EXTRAOESOPHAGEAL MANIFESTATIONS OF GASTRO-OESOPHAGEAL REFLUX

J Poelmans, J Tack

1492

SUMMARY

A variety of pulmonary and ear, nose, and throat (ENT) symptoms and disorders are considered to be extraoesophageal manifestations of gastro-oesophageal reflux disease (GORD). These extraoesophageal manifestations include asthma, chronic cough, laryngeal disorders, and various ENT symptoms. Recent studies have established that GORD underlies or contributes to chronic sinusitis, chronic otitis media, paroxysmal laryngospasm, excessive throat phlegm, and postnasal drip. Traditionally, management of extraoesophageal GORD manifestations relies on prolonged empiric therapy with high doses of proton pump inhibitors (PPI), followed by pH monitoring under PPI in refractory cases. Recent studies found no benefit of empiric long term high dose PPI therapy. The diagnostic yield of endoscopy in extraoesophageal GORD manifestations seems higher than previously appreciated while pH monitoring under PPI therapy has a low yield. Based on these new findings, a new management algorithm can be proposed that uses short term empiric PPI therapy and GORD investigations off PPI. Well designed controlled studies evaluating the proposed management algorithms and treatment approaches in this area are urgently needed.

CLINICAL MANIFESTATIONS OF EXTRAOESOPHAGEAL REFLUX

Extraoesophageal manifestations of GOR

GORD, defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the oesophagus, is one of the most common disorders affecting the gastrointestinal tract. When effects of refluxed gastric contents extend beyond the oesophagus itself, this is referred to as extraoesophageal reflux (EOR). These effects may be caused by the direct noxious effects of gastric juice on the mucosal surfaces of the upper airways (pharynx, larynx, middle ear, and nasosinusal complex) and lower airways (tracheobronchopulmonary tree). Unlike the distal oesophagus, the airways are not protected by antireflux clearance mechanisms and intrinsic mucosal properties. It is therefore conceivable that even a single reflux episode extending beyond the oesophagus may be sufficient to cause pharyngeal, laryngeal, and respiratory symptoms and signs. A second mechanism responsible for EOR is activation of reflexes involving the airways by reflux of gastric contents into the oesophagus.

As has been addressed by several reviews,[1–5] extraoesophageal manifestations of GORD include a variety of pulmonary and ENT symptoms and disorders, which are summarised in table 1.

Evidence that ENT or pulmonary disorders are manifestations of EOR
Epidemiological studies

If an airway disorder is attributable to EOR, there should be increased coexistence of both disorders compared with the general population, and clinical manifestations of EOR should respond to antireflux therapy. Establishing a correlation between GORD and airway (ENT and pulmonary) disorders is hampered by the fact that both commonly occur in the general population and by the suggestion that the majority of patients with reflux related ENT manifestations do not report classical reflux symptoms such as heartburn and regurgitation.[1 6 7] Nevertheless, in a case control study comparing 101 366 patients with erosive oesophagitis or oesophageal stricture with 101 366 controls, significant associations were found between oesophagitis or oesophageal stricture and several ENT and pulmonary disorders (table 2).[8] A case control study in 1980 children with GORD and 7920 controls revealed similar associations between GORD and paediatric ENT or pulmonary disorders.[9] A third case control study, revealed an increased risk for laryngeal and pharyngeal cancer in GORD patients (table 2).[10]

Mechanistic studies

Several studies indicate that patients with various pulmonary and ENT manifestations have a higher prevalence of GORD. The most compelling evidence for EOR is obtained when constituents of gastric juice are found in supraoesophageal locations.

See end of article for authors' affiliations

Correspondence to:
Dr J Tack, Centre for Gastroenterological Research, Catholic University of Leuven, Herestraat 49, B-3000 Leuven, Belgium; Jan.Tack@med.kuleuven.ac.be

Table 1 Suspected extraoesophageal manifestations of gastro-oesophageal reflux

Middle ear/eustachian tube
  Glue ear
  Otalgia
  Asthma
Nasal/sinusal
  Chronic sinusitis
Oral cavity
  Dental erosions
  Aphthous ulcers
  Halitosis
Pharynx/larynx
  Pharyngitis
  Posterior laryngitis, chronic laryngitis
  Vocal cord ulcers, granulomas, nodules
  Laryngeal, subglottic stenosis
  Laryngospasm
  Laryngitis stridulosa (pseudocroup)
  Cancer
  Sore throat, excessive throat phlegm
  Postnasal drip
  Frequent throat clearing
  Dysphonia
  Globus
Tracheobronchopulmonary tree
  Tracheobronchitis
  Chronic cough
  Aspiration pneumonia
  Pulmonary fibrosis
  Chronic bronchitis
  Bronchiëctasis
Other
  Sleep apnoea
  SIDS
  Sandifer's Sx (torticollis)

The simultaneous occurrence of pH drops below 4 on proximal oesophageal pH monitoring or on hypopharyngeal pH monitoring with similar distal oesophageal pH drops argues in favour of EOR. Indirect mechanisms, for instance the occurrence of reflex mediated extraoesophageal changes induced by distal oesophageal acid exposure or distension, may also contribute. In such cases, a close temporal association between (distal) oesophageal reflux events and extraoesophageal symptoms provides the most convincing evidence of causation. Besides these mechanistic studies, a response to antireflux therapy in ENT or pulmonary disorders also argues strongly in favour of causation by GORD.

