KATHOLIEKE UNIVERSITEIT LEUVEN
FACULTEIT GENEESKUNDE

SUPRAESOPHAGEAL MANIFESTATIONS OF (DUODENO-) GASTROESOPHAGEAL REFLUX IN ADULT OTORHINOLARYNGOLOGICAL PATIENTS

Johan POELMANS

Thesis submitted in fulfillment of the requirements for the degree of "Doctor in de Medische Wetenschappen"

May 24, 2004

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"the readiness is all"

voor Gerda, Jonas en Elien

LIST OF PUBLICATIONS

The work in this thesis, has been published, is accepted for publication or has been submitted for publication in the following papers:

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J. Poelmans, J. Tack and L. Feenstra. Chronic middle ear disease and gastroesophageal reflux disease: a causal relation? *Otology & Neurotology* 2001; **22**: 447-450.

J. Poelmans, J. Tack and L. Feenstra. Prospective study on the incidence of chronic ear complaints related to gastroesophageal reflux and on the outcome of antireflux therapy. *Annals of Otology, Rhinolology & Laryngology* 2002; **111**: 933-938.

J. Poelmans, L. Feenstra, I. Demedts, P. Rutgeerts and J. Tack. The yield of upper gastrointestinal endoscopy in patients with suspected reflux-related chronic ear, nose and throat symptoms. *The American Journal of Gastroenterology*. (2004; in press).

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J. Poelmans, J. Tack , L. Feenstra and J. Janssens. Episodic laryngospasm: a manifestation of gastroesophageal reflux disease? *Gastroenterology* 2000, **118** (abstract).

J. Poelmans, L. Feenstra, J. Tack and J. Janssens. Chronische onverklaarde NKO-symptomen: extra-esophagale manifestaties van gastro-esophagale refluxziekte? *Acta Oto-Rhino-Laryngologica Belgica* 2000, **54** (abstract).

AB

b.i.c
CI
CD
CRI
CSC
DC
DGI
DGI
DR
EER
EGJ
FLS
GEF
GER
GER
g.i.
HCl
Hp
IEM
IQR
LES
LPR
LS
MCF
MII
NSA
o.i.d.
OLS
OME
OR
ORL

ABBREVIATIONS

b.i.d.	= twice daily
CI	= confidence interval
CD	= crural diaphragm
CRFP	= chronic refractory feeling of pressure
CSOM	= chronic secretory otitis media
DC	= duodenal contents
DGEPR	= duodeno-gastro-esophago-pharyngeal reflux
DGER	= duodeno-gastro-esophageal reflux
DR	= distal reflux
EER	= extraesophageal reflux
EGJ	= esophagogastric junction
FLS	= frequent laryngospasm
GEPR	= gastro-esophago-pharyngeal reflux
GER	= gastroesophageal reflux
GERD	= gastroesophageal reflux disease
g.i.	= gastrointestinal
HCl	= hydrogen chloride
Hp	= Helicobacter pylori
IEM	= ineffective esophageal motility
IQR	= interquartile range
LES	= lower esophageal sphincter
LPR	= laryngopharyngeal reflux
LS	= laryngospasm
MCF	= mucociliary flow
MII	= multichannel intraluminal impedance
NSAID's	= non steroid anti-inflammatory drugs
o.i.d.	= once daily
OLS	= occasional laryngospasm
OME	= otitis media with effusion
OR	= odds ratio
ORL	= otorhinolaryngological

PPI	= proton pump inhibitor
PR	= proximal reflux
SEM	= standard error of the mean
SI	= symptom index
SIDS	= sudden infant death syndrome
t.i.d.	= three times daily
TLESR	= transient lower esophageal sphincter relaxation
TTP	= transparent throat phlegm
UES	= upper esophageal sphincter
YTP	= yellow stained throat phlegm

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CHAPTER 1: INTRODUCTION: GASTROESOPHAGEAL REFLUX DISEASE: CURRENT CONCEPTS

Gastroesophageal reflux (GER), defined as the entry of gastric contents into the esophagus, is a physiologic event. When excessive, however, GER may become a major pathophysiological factor. The common clinical condition, in which GER leads to esophageal symptoms or lesions, is referred to as gastroesophageal reflux disease (GERD), of which heartburn and acid regurgitation are the classical symptoms and reflux esophagitis and Barrett's esophagus are the most important lesions. Recent studies have established a contribution of refluxate of duodenal origin, so-called duodeno-gastro-esophageal reflux (DGER) to GERD. GER or its effects may extend beyond the esophagus and is, over the past 40 years, increasingly being recognized as a primary cause of or a major contributing factor to a wide variety of common or less common supraesophageal manifestations.

This chapter summarizes current knowledge about GERD and DGER; symptoms and signs, pathophysiology, reflux diagnostic testing and antireflux therapy. The next chapter also provides a review on possible supraesophageal manifestations of GER in otorhinolaryngological (ORL) patients; clinical presentations, pathophysiology, diagnostic testing and therapy.

A. CLINICAL PRESENTATIONS

A variety of symptoms and clinical signs may be found in patients with reflux disease. The typical or classical symptoms of GERD are heartburn and regurgitation. In addition, a number of less typical symptoms have been attributed to GERD as discussed below. Possible reflux-related supraesophageal symptoms and signs are discussed in the next chapter. Typical GERD with frequent heartburn or acid regurgitation is a prevalent clinical condition, affecting 10% to 30% of the Western population (79, 83, 120, 207).

1. Typical symptoms

Heartburn (pyrosis) is typically described as a retrosternal burning sensation that migrates upward from the epigastric region into the chest and radiates towards the throat. Regurgitation is the effortless return of gastric contents into the esophagus or mouth. An acid or bitter taste or even the taste of food may be perceived in the mouth.

Heartburn and/or regurgitation most often occur shortly after meals, on bending over or heavy lifting and may be provoked by spicy or acidic foods and drinks and fatty meals. Symptoms are relieved with antacids.

Less typical symptoms include "angina pectoris"-like chest pain, in which a cardiac origin must be excluded and dysphagia. Non-obstructive dysphagia is frequently seen in reflux disease and is generally considered not an "alarm" symptom. Obstructive dysphagia may indicate mechanical obstruction by a peptic stricture or esophageal carcinoma, arising from a pre-existing Barrett's esophagus. Odynophagia may indicate severe ulcerative esophagitis. Obstructive dysphagia, odynophagia and bleeding are considered "alarm" symptoms and suggest complicated GERD. Waterbrash is the sudden occurrence of a clear salty fluid in the mouth resulting from excess salivary gland secretion as a reflex response to reflux of gastric acid into an inflamed distal esophagus.

Non-specific upper gastrointestinal symptoms that may be related to GERD include dyspeptic symptoms such as excessive belching, bloating, vague epigastric distress and nausea (197). These symptoms, however, are not as sensitive or specific as heartburn.

Predominant symptoms of frequent heartburn and/or acid regurgitation are highly specific for GERD. Therefore a therapeutic trial with a proton pump inhibitor (PPI), without further diagnostic testing, is considered a favourable initial strategy in these patients (107).

2. Esophageal lesions

Reflux-related esophageal lesions not only include erosive esophagitis but also severe complications of GERD including peptic stricture, ulceration, Barrett's esophagus and carcinoma (162). Barrett's esophagus, a premalignant condition with changes from the normal squamous epithelium to a metaplastic intestinal type epithelium and typical staining characteristics, is currently considered an acquired condition secondary to chronic GERD and DGER.

B. PATHOPHYSIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE

The pathophysiology of GERD, although incompletely understood, is multifactorial and involves gastric and esophageal motility abnormalities allowing reflux to occur and/or compromising luminal clearance mechanisms. Offensive factors in the refluxate (i.e. gastric acid) and defective esophageal tissue resistance are also involved. Pathological reflux or

GERD occurs when the balance between offensive factors (acid reflux and potentially also duodeno-gastro-esophageal reflux) and defensive factors (luminal clearance mechanisms, mucosal resistance) is disturbed in favour of the aggressive factors.

