers EJ. Increasing incidence of Barrett's oesophagus in the general population. *Gut* 2005;**54**:1062–6
4 Reavis KM, Morris CD, Gopal DV, Hunter JG, Jobe BA. Laryngopharyngeal reflux symptoms better predict the presence of esophageal adenocarcinoma than typical gastroesophageal reflux symptoms. *Ann Surg* 2004;**239**:849–58
5 Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;**16**:274–7
6 Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;**111**:1313–17
7 Vincent DA Jr, Garrett D, Radionoff SL, Reussner LA, Stasney CR. The proximal probe in esophageal pH monitoring: development of a normative database. *J Voice* 2000;**14**:247–54
8 El-Serag HB, Sonnenberg A. Opposing times trends of peptic ulcer and reflux disease. *Gut* 1998;**43**:327–33
9 DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;**94**:1434–42
10 Byrne PJ, Power C, Lawlor P, Ravi N, Reynolds JV. Laryngopharyngeal reflux in patients with symptoms of gastroesophageal reflux disease. *Dis Esophagus* 2006;**19**:377–81
11 Halum SL, Postma GN, Bates DD, Koufman JA. Incongruence between histologic and endoscopic diagnoses of Barrett's esophagus using transnasal esophagoscopy. *Laryngoscope* 2006;**116**:303–6
12 Coppola D, Karl RC. Barrett's esophagus and Barrett's associated neoplasia: etiology and pathologic features. *Cancer Control* 1999;**6**:21–7
13 Koufman JA, Belafsky PC, Bach KK, Daniel E, Postma GN. Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. *Laryngoscope* 2002;**112**:1606–9
14 Peek RM. *Helicobacter pylori* and gastroesophageal reflux disease. *Curr Treat Options Gastroenterol* 2004;**7**:59–70
15 Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, Snel P, Goldfain D, Kolkman JJ *et al*. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004;**53**:12–20
16 Malfertheiner P, Megraud F, O'Morain C, Bazzoli F *et al*.. Current Concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007;**56**:772–81
17 Vaezi MF. Reflux-induced laryngitis (laryngopharyngeal reflux). *Curr Treat Options Gastroenterol* 2006;**9**:69–74
18 Ercan I, Cakir BÖ, Uzel TS, Sakiz D, Karaca C, Turgut S. The role of gastric *Helicobacter pylori* infection in laryngopharyngeal reflux disease. *Otolaryngol Head Neck Surg* 2006;**135**:52–5
19 Oridate N, Takeda H, Yamamoto J. *Helicobacter pylori* seropositivity predicts outcomes of acid suppression therapy for laryngopharyngeal reflux symptoms. *Laryngoscope* 2006;**116**:547–53
20 Loffeld RJ. *H. pylori* and reflux esophagitis in Turkish patients living in the Zaanstreek region in the Netherlands. *Dig Dis Sci* 2003;**48**:1846–9
21 Wright RA, Hurwitz AL. Relationship of hiatal hernia to endoscopy proven esophagitis. *Dig Dis Sci* 1979;**24**:311–14
22 Cronstedt J, Carling L, Vestergaard P, Berglund J. Oesophageal disease revealed by endoscopy in 1,000 patients referred primarily for gastroscopy. *Acta Med Scand* 1978; **204**:413–16
23 Gordon C, Kang JY, Neild PJ, Maxwell JD. Review article: the role of the hiatus hernia in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004;**20**:719–32
24 Cameron AJ. Barrett's esophagus: prevalence and size of hiatal hernia. *Am J Gastroenterol* 1999;**94**:2054–9
25 Lehmann FS, Renner EL, Meyer-Wyss B, Wilder-Smith CH, Mazzucchelli L, Ruchiti C *et al*. *Helicobacter pylori* and gastric erosions. Result of prevalence study in asymptomatic volunteers. *Digestion* 2000;**62**:82–6
26 Toljamo KT, Niemelä SE, Karttunen TJ, Karvonen AL, Lehtola JK. Clinical significance and outcome of gastric mucosal erosions: a long-term follow-up study. *Dig Dis Sci* 2006;**51**:543–7
27 Galmiche JP, Stephenson K. Treatment of gastroesophageal reflux disease in adults: an individualized approach. *Dig Dis* 2004;**22**:148–60
28 Vaezi MF. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. *Am J Med* 2003;**18**(suppl 3A):97–104S

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Dr O Reichel takes responsibility for the integrity of the content of the paper.
Competing interests: None declared