Asthma

The association between asthma and GOR has been intensively studied and this subject is addressed in a recent review by Harding.[3] According to studies in the literature, pathological GOR can be found in 30% to >80% of patients with asthma.[11] On the other hand, patients with oesophagitis are more likely to have asthma than patients without oesophagitis (table 2).[8] Although GOR may potentially exacerbate asthma, a cause and effect relationship between GOR and asthma has so far not been established. Microaspiration of gastric acid and increases in airway hyperresponsiveness due to oesophageal acid are considered potential triggers for asthma.[11] Conversely, it has been shown that asthma medications such as inhaled β_2 agonists and oral corticosteroids may increase oesophageal acid contact times.[2] A number of reviews reported beneficial results of medical and surgical antireflux therapy on asthma outcome.[12][13] The results of 12 randomised controlled trials (RCTs) of high methodological quality, which assessed the effect of medical GOR therapy on asthma outcome, were combined in a Cochrane systematic review.[14] The authors concluded that medical therapy (with histamine H_2 antagonists or PPIs) did not consistently improve pulmonary function, asthma symptoms, nocturnal asthma symptoms, or asthma medication usage. However, the same authors also concluded that a selected subgroup of asthmatics could possibly benefit from antireflux therapy and that further research and carefully conducted RCTs were needed.

Chronic cough

Many patients with GORD related cough lack heartburn or regurgitation and therefore GORD is frequently clinically silent. After asthma and sinus problems, GORD is currently considered the third leading cause of chronic cough, affecting an estimated 20% of patients.[15][16]

Table 2 Ear, nose, and throat (ENT) and pulmonary disorders associated with oesophagitis or stricture in adults, and with gastro-oesophageal reflux disease in children

	Odds ratio	95% CI
Adult ENT disorder[8][10]		
Laryngitis	2.10	1.53–2.63
Laryngeal stenosis	2.02	1.12–3.65
Dysphonia	1.81	1.18–2.80
Sinusitis	1.60	1.51–1.70
Pharyngitis	1.48	1.15–1.89
Laryngeal cancer	2.40	2.15–2.69
Pharyngeal cancer	2.38	1.87–3.02
Adult pulmonary disorder[8]		
Asthma	1.51	1.43–1.59
Pulmonary fibrosis	1.36	1.25–1.48
Pulmonary collapse	1.31	1.23–1.40
Chronic bronchitis	1.28	1.22–1.34
Bronchiectasis	1.26	1.09–1.47
COPD	1.22	1.16–1.27
Pneumonia	1.15	1.12–1.18
Paediatric extraoesophageal reflux disorder[9]		
Laryngitis	2.6	1.2–5.6
Sinusitis	2.3	1.7–3.2
Pneumonia	2.3	1.8–2.9
Bronchiectasis	2.3	1.1–4.6
Asthma	1.9	1.6–2.3

95% CI, 95% confidence interval.
COPD, chronic obstructive pulmonary disease.

Other causes of chronic cough include smoking, abnormalities that are visible on a chest radiography, intake of an angiotensin converting enzyme inhibitor, exposure to environmental irritants, and chronic bronchitis. Furthermore, asthma (positive metacholine challenge test), eosinophilic bronchitis (sputum eosinophilia), rhinosinus disease, and postnasal drip syndrome should have been excluded or treated. However, in asthma related cough not responding to asthma therapy, in eosinophilic bronchitis related cough not responding to inhaled or systemic corticosteroids, and rhinosinus disease (or postnasal drip syndrom) related cough not responding to first generation H_1 antagonists, GORD related cough may be suspected.[11]

Most antireflux therapeutic trials using antacids, H_2 antagonists, and/or prokinetic agents combined with lifestyle measures are uncontrolled studies with small sample sizes (range 9–28 patients) which have reported cough resolution in 70–100% of patients, but only after 90–179 days.[11] Two RCTs, performed in patients with abnormal oesophageal acid exposure on pH monitoring, demonstrated that omeprazole was superior to placebo in relieving GORD related cough. However, times needed for cough resolution diverged strongly in both studies.[17 18] Several uncontrolled studies of antireflux surgery in patients with GORD related chronic cough reported cough improvement or resolution in 51–100% of adult patients.[11]

ENT manifestations

There is increasing evidence that GORD causes or contributes to several ENT manifestations. This phenomenon has not only been referred to as EOR but also as supraoesophageal reflux, laryngopharyngeal reflux, and gastro-oesophago-pharyngeal reflux (GOPR). The most common GORD related ENT disorders are chronic laryngitis and, according to recent evidence, potentially also chronic sinusitis and otitis media. ENT symptoms frequently related to GORD include hoarseness, cough, globus, sore throat, excessive throat phlegm, postnasal drip, nasal congestion halitosis, and frequent throat clearing. Less common GORD related laryngopharyngeal disorders include paroxysmal laryngospasm, contact ulceration and granuloma, laryngeal and subglottic stenosis, and laryngeal and pharyngeal carcinoma (table 1).[1-4] It has been estimated that up to 10% of ENT patients may have symptoms or disorders related to GORD.[2 4] Persistent sore throat and chronic laryngitis are associated with GORD in as many as 60% of patients.[4] Globus, defined as a sensation of a lump in the throat, may be caused by GORD in up to 50% of patients.[4 7]

Laryngeal disorders

Early experiments have shown that repeated applications of gastric juice on the dog's posterior larynx caused progressive posterior laryngeal inflammation, contact ulceration, and finally granuloma.[19] The most common laryngeal abnormalities that are considered to be reflux related are confined to the posterior larynx and include oedema and erythema of the mucosa overlying the arytenoid cartilages, the interarytenoid region, and frequently also the posterior third of the true vocal folds (posterior laryngitis). Until recently, these laryngeal signs have been regarded as clinical signs of "reflux" laryngitis. A reflux finding score (RFS) has been developed based on these and other laryngeal abnormalities and the authors found that the RFS accurately documented treatment efficacy in patients with reflux related laryngeal

signs.[20] However, others have questioned the specificity of these laryngeal findings. Symptoms that are most frequently associated with chronic laryngitis are hoarseness, sore throat, excessive throat phlegm, postnasal drip, frequent throat clearing, globus, and cough.[2 21 22] Importantly however, even in patients with similar symptoms who lack abnormalities on laryngoscopic evaluation, pH monitoring and upper gastrointestinal endoscopy may reveal underlying reflux disease.[1 23]