1. The antireflux barrier

The development of GERD in most patients is related to incompetence of the antireflux barrier at the esophagogastric junction (EGJ). The lower esophageal sphincter (LES) and the crural diaphragm (CD) are the two most important components of the antireflux barrier, which under normal circumstances prevents the reflux of gastric contents into the esophagus. The LES is often considered the internal sphincter and the CD the external sphincter of the antireflux barrier. The onset of swallowing induces a central nervous system-mediated LES relaxation, which continues until the peristaltic wave has reached the distal end of the esophagus and produces closing.

The LES is a high pressure zone at the EGJ, interposed between the positive intra-abdominal pressure and the negative intrathoracic pressure, and results from the combined activity of a tonically contracted distal esophageal smooth muscle and of the CD. At rest, the end expiratory pressure mainly results from the smooth muscle segment of the LES while the end expiratory pressure fluctuations are related to CD activity (138). Stationary esophageal pull-through manometry studies revealed that in normal upright subjects at rest, the tonically contracted LES generates a closing pressure 10 to 45 mm Hg above the intragastric pressure, which serves as a zero reference. This pressure is also referred to as the LES resting pressure. While most patients with GERD have a LES resting pressure of 10-30 mm Hg, which is somewhat lower than in normal subjects, only a subset, usually those with severe erosive esophagitis, has a low LES resting pressure (<10 mm Hg). Such low LES pressure predisposes to "stress reflux" following an abrupt transient increase in intra-abdominal pressure (for instance during straining or coughing) and to "free reflux" when the LES resting pressure is 0-4 mm Hg above the intragastric pressure (37, 97).

Prolonged measurements of LES pressure with a Dent sleeve revealed that the LES is a dynamic sphincter with varying pressures throughout the day. The LES pressure is raised in the supine position and decreases in the postprandial period. During prolonged measurements of LES pressure, transient relaxations of the LES (TLESR's) have been observed both in healthy subjects and in GERD patients (29, 161, 184). TLESR's occur most commonly in the postprandial phase, are not preceded by a pharyngeal contraction, have a longer duration (15-

30 sec) than swallow-induced relaxations and are most frequently unaccompanied by esophageal peristalsis. TLESR's, defined as LES relaxations that are not induced by swallowing, are now considered the most common phenomenon responsible for individual reflux episodes. A TLESR is a vagally mediated reflex, organized in the brain stem and triggered mainly by gastric distension after a meal (77). Mechanical stimulation of the pharynx may also trigger TLESR's (134, 139). In the upright position, healthy subjects and GERD patients have a similar rate of TLESR's, but TLESR's in GERD patients are more frequently accompanied by acid reflux than TLESR's in normal volunteers (65% and 30% respectively) (136, 192). While most individuals with a sliding hernia don't have GERD, a majority of patients with moderate to severe esophagitis have a hiatal hernia. Displacement of the LES above the CD creates a hiatal hernia which may predispose to GERD in several ways. The hernia sac may act as a fluid trap permitting "re-reflux" during swallow-induced and transient LES relaxation, thereby prolonging the esophageal clearance time (196). Although the pressure gradient across the EGJ is increased during coughing and abdominal straining, a simultaneous forceful contraction of the CD also increases the pressure of the antireflux barrier and prevents reflux to occur (135, 137). This protective mechanism is deficient in individuals with a hiatal hernia (195, 231).

2. Esophageal clearance mechanisms

Refluxed gastric contents are removed from the esophagus by two related but separate esophageal clearance mechanisms. The first mechanism is so-called volume clearance, which is the actual removal of refluxed gastric contents from the esophagus by peristalsis. The second mechanism is referred to as chemical clearance: residual intraesophageal acid is neutralized by swallowed saliva (72). The acid clearance time is determined as the time needed to restore intraesophageal pH to > 4 following an acid reflux episode.

Primary peristalsis is elicited by swallowing and occurs, when awake, once every minute regardless whether or not reflux occurs. Secondary peristalsis originates in the esophagus and results from esophageal distension caused by some solid foods that require more than a single primary peristaltic wave for eventual clearance and by refluxed gastric contents.

Up to 50% of GERD patients have an impaired esophageal acid clearance function resulting in a prolonged acid clearance time. Peristaltic dysfunction, particularly the occurrence of failed peristaltic contractions and hypotensive (< 30 mm Hg) peristaltic contractions that inadequately clear the esophagus, commonly occurs in GERD patients. Its prevalence shows a

graded increase with increasing severity of esophagitis (97, 104). In both healthy subjects and GERD patients, primary peristalsis is more important than secondary peristalsis as the initial esophageal clearing event (1). As the swallowing frequency and associated primary peristalsis are markedly reduced during sleep, secondary peristalsis may be more important in clearing the esophagus at night. In GERD patients with or without esophagitis, secondary peristalsis elicited by esophageal distension with air or water is frequently impaired (183, 248). Whether peristaltic dysfunction in GERD patients is a primary abnormality or the consequence of repeated esophageal acid injury remains unclear. Motility studies before and after healing of esophagitis revealed no significant improvement in esophageal motor function (174, 214, 247).

Saliva (pH 6.4–7.8) has the capacity of neutralizing small amounts of residual acid in the esophagus after peristaltic contractions have cleared the volume of refluxed gastric contents (73). The important role of swallowed saliva in the chemical clearance of intraesophageal acid is underscored by the finding that suction aspiration of saliva significantly prolongs the acid clearance time, despite the presence of normal peristaltic contractions (71). In a recent study using combined radionuclide, pH and Bilitec® monitoring, acid GER and DGER was simulated in healthy subjects and the esophageal clearance of liquid acid (pH 2.0) and duodenal content (DC) solutions (pH 2.0) were compared. While liquid acid and DC solutions had comparable volume clearances, chemical clearance was slightly faster for DC than for acid, and suction aspiration of saliva only prolonged acid clearance time and not DC clearance time (113).

3. Offensive factors in the refluxate

Acid is indisputably the most important noxious agent in gastroesophageal refluxate, but its injurious capacities to the esophageal mucosa may involve activation of pepsin. Experiments on the rabbit's esophagus have shown that acid alone causes only minimal injury at pH<3.0 but when pepsin was added to an acidic solution, the mucosal barrier was disrupted resulting in increased hydrogen ion permeability, histological changes and hemorrhage (153). Acid suppressive therapy in the treatment of GERD is based on these findings.

Traditionally, reflux esophagitis is regarded an acid reflux-related lesion, while frequent heartburn and/or acid regurgitation are considered typical acid reflux-related symptoms (107). However, a consistent relation between the severity of typical reflux symptoms and the lesions seen on endoscopy has not been found (93, 257). Infusions of hydrochloric acid

solutions in the mid-esophagus were shown to reproduce heartburn, while the time of infusion required for the induction of heartburn gradually decreased with increasing acid concentrations (201). While these findings suggest that the pH and exposure time of intraesophageal acid determine the occurrence of heartburn, ambulatory pH monitoring studies have shown a less consistent and more complicated relationship between intraesophageal acid exposure and spontaneously occurring heartburn (3, 87, 191, 194). In 24-hour pH monitoring studies, the severity of esophageal lesions seems to be correlated to the distal esophageal acid exposure time which is particularly prolonged in Barrett's esophagus, but again considerable overlap exists (159, 208).

In addition to esophageal acid exposure time, also the composition of the refluxate may be important in the induction of lesions and symptoms. Reflux of duodenal contents into the stomach, especially in the postprandial phase, is a physiological event (13). Therefore, gastroesophageal refluxate may also contain bile, duodenal and pancreatic secretions. Experimental evidence has shown that conjugated bile acids are injurious to the rabbit's esophagus at acidic pH and that unconjugated bile acids are more noxious at neutral pH (70, 175). Studies in humans, using simultaneous pH and DGER (Bilitec®) monitoring, have not only shown that esophageal exposure to both acid and DGER is the most prevalent reflux pattern but also that both acid reflux and DGER show a graded increase in severity from controls to esophagitis patients with the highest values observed in patients with Barrett's esophagus (19, 226, 227). Patients with complicated Barrett's esophagus even have greater amounts of acid reflux and DGER than those with uncomplicated Barrett's esophagus (14, 226). These studies suggest that a synergistic activity of acid reflux and DGER contributes to the induction of esophageal lesions in patients with GERD. Some recent studies, using the symptom index, addressed the association of heartburn and acid regurgitation with both acid reflux and DGER. It was found that the occurrence of these typical reflux symptoms is most frequently related to acid reflux and rarely to DGER. This makes DGER unlikely to play a major role in the induction of these symptoms (112, 129).