Several observational studies have reported a high prevalence of GORD and improvement in suspected reflux laryngitis and its associated symptoms on antireflux therapy in 60–100% of patients.[1 24] Similar results were reported for contact granuloma and acquired subglottic stenosis.[25 26] RCTs on this subject are scarce and used small sample sizes. In a study by El-Serag and colleagues,[27] six of 12 patients (50%) receiving lansoprazole 30 mg twice daily for three months had complete resolution of laryngeal symptoms compared with only one of 10 patients (10%) in the placebo group (p = 0.04). In two other RCTs with patients selected on abnormal hypopharyngeal pH monitoring results, laryngitis symptoms improved similarly in both the experimental (high dose PPI) and placebo groups. It was concluded from these studies that a large placebo effect appears to exist in the treatment of reflux laryngitis and that no benefit of long term PPI treatment over placebo in these patients was proven.[22 28]

Recent additions to extraoesophageal manifestations of GOR
Chronic sinusitis

Like GORD, chronic sinusitis is a common clinical condition. There is increasing evidence from observational studies that both paediatric and adult patients with chronic sinusitis frequently have associated GORD and EOR and that these patients may benefit from medical antireflux therapy. GORD and EOR may contribute to the pathogenesis of chronic sinusitis by causing sinonasal congestion, compromised sinus drainage, and inflammation.[29]

Otitis media

Otitis media with effusion (OME) is a prevalent condition and the most common cause of hearing loss in childhood. Recently, Tasker et al reported high concentrations (up to a 1000-fold greater than serum levels) of pepsin/pepsinogen in 59 of 65 middle ear effusion samples from children with OME.[30] The authors concluded that reflux of gastric juice into the middle ear may be the primary factor in the initiation of OME in children.

Using upper gastrointestinal endoscopy and 24 hour pH monitoring, we prospectively assessed the coexistence of GORD in consecutive adult patients with chronic secretory otitis media (CSOM) or with a chronic refractory feeling of pressure in the ear(s) (CRFP). All patients with CSOM and most patients with CRFP had evidence of GORD (oesophagitis and/or abnormal pH metry). Medical antireflux therapy with open label PPI led to cessation of middle ear drainage and CRFP after, on average, 11 weeks and four weeks, respectively.[31 32] These studies indicate that GORD may directly cause or contribute to chronic ear problems, both in children and in adults. RCTs evaluating the effect of antireflux therapy are lacking.

Excessive throat phlegm and postnasal drip

It has been suggested that unexplained excessive throat phlegm may also be a manifestation of GOR but formal

evidence is lacking.[21] [33] [34] We recently assessed the prevalence of GOR as well as duodeno-gastro-oesophageal reflux (DGOR) in 59 consecutive patients with chronic complaints of excessive throat phlegm. About half of these patients reported a feeling of phlegm descending from the nasopharynx (postnasal drip). Endoscopy and pH monitoring established a diagnosis of pathological GOR in 75% of patients. After a median of four weeks of open label PPI therapy, most patients improved and 61% became asymptomatic. Pathological DGOR was present in 56% of patients and these had predominantly yellow throat phlegm rather than transparent throat phlegm. The role of DGOR in yellow throat phlegm was further established by pathological proximal DGOR monitoring and by demonstrating the presence of bile acids in yellow throat phlegm samples. We concluded that unexplained excessive throat phlegm is a sign suggestive of GOR and GOPR, and unexplained yellow throat phlegm a sign suggestive of duodeno-gastro-oesophago-pharyngeal reflux.[35] So far, no RCTs of antireflux treatment have been reported for throat phlegm.

Paroxysmal laryngospasm

Paroxysmal laryngospasm, defined as a prolonged and forceful adduction of the vocal folds resulting in glottic closure and airway obstruction, is a vagally mediated reflex response of the larynx to noxious stimuli, potentially including gastric acid. Clinically, laryngospasm episodes are associated with an acute choking sensation at the laryngeal level, apnoea, and aphonia. A number of case series suggest a possible association between paroxysmal laryngospasm and GORD and successful outcome of antireflux treatment has been reported,[36–39] but more extensive prospective studies are lacking.

We recently prospectively assessed the role of GOR in 35 consecutive patients with paroxysmal laryngospasm. Using upper gastrointestinal endosopcy and pH monitoring, GORD was established in 94% of patients. In a subset of patients experiencing laryngospasm during the measurement, a close temporal association between laryngospasm and GOR episodes was found. Patients with more frequent laryngospasm episodes had a higher prevalence of hiatus hernia, higher distal and proximal oesophageal acid exposure times, and a higher prevalence of abnormal DGOR. On open label PPI therapy and lifestyle measures, laryngospasm ceased completely in all patients within six weeks. This study not only supports the role of GOR in the pathogenesis of laryngospasm but also suggests that laryngospasm in adult patients with unimpaired vocal fold mobility might be considered a typical, although often unrecognised, supraoesophageal manifestation of GOR.[40] RCTs evaluating the effect of antireflux therapy in laryngospasm are lacking.

Chronic cough

Similar to the pathophysiology of GORD associated asthma, GORD associated cough may be caused by an oesophago-bronchial cough reflex and microaspiration. However, as coughing is associated with increased intra-abdominal pressure, it may by itself induce reflux. Hence the use of a symptom marker during pH monitoring, with a variable interval between occurrence of the event and pressing the marker button, does not necessarily establish that reflux preceded and triggered cough. In a recent study, simultaneous manometric assessment, which allows exact determination of the moment of coughing, was shown to allow the distinction between patients with reflux preceding cough and those in whom reflux events occurred during or after coughing.[41] The study also revealed that in some patients weakly acidic reflux episodes, not reaching a nadir pH of 4, preceded cough. Furthermore, as has been proposed by some investigators,[42] simultaneous manometry and pH assessment suggested the occurrence of a self perpetuating feedback cycle between cough and GORD in some patients where cough precipitates reflux and reflux elicits cough.[41]

MANAGEMENT OF EXTRAOESOPHAGEAL MANIFESTATIONS OF GOR
Traditional (classical) management algorithm

Most handbooks and reviews recommend an empiric trial of double dose PPI therapy for at least three months as the initial step in the diagnosis and treatment of most patients with suspected EOR manifestations of GORD. This is recommended for selected asthmatics, especially those refractory to conventional therapy with bronchodilators and anti-inflammatory agents, for patients with suspected reflux related cough, and for patients with suspected reflux related laryngeal disorders.[2] [5] [11] [43] In those not responding to the three month empirical trial, oesophageal 24 hour pH monitoring while on therapy is recommended. The current management algorithm is summarised in fig 1.

Distal oesophageal acid exposure, measured 5 cm proximal to the lower oesophageal sphincter (LOS), is considered the most sensitive test for demonstrating pathological acid reflux. Several investigators have advocated the use of dual pH monitoring, with a second probe just below the upper oesophageal sphincter (UOS), when investigating supra-oesophageal reflux as a cause of pulmonary and ENT disorders.[44–46] Although initial studies suggested that hypopharyngeal monitoring for acid reflux is the most sensitive test for identifying patients with GORD related ENT disorders, there are considerable technical difficulties with pH monitoring in the pharynx, and this technique has so far not gained widespread acceptance.[47] [48]

Evidence underlying the traditional management algorithm

Several assumptions underlie the application of the traditional management algorithm in EOR. Firstly, it is assumed that response to PPI therapy, in EOR manifestions of GORD,
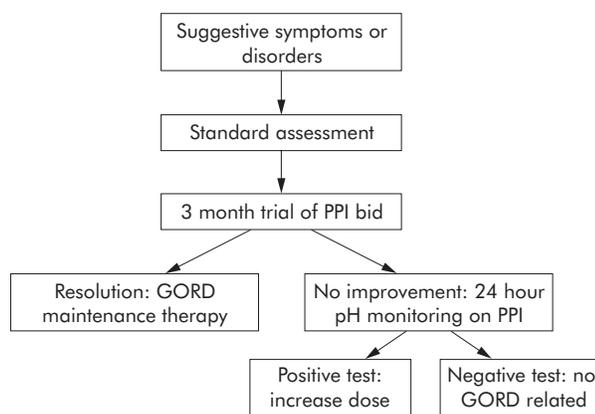

Figure 1 Traditional management algorithm for extraoesophageal manifestations of gastro-oesophageal reflux disease (GORD). PPI, proton pump inhibitor.

1495

requires higher doses and a prolonged treatment duration compared with classical GORD. This is mainly based on observations of open label studies where oesophageal manifestations responded rapidly while for most of the EOR symptom improvement and healing of laryngitis occurred after the first eight weeks of treatment.[21 49] Evidence from controlled studies is scarce. In two small RCTs, using high dose PPI therapy, laryngitis symptoms resolved after three months[18] and chronic cough improved after 8–16 weeks.[27]

A second assumption is that pH monitoring during high dose PPI therapy is the optimal way to demonstrate ongoing GORD in those patients that fail the initial empirical treatment. This is mainly based on studies with standard PPI therapy in typical GORD, where in about half of the patients with persistent oesophagitis and reflux symptoms, in spite of standard dose PPI therapy, persisting acid reflux under PPI therapy can be demonstrated.[50–53] Only one study reported on a small group of laryngitis patients who were refractory to 80 mg of omeprazole.[54]

Finally, the algorithm provides little or no room for oesophageal endoscopic examination, clearly assuming that this has little or no diagnostic value. It is generally accepted that the prevalence of pathological findings at endoscopy in EOR patients is low but studies on which this assumption is based are hampered by low number of patients or less accurate assessments of oesophagitis, such as radiology.[1 6 45 55 56]

Recent developments

Recently, the specificity of laryngoscopic findings indicating acid reflux and assessed by the RFS has been challenged. Experience from clinical practice learned that many patients with these laryngeal signs do not respond to antireflux therapy and have no abnormal reflux on oesophageal and hypopharyngeal pH monitoring. A recent study reported that the majority (86%) of 105 healthy volunteers had one or more laryngoscopic findings included in the RFS and some of the signs reached a prevalence of 70%, thereby questioning the diagnostic specificity of laryngoscopic findings thought to indicate GORD.[57] In a recent RCT by Vaezi et al, less than 30% of 145 patients with symptomatic suspected ''reflux'' laryngitis had abnormal pH results on initial pH monitoring and the presence of laryngeal signs or symptoms did not correlate with abnormal baseline pH.[58] A need for further studies was highlighted to allow for better characterisation of the ENT patient population with EOR.