In some patients, it has been shown that DGER also occurs in the absence of acid reflux and may cause symptoms and/or esophagitis (185, 211, 249). Approximately 50% of 25 mechanically ventilated, critically ill patients in whom acid reflux was adequately suppressed with ranitidine developed esophagitis that was significantly related to the presence of pathological DGER (249). A recent study evaluated the role of acid and DGER in a subset of 65 GERD patients with continuing reflux symptoms during prolonged and high dosed PPI-

therapy. With continuing PPI therapy, persistent esophagitis was found in 51% of the patients. On 24-hour ambulatory pH and Bilitec® monitoring, 37% of the patients had pathological acid exposure, 64% had pathological DGER and 26% had pathological exposure to both acid and DGER which was significantly associated with esophagitis. (211).

In multichannel intraluminal impedance (MII), a recent technique for evaluating GER, reflux-episodes are detected by changes in resistance to alternating current between two metal electrodes produced by the presence of bolus inside the esophageal lumen. As different types of refluxed gastric contents may have different conductivities, intraluminal impedance may characterize the refluxate as liquid, gas or mixed reflux. Simultaneous pH monitoring may further identify reflux-episodes as acid or non-acid. It has been demonstrated recently that, although the rate of TLESR's and the number of accompanying reflux episodes are similar in healthy subjects and GERD patients, patients with reflux disease had, compared to controls, a significantly higher proportion of acidic reflux events and of liquid reflux (193). Moreover, combined MII and pH monitoring not only allows quantification of the proximal distribution and duration of non-acid reflux events but also evaluation of a temporal association of symptoms with non-acid reflux episodes. Therefore, this technique may become an important clinical tool, particularly to assess GER in patients refractory to treatment, in patients with less typical and supraesophageal symptoms and in pediatric patients (241).

4. Esophageal mucosal resistance

Mucosal resistance refers to the intrinsic defence mechanisms within the esophagus that protect the mucosa against acid injury. This mucosal resistance is important as is illustrated by the absence of damage to the canine esophageal mucosa following continuous exposure to HCL (pH 2.0) for 3.5 hours (165). These findings are confirmed in humans by the absence of symptoms and esophageal damage following a continuous perfusion with HCl (pH 1.1) for 30 min (Bernstein test) (8). The most important factors in mucosal resistance can be categorized as pre-epithelial, epithelial and post-epithelial defence mechanisms. The pre-epithelial defence consists of protective factors within swallowed saliva and esophageal submucosal secretion and includes mucins and bicarbonate that may neutralize H^+ ions to some limited extent. Swallowed saliva also contains a number of peptide growth factors that may enhance mucosal repair including epidermal growth factor (EGF) and transforming growth factor α (TGF α) (177). Some patients with esophagitis may have a decreased salivary or esophageal submucosal gland secretion of these pre-epithelial protective factors. The epithelial defense

consists of a 30-40 cell layered stratified squamous epithelium with tight intercellular junctions and an intercellular glycoprotein matrix, which are initially impermeable to H^+ ions. In addition, the epithelial cells have an active cellular ionic transport mechanism that enables the cells to maintain a normal intracellular pH even when H^+ ions have penetrated the intercellular regions. Defects of the intercellular matrix, leading to increased intercellular space, have been reported for both erosive and non-erosive reflux disease (216). The post-epithelial defense is related to the diffusion from the blood supply of bicarbonate which is required to preserve the buffering capacities of the cells and the intercellular space (152).

5. Esophageal sensitivity

While in a substantial group of GERD patients, particularly in those with Barrett's esophagus or peptic stenosis, acid reflux is unperceived, other patients with an "acid-sensitive esophagus" have normal findings on endoscopy and normal acid exposure on pH monitoring but perceive their few physiologic reflux episodes intensively (191). While these observations suggest different esophageal sensitivity thresholds, the underlying mechanisms for these differences in sensitivity remain unclear.

C. DIAGNOSTIC TESTING OF (DUODENO)-GASTRO-ESOPHAGEAL REFLUX

Reflux may be assessed by a variety of diagnostic tests of which a therapeutic trial with a proton pump inhibitor (PPI), upper gastrointestinal (g.i) endoscopy and 24-hour esophageal pH monitoring are the most commonly used. Other methods to investigate reflux include the acid perfusion (Bernstein) test, esophageal manometry and 24-hour ambulatory esophageal DGER monitoring with the Bilitec® 2000 probe and, more recently, intraluminal electrical impedance monitoring. However, at present, there is no gold standard for the diagnosis of GERD.

1. Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy is performed to document esophageal injury and establish a diagnosis of erosive esophagitis or Barrett's esophagus. The Savary-Miller classification (149) (Table 1), which serves as a basis for reimbursement in Belgium, and the better validated L.A. classification (Table 2), allow grading the severity of esophagitis.

While the specificity of upper g.i. endoscopy for GERD is excellent (90-95%), its sensitivity compared to 24-hour esophageal pH monitoring is lower (60-70% at best) (168, 172). Despite the high specificity of heartburn and acid regurgitation for the diagnosis of GERD, neither their presence nor their frequency is predictive of the severity of endoscopic esophageal acid injury. In prospective studies, erosive esophagitis is found in only 45% to 60% of patients with frequent heartburn or regurgitation (93, 257). The others have non-erosive GERD with mucosal erythema, edema or a normal appearing esophagus. However, not all patients with esophagitis are symptomatic. Frequent heartburn is perceived in only 50-65% of patients with esophagitis and up to 30% of patients with Barrett's esophagus have no heartburn at all (107, 110, 169, 206). One possible explanation for this may be a mucosal insensitivity to gastric acid. Erosive esophagitis usually indicates a more severe form of GERD in which up to 80% of patients need continuous PPI treatment for maintaining symptom relief and healing with endoscopic and symptomatic relapse when medication is interrupted or decreased. At long term follow up, less than 25% of patients with esophagitis on initial endoscopy will progress to a more severe stage of endoscopic esophagitis (150). Less than 15% of patients with reflux symptoms and non-erosive GERD will progress to erosive esophagitis over 6 months (158).

Table 1. Savary-Miller endoscopic grading system

Grade 0	Normal mucosa
Grade 1	Single, erosive or exudative lesion, oval or linear, taking only one longitudinal fold
Grade 2	Noncircular multiple erosions or exudative lesions taking more than one longitudinal fold with or without confluence
Grade 3	Circular erosive or exudative lesion
Grade 4	Chronic lesions: ulcers, strictures, or short esophagus, isolated or associated with lesions grade 1-3
Grade 5	Barrett's epithelium isolated or associated with lesions grade 1-3

Ollyo JB, Lang F, Fontolliet C, Monnier P. Savary-Miller's new endoscopic grading of reflux-esophagitis: a simple, reproducible, logical, complete and useful classification. Gastroenterology 1990; 99: A100.

These findings indicate that long term acid suppression in order to provide symptom relief is a safe procedure in the majority of classical reflux patients and that upper g.i. endoscopy is

recommended in selected patients, i.e. in patients with "alarm" symptoms, patients with longstanding symptoms of at least 5 years and patients unresponsive to PPI therapy.

Table 2. Los Angeles classification

Grade A	One or more mucosal breaks confined to the folds, each no longer than 5 mm
Grade B	At least one mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of the mucosal folds
Grade C	At least one mucosal break continuous between the tops of two or more mucosal folds but not circumferential
Grade D	Circumferential mucosal break

During endoscopy, a hiatal hernia is diagnosed when >2 cm of gastric mucosa appears above the diaphragm. In addition to upper g.i. endoscopy, other diagnostic tests are frequently performed in patients with suspected GERD.

2. 24-hour ambulatory esophageal pH monitoring

The 24-hour ambulatory pH monitoring is the most widely used test to quantify esophageal acid exposure and to study a temporal association between symptoms and acid reflux. Placement of the pH electrode is standardized: a 2 mm diameter catheter containing a single or multiple antimony electrodes is inserted transnasally into the esophagus. The distal pH electrode is placed 5 cm above the proximal border of the LES, which is identified by manometry. This position of the distal electrode avoids its displacement into the stomach during swallowing, when the esophagus shortens. The pH probe and a separate skin reference electrode are connected to a portable digital recorder that is worn on a belt (Digitrapper Mk III, Synectics Medical, Stockholm Sweden). The stored data are analyzed with a computer program (Synectics Medical, Stockholm Sweden), summarized in a report and graphically represented as a 24-hour pH monitoring tracing. Depending on a number of variables that can be calculated, the study may be considered as either physiological or pathological. The most important measurement is the total percentage of time of intraesophageal pH<4 (180). Although reported sensitivities (76-96%) and specificities (86-98%) of distal esophageal pH monitoring are high for diagnosing GERD (56, 90, 171, 179), this method also has some

limitations. Unfortunately, and contrary to pH monitoring results in erosive esophagitis patients, who rarely need further pH testing in clinical practice because GERD in these patients is already proven, more considerable overlap has been reported in esophageal acid exposure times between non-erosive GERD patients and controls. This may render individual pH monitoring results more difficult to interpret in these patients (102, 130, 179, 235). Moreover, several studies showed a high but imperfect reproducibility of pH monitoring results (77- 85%) (92, 230, 246).

As the patient is instructed to indicate the occurrence of symptoms by pressing an event marker button on the pH data logger, symptoms like heartburn, chest pain, wheezing and coughing can be correlated with acid reflux episodes providing more certainty on causality.

Prolonged pH monitoring is most frequently used in patients experiencing typical reflux symptoms unresponsive to aggressive medical antireflux therapy with no abnormalities on upper g.i. endoscopy, in patients in whom antireflux surgery is considered and in patients with less typical symptoms. In the patient with suspected reflux-related supraesophageal manifestations, a pH monitoring performed at an initial stage allows a diagnosis of coexisting GERD. However, the causality of symptoms remains to be established, for instance by a treatment trial. Therefore, one may also prefer initial empirical treatment with a high dosed PPI, to perform pH monitoring only in those patients unresponsive to therapy after 4 to 8 weeks (48).

A catheter containing multiple electrodes allows simultaneous pH monitoring of distal and proximal esophageal acid exposure. Contrary to the distal electrode, the location of the proximal electrode has not been standardized. While some investigators place the electrode 1 to 2 cm below the distal border of the UES, others place the probe in the UES or 2 cm above the proximal border of the UES (in the hypopharynx). While these techniques require the availability of dual probes with variable lengths separating the sensors, another more practical and frequently applied method is to use a standard dual pH probe with 15 cm separation between the sensors (the distal sensor is placed 5 cm and the proximal sensor 20 cm above the LES).

3. Acid perfusion (Bernstein) test

The acid perfusion (Bernstein) test is used to determine whether the patient's symptoms are related to acid in the esophagus (8). A test is considered positive when intraesophageal infusion of a 0.1 N hydrochloride acid solution provokes the patient's symptom of heartburn

or chest pain, which is subsequently relieved with a saline infusion. Because of lower sensitivity and specificity in diagnosing GERD and in symptom correlation with acid reflux episodes, Bernstein testing has been replaced by 24-hour esophageal pH monitoring in clinical practice.

4. Esophageal manometry

Although, in clinical practice, manometry of the esophagus by a stationary pull-through technique has no role in the diagnosis of uncomplicated GERD, this method is used to determine accurately the location of the LES before the pH probe is introduced (95). Esophageal manometry provides information about the LES resting pressure and the timing and completeness of LES relaxation during standardized swallows. This technique also evaluates primary esophageal peristalsis by assessing the presence, propagation and amplitude of contraction waves. An esophageal motility disorder, particularly "ineffective esophageal motility" (IEM), defined as > 30% ineffective contractions (amplitude < 30 mm Hg or failed peristalsis) out of 10 wet swallows, is a more prevalent finding and is found in 30 to 40% of patients with esophagitis (117). With these peristaltic abnormalities, the esophagus is less effectively cleared from refluxed gastric acid. Esophageal manometry is often considered an essential test prior to antireflux surgery. IEM is suggestive of a weak contractile activity and some advocate adaptation of the surgical approach in these patients: an incomplete (240°) rather than a complete (360°) antireflux wrap is preferred to reduce the risk of postoperative dysphagia (48). Others, however, failed to demonstrate the usefulness of preoperative manometry in predicting postoperative dysphagia (53).

5. 24-hour esophageal Bilitec® 2000 monitoring

The fiberoptic spectrophotometer Bilitec® 2000 (Synectics Medical) is used to quantify DGER in an ambulatory fashion. The system consists of a miniaturized probe of 2.5 mm diameter that carries light signals into the esophagus and back via a plastic fiberoptic bundle. Bilirubin, the most common pigment in bile, has a characteristic absorbance spectrum, and its presence can be detected by continuous monitoring of the absorbance at two different wavelengths (470 nm with a reference pulse of 565 nm). Although bilirubin probably is not a noxious agent in duodeno-gastro-esophageal refluxate, its concentration correlates well with the concentration of putative noxious factors such as bile salts and pancreatic enzymes and therefore bilirubin is considered a good tracer for DGER (6, 209, 225). Bilitec® is a validated

method to study DGER. Clinical studies in esophageal manifestations of reflux disease have shown that DGER is an important co-factor related to extent of the reflux, the presence of lesions and the response to PPI therapy in GERD (210, 211, 229).

6. Empirical treatment trial

In recent years, an empirical trial with PPI's has become a widely accepted initial diagnostic and management strategy in patients with suspected GERD. PPI's are potent inhibitors of gastric acid secretion and have markedly reduced the time to heal esophagitis (30, 52, 127, 173). In most patients, typical symptoms are relieved within 1 to 2 weeks. When symptoms have disappeared on therapy and recur when medication is stopped, one may assume a diagnosis of GERD.

In a purely diagnostic approach, a high dosed PPI (omeprazole 40-60 mg daily, also called the "omeprazole test") is administered during 1 week in patients with typical reflux symptoms or non-cardiac chest pain. In case of symptom improvement of at least 50%, the patient is diagnosed with GERD and therapy may be continued or gradually decreased to the lowest effective maintenance dose. When there is no or minimal symptom improvement, the PPI-dose can be increased for up to 2 months. If no symptom improvement is obtained after that period, further diagnostic testing (upper g.i. endoscopy and/or pH monitoring) is indicated. Using a similar approach, empirical therapy has been shown to have a sensitivity of 78 % to 83% and specificity of 86% in diagnosing GERD, compared to traditional testing (51, 181).

An empirical treatment trial is not suitable for patients presenting with "alarm" symptoms (dysphagia, odynophagia, gastrointestinal bleeding) suggesting complicated GERD and in patients with symptoms for more than 5 years. In these patients, an upper g.i. endoscopy is warranted (94).

D. ANTIREFLUX THERAPY

The aim of antireflux treatment in patients with GERD is to relieve symptoms, to heal reflux esophagitis and to prevent complications and recurrence of symptoms and lesions.