The assumption that extraoesophageal symptoms and disorders respond less quickly and less completely to acid suppression has also been questioned by several recent observations. We treated 405 consecutive patients with suspected GORD related ENT symptoms with open label PPIs and followed them up at two week intervals. These patients' symptoms comprised a broad spectrum of possible EOR manifestations, including chronic cough, hoarseness, throat symptoms, and globus. After only four weeks of standard dose PPI therapy, the predominant ENT complaints were markedly reduced in the majority of patients. The highest and fastest symptom relief occurred in patients with non-productive cough.[7] As this was an uncontrolled study, a placebo effect may have contributed, but the study demonstrates the potential for rapid symptom relief with standard dose PPI therapy in clinical practice. Longer term RCTs in laryngitis have also failed to confirm the increased gain of

long term double dose PPI therapy compared with placebo.[22 28] Most recently, Vaezi et al studied 145 patients with symptomatic suspected ''reflux'' laryngitis and treated them in a double blind randomised fashion with placebo or esomeprazole 40 mg twice daily for 16 weeks. No difference in treatment response was observed at any point in time.[58] In a review of treatment of GORD related cough with antireflux therapy consisting primarily of standard doses of PPI, marked improvement in or resolution of cough was reported in 38 of 44 patients (86%) after four weeks and in the remaining patients after eight weeks.[59] These recent observations suggest that initial PPI therapy may be of shorter duration, possibly only using standard PPI doses, and clearly question the benefit of empirical prolonged PPI therapy as an initial step in EOR manifestations.

Several recent observations have questioned the use of pH monitoring under PPI as a method of demonstrating ongoing reflux. We reported that pH monitoring during standard PPI therapy was abnormal in 37% of patients with typical GORD symptoms that persisted during PPI therapy, and only 12% had a positive symptom association probability for symptoms and acid reflux events.[60] In a recent preliminary study, Levy et al found that only 14% of patients had pathological pH monitoring during standard PPI therapy.[61] Similarly, Vaezi and Charbel reviewed 250 pH tracings in patients on PPI twice daily and reported that only 7% of typical and 0% of atypical GORD patients tested abnormal.[62] In spite of these low percentages, normal pH monitoring during PPI therapy does not exclude ongoing reflux as a cause of symptoms. Bile reflux monitoring or impedance monitoring during PPI therapy was able to establish ongoing non-acidic reflux as a cause of persisting symptoms in the majority of patients with PPI refractory typical GORD.[60 63 64] In patients with ENT manifestations of GORD, we demonstrated that the presence of DGOR was a predictor of incomplete response to PPI therapy.[65]

These studies indicate that assessment of reflux during PPI therapy requires combined monitoring of acid and non-acid reflux, using pH and impedance or bile reflux monitoring. Given the limited availability of the latter methods, it will be more practical in most centres to perform pH monitoring off PPI therapy. In patients with a normal acid secretory capacity, reflux, and a temporal relationship between symptoms and reflux events, are best demonstrated by oesophageal pH monitoring without acid suppression. Distal oesophageal acid exposure, measured 5 cm proximal to the LOS, is the standard test for demonstrating pathological acid

Table 3 Prevalence of erosive oesophagitis at upper gastrointestinal endoscopy in patients with suspected gastro-oesophageal reflux disease related ear, nose, and throat symptoms

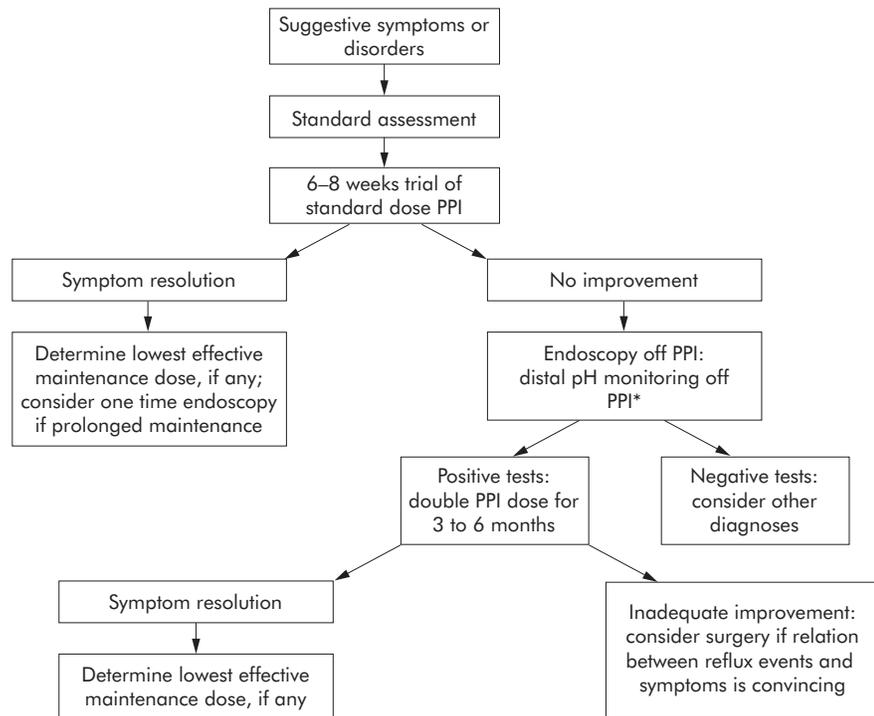| Study	n	Prevalence of oesophagitis (%)
Wiener et al, 1986[66]	11	27
Ossakow et al, 1987[67]	64	10
Batch 1988[68]	104	63
McNally et al, 1989[69]	11	55
Ness et al, 1992[70]	22	54
Tauber et al, 2002[71]	30	43
Koufman et al, 2002[72]	58	19
Poelmans et al 2004[7]	405	52
Total	705	46

Figure 2 Proposed new management algorithm for extraoesophageal manifestations of gastro-oesophageal reflux disease based on recent developments. *pH and impedance monitoring while on proton pump inhibitor (PPI) therapy may become an alternative option in the future.