1. Lifestyle and dietary modifications

With the availability of PPI's, the importance of including lifestyle measures in the treatment of GERD-patients has been debated. However, by following recommendations on lifestyle

measures, some patients with mild or intermittent symptoms may avoid regular medication intake. Lifestyle modifications may include the avoidance of foods and drinks the last 2 to 3 hours before going to sleep, the avoidance of recumbency after a meal, elevation of the head end of the bed with 20 to 25 cm and cessation of smoking. Dietary modifications consist of a low-fat diet, elimination or limitation of esophageal irritants from the diet such as acidic drinks, tomato products, coffee and alcohol and avoidance of chocolate carminatives that lower LES pressure. Medications that decrease LES pressure and promote reflux include anticholinergics, calcium channel blockers, sedatives, tranquillizers and nitrates. Other medications such as ferrous sulphate, NSAID's and alendronate may cause direct esophageal injury (pill-induced esophagitis). One should be cautious in using these medications in GERD patients.

2. Pharmacological therapy

PPI's are the most effective pharmacological treatment for GERD and they all have an excellent safety profile with minimal side effects similar to placebo in clinical trials. PPI's (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) profoundly reduce gastric acid secretion by inhibiting the H^+K^+ ATPase enzyme that catalyzes the terminal step of acid secretion in the parietal cell. Continuous therapy with standard doses of PPI's is clearly superior to therapy with H_2 blockers, providing improved symptom relief and healing of esophagitis in up to 85% of patients after 8 weeks (16, 74, 176). A long term follow up study revealed continued success and safety of omeprazole therapy for up to 11 years (108). Some patients may need higher doses of PPI's for adequate acid suppression. A subgroup of patients, however, appears unresponsive to even high doses of PPI's. In these refractory patients, persisting lesions and symptoms can be related to non-acidic gastroesophageal reflux of gastric and/or duodenal origin, which cannot be abolished by acid suppression (211, 232, 249). Adding the gamma-aminobutyric $acid_B$ ($GABA_B$) receptor agonist baclofen to PPI therapy has recently been shown to reduce duodenal reflux and associated symptoms in these patients (111). This effect of baclofen can be explained by its inhibitory action on the occurrence of transient lower esophageal sphincter relaxations (TLESR's), which are considered the main pathophysiological mechanism underlying acid and non-acid reflux events (37, 193).

3. Antireflux surgery

Antireflux surgery aims at restoring a competent gastroesophageal barrier and may be considered in patients with complicated GERD and in those who require long term therapy. Most frequently, a Nissen-fundoplication (360° wrap) or, for instance in case of esophageal dysmotility, a Toupet partial fundoplication (240° wrap) can be performed laparoscopically through a transabdominal approach. The introduction of laparoscopic procedures has minimized postoperative discomfort and recovery and has reduced many of the risks associated with abdominal surgery under general anaesthesia. Some patients, in whom a laparoscopic procedure is contraindicated or technically impossible, may still require antireflux surgery through an open procedure or a transthoracal approach.

4. Endoluminal antireflux procedures

Recently, several new endoscopic procedures, aimed at improving the gastroesophageal barrier function of the LES, have been developed. These techniques include gastroplication with the Endocinch suturing device, the Stretta procedure with applications of temperature-controlled radiofrequency energy into the muscular layer of the LES and submucosal injection of a biopolymer (ethylene-vinyl-alcohol; Enteryx). Additional clinical studies are required to further determine the role of these endoluminal antireflux procedures in the treatment of GERD (65).

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CHAPTER 2: LITERATURE REVIEW ON SUSPECTED REFLUX-RELATED ORL DISORDERS

More than a century ago, at the American Otorhinolaryngological Association meeting of 1903, Dr. LA Coffin presented a paper entitled, "The relationship of upper airway passages to diseases of the gastrointestinal tract" (22). Dr. Coffin noted that "he had been struck by the large number of his clinic patients who complained only of post-nasal catarrh....As the anterior nares frequently escaped the disease altogether, it was evident that one must look elsewhere than to the inspired air....The chief cause was the irritation resulting from the eructations of gases from the stomach....". Dr. Coffin concluded that "hyperacidity was the most common cause and the reason it was overlooked was that the great majority of these persons gave no symptoms pointing to a gastric disorder". In the discussion that followed, Dr. MacCuen Smith stated that ".... so-called 'bilious spells' were often associated with coryza and hoarseness and more or less pain, and the patient at the same time became weak from intestinal intoxication....". Dr. Thompson commented that "the regurgitation of irritating secretion during sleep was often responsible for pharyngitis and rhinitis" (22).

The pharynx is the crossway between the respiratory tract and the digestive tract. It integrates two vital but mutually exclusive functions: respiration and swallowing. The nasal cavity and the pharynx both constitute the upper part of the respiratory system, also referred to as the upper airways. The oral cavity and the pharynx together constitute the upper part of the digestive system. During swallowing, the airways are protected against aspiration by simultaneous laryngeal closure. Anatomically, the pharynx is a tubular structure that connects the posterior part of the nose and the oral cavity with the trachea and the upper esophageal sphincter (UES). Although the pharynx may be considered as a functional and anatomical unit, it can be divided in three separate parts according to their localisation: the nasopharynx, the orophaynx and the laryngopharynx. The nasopharynx is the upper part of the pharynx and extends from the skull base and the posterior nose to the superior surface of the soft palate; the orifices of the Eustachian tubes are located on both sides in its lateral wall. The oropharynx is the middle part of the pharynx and extends from the inferior surface of the soft palate to the superior border of the epiglottis; the oropharynx is the visible part of the pharynx on clinical inspection of the throat. The laryngopharynx consists of the larynx with the vocal folds anteriorly and the hypopharynx posteriorly. It extends from the superior border of the epiglottis to the first ring of the trachea anteriorly and to the UES posteriorly. The mucosa of

the pharyngeal wall contains a friction-resistant stratified squamous epithelium amply supplied with mucus-producing glands. Most parts of the larynx are lined with a pseudo-stratified ciliated columnar epithelium with goblet cells, similar to respiratory mucosa. However, the vocal folds are covered with stratified epithelium and are better suited to withstand friction caused by vocal fold contact.

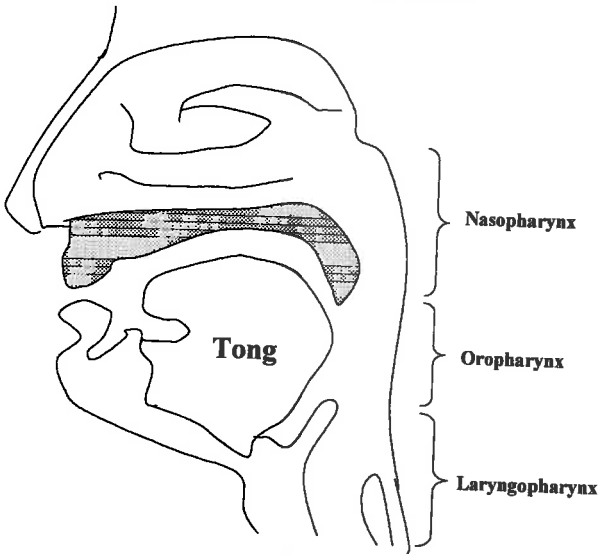

Figure 1. Schematic representation of the anatomy of the pharynx.

Over the last 40 years supraesophageal manifestations, including a variety of pulmonary and ORL disorders, have been increasingly recognized to be associated with GERD (Table 1). Observational studies using objective tests to diagnose GERD suggested that up to 80% of patients with refractory hoarseness, up to 50% of patients with globus, 10% to 20% of patients with chronic cough and a smaller but distinct group of patients with laryngeal cancer may have GERD as a primary cause (18, 62).

The most exhaustive study, demonstrating a high prevalence of GERD among 225 consecutive patients with ORL symptoms and disorders was performed by Koufman (114). Using 24-hour pH monitoring in 182 of these, GERD was a frequent finding in patients with laryngeal stenosis (78%), laryngeal carcinoma (71%), reflux laryngitis (60%), globus (58%) and chronic cough (52%). Patients with laryngeal carcinoma or stenosis had more severe acid reflux than patients with laryngitis or chronic ORL symptoms. This finding implicates a dose-

response relationship which adds further support to a causal association between GERD and ORL disorders.

However, both, GERD and ORL disorders are common in the human population and could also coexist without direct interaction.