reflux, but the use of a second probe just below the UOS has been proposed for the investigation of supraoesophageal reflux as a cause of pulmonary and ENT disorders.[44 45] We assessed the yield of a proximal pH probe in a large group of patients who underwent pH monitoring. We observed that proximal acid exposure did not distinguish patients with typical from atypical GORD manifestations, and that proximal acid exposure was almost exclusively dependent on distal acid exposure.[46]

Finally, the use of endoscopy in the diagnostic workup has recently also been reassessed. We compared the prevalence and severity of oesophagitis in 405 patients with suspected GORD related chronic ENT symptoms and 545 typical GORD patients. The prevalence of erosive oesophagitis (52% v 38%; p<0.05) and peptic ulcer (8% v 4%, p<0.05) was significantly higher in patients with GORD related ENT symptoms compared with typical GORD. Oesophagitis prevalence was highest in patients with predominant cough and lowest in globus and throat symptoms. The response rate to open label PPI therapy was significantly higher in patients with erosive oesophagitis, especially during the first eight weeks.[7] These findings are in agreement with several other recent studies that demonstrated abnormal endoscopic findings in approximately 45% of patients (table 3).[66–72]

PROPOSED NEW MANAGEMENT ALGORITHM
The diagnostic and treatment approach to patients with suspected EOR manifestations of GORD should take into account the recent developments and limitations outlined above. The proposed management algorithm is summarised in fig 2. If a standard ENT or pulmonary investigation fails to indicate other causes, underlying reflux may be suspected. In the absence of a demonstrable gain of long term double dose PPI therapy, short term standard dose PPI therapy combined with lifestyle measures, similar to what is customary in typical GORD, seems a logical first approach. This avoids

prolonged high dose PPI therapy when GORD is not really established, and only presumed on the basis of an atypical symptom pattern and questionable laryngeal findings. In the case of adequate response, treatment can be tapered down to determine the minimal required maintenance dose, if any.[73] In those who require maintenance therapy, a one time endoscopy seems advisable to rule out Barrett's oesophagus. In those who do not respond favourably to short term standard dose PPI therapy, it seems advisable to stop PPI therapy, and to perform endoscopic examination, preferably four weeks after cessation of therapy.[74] The finding of erosive oesophagitis establishes the presence of GORD but this will be the case in less than half of the patients (table 3).[7 66–72] Oesophageal pH monitoring off PPI may demonstrate pathological acid exposure in endoscopy negative patients, and is also the most appropriate examination to establish a temporal relationship between symptoms and reflux events. This approach takes advantage of the potential yield of endoscopy in EOR manifestations[7] and avoids the low yield of pH monitoring during PPI therapy.[60–64] In the future, if more widely available, combined pH and impedance monitoring on PPI therapy could be considered an alternative approach, but at present the literature provides no data on the yield, therapeutic implications, or clinical outcome of such measurements. In patients with a normal pH study, other causes of the symptoms should be considered. In patients with an abnormal pH study, PPI dose may be increased and therapy can be prolonged for three months or more. Antireflux surgery may be considered in patients with a previous good symptomatic response to PPI therapy who require chronic PPI therapy, or in patients with an insufficient response to PPI therapy in whom a convincing relationship between reflux and symptoms or lesions has been demonstrated. It should be pointed out that the current management algorithm is based mainly on studies that failed to demonstrate benefit from the previous treatment algorithm,

and on recent diagnostic studies and controlled and uncontrolled therapeutic studies. Outcome studies based on the newly proposed algorithm, perhaps comparing them with the previous algorithm, are needed and may help to further provide useful guidelines to clinicians based on evidence.

1498

. . . .

Authors' affiliations

J Poelmans, Department of Otorhinolaryngology-Head and Neck Surgery, University Hospitals Leuven, Belgium

J Tack, Department of Medicine, Division of Gastroenterology, University Hospitals Leuven, Belgium

Conflict of interest: None declared.