Table1: **Suspected GERD-related supraesophageal manifestations**

MIDDLE EAR/EUSTACHIAN TUBE
- Glue ear
- Otalgia

NASAL/SINUSAL
- Chronic sinusitis

ORAL CAVITY
- Dental erosions
- Aphtous ulcers
- Halitosis

PHARYNX/LARYNX
- Pharyngitis
- Posterior laryngitis, chronic laryngitis
- Vocal cord ulcers, granulomas, nodules
- Laryngeal, subglottic stenosis
- Laryngospasm
- Laryngitis stridulosa (croup)
- Malignancy
- Sore throat, excessive throat phlegm, frequent throat clearing
- Dysphonia
- Globus pharyngeus

TRACHEOBRONCHOPULMONARY TREE
- Tracheobronchitis
- Chonic cough
- Asthma
- Aspiration pneumonia
- Pulmonary Fibrosis
- Chronic bronchitis
- Bronchiëctasis

OTHER
- Sleep apnea
- SIDS
- Sandifer's Sx (torticollis)

In case of a causal association between GERD and ORL disorders, GERD patients would be expected to have a higher prevalence of ORL disorders than controls. In a recent case control study, comparing 101.366 patients with erosive esophagitis or esophageal stricture with 101.366 controls, El-Serag and Sonnenberg examined the relationship between esophagitis and various ORL disorders (Table 2). They found significant associations of GERD with laryngitis, laryngeal stenosis, dysphonia, sinusitis and pharyngitis (47).

Furthermore, pathophysiological mechanisms should explain how GERD causes or contributes to ORL disorders or how GERD and ORL disorders might interact. Gastroesophageal or supraesophageal reflux should be able to elicit or exacerbate the ORL disorder. The most convincing obtainable evidence for supraesophageal reflux consists of finding gastric juice constituents or proximal pH drops below 4 associated with esophageal

pH drops below 4. Indirect mechanisms, for instance the occurrence of reflex-mediated supraesophageal changes induced by distal esophageal acid exposure or distension, may also contribute. In such case, a close temporal association between (distal) esophageal reflux events and supraesophageal symptoms provides strong evidence of causation. Since the causes and exacerbating factors of various ORL disorders may be multifactorial, predictive values should identify subsets of patients who respond favourably to antireflux therapy and/or patients with an excellent response to acid suppressive maintenance therapy.

Table 2: **ORL disorders associated with esophagitis or stricture**

ORL disorder	Odds Ratio	95% CI
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

CI = confidence interval
El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997; 113: 755-60.

Finally, if GERD causes or contributes to ORL disorders, antireflux therapy should improve or even resolve these ORL disorders in many patients.

The following section provides a review on suspected reflux-related supraesophageal manifestations in ORL patients: clinical presentations, pathophysiology, diagnostic testing and therapy.

A. CLINICAL PRESENTATIONS

The most common clinical presentations of GERD-related ORL disorders or chronic symptoms include chronic laryngitis, hoarseness, cough, globus, sore throat, excessive throat phlegm and frequent throat clearing. Less common presentations include paroxysmal laryngospasm, laryngeal and subglottic stenosis and laryngeal carcinoma. More recently, a

possible causal association between GERD and commonly occurring ear and sinonasal problems has been explored.

Most frequently, a patient's history does not indicate reflux as the cause of ORL manifestations. Several authors have reported a low prevalence of classical reflux symptoms i.e. heartburn and/or regurgitation (6-43%) in patients with suspected GERD-related ORL manifestations (114, 148, 155). GERD in ORL patients without classical reflux symptoms may therefore be referred to as "occult" or "silent" GERD.

1. Chronic laryngitis, contact ulceration and contact granuloma

With repeated applications of gastric juice on the dog's posterior larynx, Delahunty and Cherry experimentally produced progressive posterior laryngeal inflammation, contact ulceration and finally, after 6 weeks, contact granuloma (27). Expanding on these early observations, most studies on possible GERD-related ORL disorders in humans focused on laryngeal disorders i.e. contact ulcerations, contact granulomas and chronic laryngitis.

In 1968, Cherry and Margulies reported on three patients with laryngeal contact ulcers and associated GERD, diagnosed by the acid barium test. On antireflux therapy, the contact ulcers disappeared and the larynx normalized (21). Ward and Berci demonstrated hiatal hernias in 20 of 28 patients with chronic laryngitis and contact granulomas and reported resolution or regression of granulomas on antireflux therapy in 26 patients (237). Wani and Woodson reported complete resolution of laryngeal contact granulomas on PPI therapy in 14 of 18 prospectively treated patients (236). In a recent prospective study, using 24-hour esophago-pharyngeal pH monitoring, comparing 26 contact granuloma patients with 19 healthy controls, Ylitalo and Ramel demonstrated that pharyngeal acid exposure was significantly more prevalent in patients with contact granuloma (256).

In 1972, Delahunty reported on 9 patients with "intractable" (refractory to conventional therapy) posterior laryngitis. All patients also had GERD, diagnosed by the acid barium test, and they improved significantly within 6 to 8 weeks following antireflux therapy (26). In 86 patients with chronic "aspecific" laryngitis, Ward and Berci reported a favourable response on antireflux treatment. However, upon cessation of antireflux therapy, the original symptoms recurred in two thirds of the patients. Most patients (80%) also had a hiatal hernia (237). Koufman found pathological reflux on 24-hour pH monitoring in 60% of 48 patients with chronic laryngitis; 17% had only pharyngeal reflux (114). Studies using simultaneous three-

site pharyngo-esophageal pH monitoring revealed that proximal esophageal and pharyngeal acid reflux are significantly more prevalent and the ratio of proximal to distal acid reflux episodes is significantly increased in posterior laryngitis patients compared to normal controls and typical GERD patients (188). A subsequent study also showed a higher prevalence of pharyngeal acid reflux in posterior laryngitis patients compared to healthy controls (222).

Symptoms that are most frequently associated with chronic laryngitis are hoarseness, sore throat, excessive throat phlegm, frequent throat clearing and cough (67, 146, 178).

On histopathological examination, posterior laryngitis is characterized by hyperplasia of the squamous epithelium and a chronic inflammatory infiltrate in the submucosa (100). As the disease process progresses, epithelial ulceration, formation of granulation tissue and submucosal fibrosis may be seen. Subsequently, a laryngeal contact granuloma may develop which consists of granulation tissue with an ulcerated surface (133). The histopathological features of posterior laryngitis and of contact granuloma are non-specific and the diagnosis of a reflux-related laryngeal disorder is based on the clinical history and localisation of the lesion.

2. Laryngopharyngeal symptoms

Suspected reflux-related chronic laryngopharyngeal symptoms, previously also referred to as "cervical symptoms", including sore throat, excessive throat phlegm, frequent throat clearing, hoarseness, globus and cough are not necessarily associated with laryngeal inflammation and the laryngeal examination may be normal in up to 50% of these patients (4, 114, 155).

Smit et al investigated 72 patients with chronic hoarseness and/or globus but without clear signs of posterior laryngitis or other laryngeal abnormalities. Pathological reflux (i.e. gastroesophageal reflux with or without gastropharyngeal reflux) was found in 18 of 25 patients (72%) with globus combined with hoarseness, in 8 of 27 patients (30%) with globus alone and in 7 of 20 patients (35%) with hoarseness alone. Seven (10%) of all 72 patients had prolonged acid exposure at the laryngopharyngeal junction in the presence of a normal gastroesophageal pH registration. Seventeen of 26 patients (65%) with pathological gastroesophageal reflux on pH monitoring (with or without gastropharyngeal reflux), had abnormal findings in the esophagus at endoscopy (esophagitis in 16 patients and Barrett's esophagus). Patients with complaints of both globus and hoarseness had the highest prevalence of pathological reflux as compared to patients with globus or hoarseness as a

solitary symptom. The authors strongly recommended upper g.i. endoscopy for symptomatic ORL patients with pathological gastroesophageal reflux (199).