REFERENCES

1 **Richter JE**. Extraoesophageal presentations of gastroesophageal reflux disease. *Semin Gastrointest Dis* 1997;**8**:75–89.
2 **Wong RK**, Hanson DG, Waring PJ, et al. ENT manifestations of of gastroesophageal reflux. *Am J Gastroenterol* 2000;**95**(8 suppl):S15–S22.
3 **Harding SM**. Recent clinical investigations examining the association of asthma and gastroesophageal reflux. *Am J Med* 2003;**115**(suppl 3A):39S–44.
4 **Vaezi MF**. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. *Am J Med* 2003;**115**(suppl 3A):97S–104.
5 **Malagelada JR**. Review article: supra-esophageal manifestations of gastro-esophageal reflux disease. *Aliment Pharmacol Ther* 2004;**19**(suppl1):43–8.
6 **Ossakow SJ**, Elta G, Bogdasarian R, et al. Oesophageal reflux and dysmotility as the basis of persistent cervical symptoms. *Ann Otol Rhinol Laryngol* 1987;**96**:387–92.
7 **Poelmans J**, Feenstra L, Demedts I, et al. The yield of upper gastrointestinal endoscopy in patients with suspected reflux-related chronic ear, nose and throat symptoms. *Am J Gastroenterol* 2004;**99**:1419–26.
8 **El-Serag HB**, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology* 1997;**113**:755–60.
9 **El-Serag HB**, Gilger M, Kuebeler M, et al. Extraesophageal associations of gastroesophageal reflux disease in children without neurological defects. *Gastroenterology* 2001;**121**:1294–9.
10 **El-Serag HB**, Hepworth EJ, Lee P, et al. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. *Am J Gastroenterol* 2001;**96**:2013–18.
11 **Harding SM**. Pulmonary complications of gastroesophageal reflux. In: Castell DO, Richter JE, eds. In:*The esophagus*, 4th, edn. Philadelphia: Lippincott Williams and Wilkins, 2004:530–45.
12 **Field SK**, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux? A critical review of the literature. *Chest* 1998;**114**:275–83.
13 **Field SK**, Gelfand GAJ, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999;**116**:766–74.
14 **Coughlan JL**, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. *Thorax* 2001;**56**:198–204.
15 **Irwin RS**, Madison JM. Anatomic diagnostic protocol in evaluating chronic cough with specific reference to gastroesophageal reflux disease. *Am J Med* 2000;**108**(suppl 4A):126S–30.
16 **D'Urzo A**, Jugovic P. Chronic cough. Three most common causes. *Can Fam Physician* 2002;**48**:1311–16.
17 **Ours TM**, Kavaru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;**94**:3131–8.
18 **Kiljander TO**, Salomaa ERM, Hietanen EK, et al. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;**16**:633–8.
19 **Delahunty JE**, Cherry J. Experimentally produced vocal cord granulomas. *Laryngoscope* 1968;**78**:1941–7.
20 **Belafsky PC**, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;**111**:1313–17.
21 **Hanson DG**, Kamel PL, Kahrilas PJ. Outcomes of anti-reflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995;**104**:550–5.
22 **Noordzij JP**, Khidr A, Kufman JA. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope* 2001;**111**:2147–51.
23 **Smit CF**, van Leeuwen JA, Mathus-Vliegen LM, et al. Gastropharyngeal and gastroesophageal reflux in globus and hoarseness. *Arch Otolaryngol Head Neck Surg* 2000;**126**:827–30.
24 **Delahunty JE**. Acid laryngitis. *J Laryngol Otol* 1972;**86**:335–42.
25 **Ylitalo R**, Ramel S. Extraesophageal reflux in patients with contact granuloma: a prospective controlled study. *Ann Otol Rhinol Laryngol* 2002;**111**:441–6.
26 **Jindal JR**, Milbrath MM, Shaker R, et al. Gastroesophageal reflux disease as a likely cause of ''idiopathic'' subglottic stenosis. *Ann Otol Rhinol Laryngol* 1994;**103**:186–91.
27 **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**:979–83.
28 **Eherer AJ**, Habermann W, Hammer HF, et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled study. *Scand J Gastroenterol* 2003;**38**:462–7.
29 **Loehrl TA**, Smith TL. Chronic sinusitis and gastroesophageal reflux: are they related? *Curr Opin Otolaryngol Head Neck Surg* 2004;**12**:18–20.
30 **Tasker A**, Dettmar PW, Panetti M, et al. Is gastric reflux a cause of otitis media with effusion in children? *Laryngoscope* 2002;**112**:1930–4.
31 **Poelmans J**, Tack J, Feenstra L. Chronic middle ear disease and gastroesophageal reflux disease/a causal relation? *Otol Neurotol* 2001;**22**:447–50.
32 **Poelmans J**, Tack J, Feenstra L. Prospective study on the incidence of chronic ear complaints related to gastroesophageal reflux and on the outcome of antireflux therapy. *Ann Otol Rhinol Laryngol* 2002;**111**:933–8.
33 **Noordzij JP**, Khidr AK, Desper E, et al. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. *Laryngoscope* 2002;**112**:2192–5.
34 **Toohill RJ**, Kuhn JC. Role of refluxed acid in pathogenesis of laryngeal disorders. *Am J Med* 1997;**103**(suppl 5A):100S–6.
35 **Poelmans J**, Tack J, Feenstra L. The role of (duodeno)esophagopharyngeal reflux in chronic unexplained excessive throat phlegm. *Dig Dis Sci* 2005;**50**:824–32.
36 **Bortolotti M**. Laryngospasm and reflex central apnoea caused by aspiration of refluxed gastric content in adults. *Gut* 1989;**30**:233–8.
37 **Loughlin CJ**, Koufman JA. Paroxysmal laryngospasm secondary to gastroesophageal reflux. *Laryngoscope* 1996;**106**:1502–5.
38 **Maceri RM**, Zim S. Laryngospasm: an atypical manifestation of severe gastroesophageal reflux disease (GERD). *Laryngoscope* 2001;**111**:1976–9.
39 **Morrison M**, Rammage L, Emmani AJ. The irritable larynx syndrome. *J Voice* 1999;**13**:447–55.
40 **Poelmans J**, Tack J, Feenstra L. Paroxysmal laryngospasm: a typical but underrecognized supraesophageal manifestation of gastroesophageal reflux. *Dig Dis Sci* 2004;**49**:1868–74.
41 **Sifrim D**, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour ambulatory pressure, pH, and impedance monitoring. *Gut* 2005;**54**:449–54.
42 **Ing AJ**, Ngu MC, Breslin ABX. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med* 1994;**149**:160–7.
43 **Kiljander TO**. The role of proton pump inhibitors in the management of gastroesophageal reflux disease-related asthma and chronic cough. *Am J Med* 2003;**115**(suppl 3A):65S–71.
44 **Jacob P**, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with ''reflux laryngitis. '' *Gastroenterology*, 1991;**100**:305–10.
45 **Sataloff RT**, Castell DO, Katz PO, et al. *Reflux laryngitis and related disorders*. San Diego: Singular Publishing Group, 1999.
46 **Cool M**, Poelmans J, Koek G, et al. Characteristics and clinical relevance of proximal esophageal pH monitoring. *Am J Gastroenterol* 2004;**99**:2317–23.
47 **Champion GL**, Richter JE. Atypical presentations of gastroesophageal reflux disease: chest pain, pulmonary and ear, nose, throat manifestations. *Gastroenterologist* 1993;**1**:18–33.
48 **Kahrilas PJ**, Ergun GA. Otolaryngologic manifestations of GERD. In: Richter JE, eds. *Ambulatory esophageal pH monitoring:a practical approach and clinical applications*, 2nd edn. New York: Igaku-Shoin, 1997:133–48.
49 **Kamel PL**, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med* 1994;**96**:321–6.
50 **Klinkenberg-Knol EC**, Meuwissen SGM. Combined gastric and esophageal 24-hour pH monitoring and esophageal manometry in patients with reflux disease resistant to treatment with omeprazole. *Aliment Pharmacol Ther* 1990;**4**:485–95.
51 **Fass R**, Mackel C, Sampliner RE. 24-hour pH monitoring in symptomatic patients without erosive esophagitis who did not respond to antireflux treatment. *J Clin Gastroenterol* 1994;**19**:97–9.
52 **Holloway RH**, Dent J, Narielvala,F, et al. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole. *Gut* 1996;**38**:649–54.
53 **Katzka DA**, Paoletti V, Leite L, et al. Prolonged ambulatory pH monitoring in patients with persistent gastroesophageal reflux disease symptoms: testing while on therapy identifies the need for more aggressive anti-reflux therapy. *Am J Gastroenterol* 1996;**91**:2110–13.
54 **Bough DI**, Sataloff RT, Castell DO, et al. Gastroesophageal reflux laryngitis resistant to omeprazole therapy. *J Voice* 1995;**9**:205–11.
55 **Koufman JA**. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD). *Laryngoscope* 1991;**101**(suppl):1–78.
56 **Koufman JA**, Belafsky P, Bach K, et al. Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. *Laryngoscope* 2002;**112**:1606–9.
57 **Hicks DM**, Ours TM, Abelson TI, et al. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice* 2002;**16**:564–79.
58 **Vaezi M**, Richter J, Stasney CR, et al. A randomized, double-blind, placebo-controlled study of acid suppression for the treatment of suspected laryngopharyngeal reflux. *Gastroenterology* 2004;**126**:A22.
59 **Poe RH**, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. *Chest* 2003;**123**:679–84.
60 **Tack J**, Koek G, Demedts I, et al. Gastroesophageal reflux disease poorly responsive to proton pump inhibitors: acid reflux, bile reflux or both? *Am J Gastroenterol* 2004;**99**:981–8.
61 **Levy AH**, Banwait KS, DiMarino AJ, et al. Utility of twenty-four hour esophageal pH monitoring in patients with persistent symptoms on PPI therapy. *Gastroenterology* 2004;**126**:A19.