3. Chronic hoarseness

Several studies addressed the relationship between chronic hoarseness and GERD. The prevalence of GERD in patients with hoarseness ranges from 55 to 79%. Mc Nally et al found abnormal pH monitoring results in 6 of 11 patients (55%) with chronic hoarseness, when no other cause could be identified on ORL clinical examination (131). Wiener et al found pathological pH-metry results in 26 of 33 patients (79%) with chronic hoarseness refractory to conventional therapy and laryngoscopic signs of laryngopharyngeal reflux (245). Katz found hypopharyngeal acid reflux in 7 of 10 patients with suspected reflux-related hoarseness, 3 of these patients had pharyngeal reflux without abnormal esophageal acid exposure (103). In contrast to the three previous studies which may be biased by the patient's inclusion criteria that consisted of the ORL specialist's suspicion of GERD because of failed conventional therapy or absence of other causes, Ness et al examined 28 consecutive ORL patients with hoarseness as a predominant symptom. Fourteen patients (50%) had pathological acid reflux and also 14 patients (50%) had esophagitis and hiatus hernia (144). Smit et al found pathological esophageal acid exposure in 7 of 20 patients (35%) with hoarseness but without clear laryngoscopic signs of posterior laryngitis (199).

4. Chronic cough

Irwin et al suggested that, using a diagnostic protocol based on evaluating the anatomical regions with the afferent pathways of the cough reflex, the cause of chronic cough can be found in nearly all patients. Following this protocol, postnasal drip (41%), asthma (24%) and GERD (21%) were the most frequently found causes of chronic cough (82). Fitzgerald et al reported that antireflux therapy completely relieved symptoms in 14 of 20 patients with chronic cough of unknown origin. Fifteen patients also had classical reflux symptoms (54). Batch and Thomson reported on seven patients with predominant nocturnal cough who had symptom relief following antireflux therapy (5). Using 24-hour pH monitoring, Koufman documented abnormal reflux in 13 of 25 patients (52%) with chronic cough of which 22% had only pharyngeal reflux (114).

Table 3 summarizes the outcome of medical antireflux therapy for reflux-related cough in adults.

Table 3: **Outcome of medical antireflux therapy for GERD-related cough**

Author	N	Intervention	RR (%)	Time to cough resolution
Irwin et al	28	Ls, H_2 and/or Pr	100	179 days
Smyrnios et al	20	Ls, H_2 +/- Pr	97	97 days
Vaezi and Richter	11	H_2 or PPI	100	53 days
Ours et al	17	PPI	35	14 days
Kiljander et al	21	PPI	unclear	improved at 56 days
Poe and Kallay	56	PPI +/- Pr	79	4 w (86%)/ 8 w (14%)

* Studies by Ours et al and Kiljander et al were double-blind placebo-controlled
N, number of patients; RR, response rate; Ls, antireflux lifestyle measures;
H_2, H_2 antagonist; +/-, with or without ;Pr, prokinetic agent; PPI, proton pump inhibitor;
w, weeks.

Coughing is associated with increased intra-abdominal pressure which may induce reflux. In the absence of simultaneous manometric assessment, pH monitoring does not exclude cough-induced reflux as a confounding factor. On the other hand a self-perpetuating feedback cycle between cough and GERD, where cough precipitates reflux and reflux elicits cough, has been proposed by several investigators (80).

5. Globus

A sensation of a lump in the throat is referred to as globus, globus sensation or globus pharyngeus. Globus is usually a constant symptom that does not interfere with swallowing and should not be confused with dysphagia. The symptom may be relieved by deglutition (for instance during a meal) and disappears during sleep.

Globus may be related to laryngoscopic findings suggestive of laryngopharyngeal reflux (i.e. posterior laryngeal edema and erythema and pharyngeal erythema) (254).

Globus sensation in patients with a normal ORL clinical examination has been linked to a variety of potential esophageal disorders including esophageal dysmotility, (i.e. achalasia and ineffective esophageal motility), a hypertensive upper esophageal sphincter and altered visceral afferent sensation (25, 49, 142).

Globus has also been related to gastroesophageal reflux disease. On upper gastrointestinal endoscopy in globus patients, Batch and Lorenz et al found esophagitis in 63% of 104 patients and in 47% of 51 patients respectively (4, 122). 24-hour pH monitoring studies show more variable results. While some authors reported a rather high prevalence of GERD ranging from 52% to 65% (4, 114, 215), others found GERD in only 14% (251) and 18% (156) of globus patients.

6. Other ORL disorders

- Paroxysmal laryngospasm

Paroxysmal laryngospasm (LS), defined as a prolonged and forceful adduction of the vocal folds resulting in glottic closure and airway obstruction, is considered an uncommon but severe and highly significant manifestation of GERD (114, 217). Laryngospasm (LS) is a vagally mediated reflex response of the larynx to noxious stimuli including gastric acid. Although a possible association between paroxysmal LS and GERD is suspected (114, 217) and successful outcome of antireflux treatment has been reported (123, 124, 140), very few studies prospectively investigated the role of GERD in LS-patients. Bortolotti reported severe pathological reflux on 24-hour pH monitoring in 2 LS-patients, with LS-episodes preceded by acid reflux in the proximal esophagus (9). The LS-episodes ceased on antireflux therapy. Loughlin and Koufman found pathological esophageal reflux on pH-metry in 6 of 12 LS-patients (50%) and hypopharyngeal reflux in 5 patients (42%). Using the barium esophagogram, esophagitis was demonstrated in 3 patients. Eleven of the 12 patients (92%) had findings establishing the presence of GERD. On antireflux therapy with omeprazole, paroxysmal LS resolved in all patients within 1 to 4 months (123).

- Laryngeal and subglottic stenosis

Although frequently related to endotracheal intubation, several authors reported an association between subglottic stenosis and GERD, most likely due to tissue injury, inflammation and complicated healing with fibrosis and scarring.

Gaynor documented hypopharyngeal reflux on 24-hour pH metry in 8 of 20 intubated patients (40%) in an Intensive Care Unit (61). Koufman found abnormal esophageal acid exposure in 23 of 25 patients (92%) with acquired laryngeal stenosis and 10 of 14 patients (71%) had pharyngeal reflux (114). These high prevalences of pathological reflux indicate that GERD

might be considered a primary cause of or an important contributor to the development of laryngeal stenosis following endotracheal intubation.

Bain et al reported the development of a subglottic stenosis in a 57-year old woman without a history of trauma, surgery or intubation. Her idiopathic subglottic stenosis resolved following Nissen-fundoplication and endoscopic laryngeal surgery (2). Jindal et al reported 7 patients with idiopathic subglottic stenosis who all had pathological reflux on 24-hour pH metry. Six patients had failed to respond to previous radical surgical intervention; their subglottic stenosis only resolved following surgery combined with antireflux treatment. In the seventh patient, the subglottic stenosis resolved on antireflux therapy only (89). Maronian et al found pharyngeal reflux in 5 of 7 patients (71%) with idiopathic subglottic stenosis (128).

- Laryngeal carcinoma

Nicotine and alcohol are well known risk factors in head and neck malignancies including laryngeal squamous cell cancer. Chronic laryngeal inflammation caused by GERD may also contribute to the development of laryngeal cancer. It is estimated that 10% of patients with chronic laryngitis eventually develop laryngeal cancer (57).

Morrison and Koufman each reported 6 patients and Ward and Hanson reported 19 patients with laryngeal cancers who never smoked and used no or minimal alcohol (114, 140, 238). All these patients had documented GERD on barium esophagogram, endoscopy or 24-hour pH monitoring.