62 **Vaezi MF**, Charbel S. On-therapy pH monitoring: Usually recommended but should we do it? *Gastroenterology* 2004;**126**:A82.

63 **Vela MF**, Camacho-Lobato L, Srinivasan R, *et al.* Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001;**120**:1599–606.

64 **Shay S**, Tutuian R, Sifrim D, *et al.* Twenty-four hour impedance and pH monitoring (24-hr Imp-pH) in the evaluation of GERD patients with persistent symptoms despite bid proton pump inhibitors (PPI): A multicenter study. *Gastroenterology* 2004;**126**:A324.

65 **Poelmans J**, Tack J, Sifrim D, *et al.* Role of bile reflux in patients with gastroesophageal reflux-related ENT symptoms. *Neurogastroenterology* 1999;**11**:A281.

66 **Wiener GJ**, Copper JB, Wu WC, *et al.* Is hoarseness an atypical manifestation of gastroesophageal reflux (GER)? An ambulatory 24-hour pH study. *Gastroenterology* 1986;**90**:A1691.

67 **Ossakow SJ**, Elta G, Bogdasarian R, *et al.* Esophageal reflux and dysmotility as the basis of persistent cervical symptoms. *Ann Otol Rhinol Laryngol* 1987;**96**:387–92.

68 **Batch AJG**. Globus pharyngeus (part 1). *J Laryngol Otol* 1988;**102**:152–8.

69 **McNally PR**, Maydonovic CL, Prosek RA, *et al.* Evaluation of gastroesophageal reflux as a cause of idiopathic hoarseness. *Dig Dis Sci* 1989;**34**:1900–4.

70 **Ness J**, Sontag S, Schnell T. Prevalence of gastroesophageal reflux (GER) in consecutive patients with hoarseness. *Gastroenterology* 1992;**102**:A134.

71 **Tauber S**, Gross M, Issing WJ. Association of laryngopharyngeal symptoms with gastroesophageal reflux disease. *Laryngoscope* 2002;**112**:879–86.

72 **Koufman JA**, Belafsky P, Bach K, *et al.* Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. *Laryngoscope* 2002;**112**:1606–9.

73 **Poelmans J**, Feenstra L, Tack J, *et al.* Determinants of long-term outcome of patients with reflux-related ENT symptoms. *Dig Dis Sci* 2005 (in press).

74 **Johnson DA**, Benjamin SB, Vakil NB, *et al.* Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomised, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol* 2001;**96**:27–34.

1499

EDITOR'S QUIZ: GI SNAPSHOT ....

Answer

From question on page 1491

Small bowel biopsies revealed diffuse nodular lymphoid hyperplasia (NLH), a rare lymphoproliferative condition characterised by numerous hyperplastic lymphoid nodules, 3–6 mm in diameter. The nodules are indistinguishable from those that normally occur in the gastrointestinal tract. NLH is most commonly seen in the small bowel. The exact aetiology of the condition is unknown but there is an association with immunodeficiency. Measurement of her serum immunoglobulins levels revealed hypogammaglobulinaemia consistent with common variable immunodeficiency. This is associated with recurrent sinopulmonary bacterial infections and gastrointestinal disorders, most commonly chronic diarrhoea. Her anaemia improved with oral iron supplementation and she was commenced on intravenous immunoglobulin therapy.

doi: 10.1136/gut.2005.067082