Several authors, using 24-hour esophageal and laryngopharyngeal pH monitoring studies, demonstrated a high incidence of pathological reflux in laryngeal or hypopharyngeal carcinoma patients. Copper et al found abnormal reflux in the distal esophagus and/or at the level of the upper esophageal sphincter (UES) in 20 of 24 patients (83%) with laryngeal or pharyngeal squamous cell carcinoma. Esophageal acid exposure was pathological in 5 patients and acid exposure at the level of the UES was abnormal in 4 patients. Eleven patients had pathological reflux at both locations (24). Galli et al not only found pathological (distal and/or proximal) esophageal reflux in 17 of 21 patients (81%) with laryngeal or hypopharyngeal cancer but also observed laryngopharyngeal cancer in 4 patients with achlorhydria due to previous gastrectomy and suggested that biliary reflux might have contributed to the carcinogenesis in these patients (58). Lewin et al found laryngopharyngeal reflux in 85 % of 40 patients with early laryngeal carcinomas or dysplasia (118).

However, the results of a recent prospective controlled study comparing pH monitoring results in 40 laryngeal cancer patients and in 40 healthy volunteers did not support the

hypothesis of gastro-esophago-hypopharyngeal reflux as being an independent risk factor for laryngeal cancer. Pathological acid exposure, as compared with the upper levels of normality among the healthy volunteers, was found in the hypopharynx in only 6 laryngeal cancer patients (16%) and in the distal esophagus in 10 patients (25%). Only 1 patient (3%) had pathological acid exposure in both locations. The mean acid exposure time and the mean value of the number of reflux events did not differ significantly between cancer patients and control subjects at either location (63). On the other hand, in a recent case control study, El-Serag et al found a modestly increased risk for laryngeal or pharyngeal cancers in the presence of GERD. Using the hospitalization and outpatients databases of the US Department of Veterans Affairs, 8.228 hospitalized patients with laryngeal cancers and 1.912 with pharyngeal cancers were compared to 32.912 and 7.648 hospitalized controls while 9.292 outpatients with laryngeal cancer and 2.769 outpatients with pharyngeal cancer were compared to 37.168 and 11.076 outpatient controls without cancer. In a multivariate logistic regression that was controlled for age, gender, ethnicity, smoking, and alcohol, GERD was associated with an adjusted odds ratio (OR) of 2.40 for laryngeal cancer among hospitalized patients (95% CI 2.15-2.69, $p<0.0001$) and an adjusted OR of 2.38 (95% CI 1.87-3.02, $p<0.0001$) for pharyngeal cancer. For outpatients, GERD was associated with an adjusted OR of 2.31 (95% CI 2.10-2.53) for laryngeal cancer and an adjusted OR of 1.92 (95% CI 1.72-2.15) for pharyngeal cancer (44).

- 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 found high concentrations (up to a 1000-fold greater than in serum) of pepsin/pepsinogen in 59 of 65 middle ear effusion samples (91%) from children with OME. The authors concluded that reflux of gastric juice into the middle ear may be the primary factor in the initiation of OME (212).

- Chronic sinusitis

Like GERD, chronic sinusitis is a common clinical condition. A possible causal association between GERD, chronic nasal symptoms and chronic sinusitis has been increasingly suggested, both, in children and in adults (10, 23, 33, 35, 121, 163, 221). Retrospective (10, 33) as well as prospective (35, 163) studies not only showed a high prevalence of GERD and of gastro-esophago-pharyngeal reflux (GEPR) in particular, but also improvement of sinus symptoms on antireflux therapy in patients with chronic sinusitis.

In a retrospective study on the outcome of antireflux therapy in pediatric chronic sinusitis, Bothwell et al. reported that 25 of 28 children (89%), who were believed to be appropriate candidates for sinus surgery, responded favourably with regard to their sinus symptoms following medical antireflux therapy and avoided sinus surgery during the follow up period of two years. Twenty-two of 26 patients (85%) who initially underwent 24-hour pH monitoring, had abnormal reflux (10). In consecutive children with chronic sinusitis, Phipps et al prospectively assessed the prevalence of GERD and nasopharyngeal reflux using pH-metry; they also evaluated the response of sinusitis to antireflux therapy in those diagnosed with GERD. Nineteen of 30 patients (63%) had abnormal esophageal reflux while 6 of these 19 patients (32%) also had nasopharyngeal reflux. Fifteen of 19 patients (79%) improved on antireflux treatment (163). The authors of both studies recommended that children with chronic sinusitis, refractory to aggressive conventional medical management, should be evaluated for GERD and, when GERD is present, should be treated accordingly before considering sinus surgery.

In a recent prospective study, DiBaise et al. found abnormal reflux on pH metry in 9 of 11 adult patients (82%) with chronic resistant sinusitis (all patients had previously undergone sinus surgery). These pH-metric findings were similar in a control group of 19 GERD patients. On antireflux therapy with omeprazole b.i.d. for 3 months, individual sinus symptoms and global satisfaction were modestly improved in 25-89% and 91% respectively (35).

In a large case control study, El-Serag and Sonnenberg found that adults with erosive esophagitis were more likely to have sinusitis than were the controls (see Table 2) (47). In another case control study, children with GERD also had an increased risk for sinusitis compared to controls (Odds Ratio, 2.3; CI 1.7-3.2; $p< 0.0001$) (46). Furthermore, Chambers et al found that GERD was a predictor of poor symptomatic outcome after sinus surgery (17). Finally, Ulualp et al. reported that the prevalence of GEPR on 24-hour pH monitoring is significantly higher in adult patients with chronic sinusitis unresponsive to conventional therapy compared to normal controls (7 of 11 patients had GEPR vs 2 of 11 normal controls; $p< 0.05$) (221). These findings suggest that GERD and GEPR in particular may contribute to the pathogenesis of chronic sinusitis, most likely by causing sinonasal edema and compromised sinus drainage via the osteomeatal complex, ultimately leading to inflammation (35).

B. PATHOPHYSIOLOGY

GER or its effects may extend beyond the esophagus, thereby potentially causing or contributing to a wide variety of supraesophageal manifestations (47, 169).

Reflux of gastric contents beyond the esophagus into the pharynx, referred to as gastro-esophago-pharyngeal reflux (GEPR), is considered the most important causal mechanism in the pathophysiology of reflux-related supraesophageal manifestations. A second mechanism may consist of vagally-mediated reflexes, elicited from the esophagus through reflux-related esophageal distension or acid-related esophageal sensory stimulation (169).

Several animal and human studies indicate the importance of direct acid injury to the mucosa of the larynx and airways.

Animal studies found that intermittent application of gastric juice over 2 to 4 weeks caused laryngeal injury, inflammation and complicated healing (27, 119). Delahunty and Cherry, who produced vocal fold granulomas experimentally in 1968, did so within 4 weeks by applying gastric juice on the dog's posterior larynx, particularly on the lateral part with the vocal processes, for only 30 min/d, 5 d/wk, with no exposure over the weekends. They produced erythema within the first week that did not resolve over the weekend at the end of the second week. Subsequently, ulceration and granulomas were produced (27). Simulating the potential situation of the intubated patient, Little and Koufman et al. created injury to the subglottic mucosa in a dog model and subsequently produced severe stenosis within 2 weeks by applying gastric juice on the injured subglottic region for only 1 min/d, every other day. Subglottic stenosis was more pronounced with gastric juice solutions at low pH (pH 1.3 and 1.9 compared to pH 2.9) (119). Interestingly, in a subsequent similar experiment by the same investigator, no subglottic stenosis was produced within 2 weeks with applications of "synthetic" gastric juice solutions (hydrochloride at different pH with porcine pepsin) (114). These results might suggest that, in the initial experiment, substances of gastric juice other than acid and pepsin could have enhanced the noxious effects of acid and pepsin on the injured subglottis resulting in stenosis. Wynne et al, using scanning electron microscopy, demonstrated that even a single instillation of gastric juice at acidic pH (1.5) in the mouse trachea caused extensive mucosal desquamation with almost complete loss of ciliated and non-ciliated epithelium within 6 hours, persisting for at least 3 days; delayed regeneration was seen at 7 days. This model for acute severe tracheobronchitis, following aspiration of a gastric

juice amount that is too small to induce a clinically significant pneumonia, shows that the character of the tracheal injury and the time course of the regeneration are similar to the scanning electron microscopy findings after murine influenzal tracheitis (255). In addition to these direct noxious effects upon laryngeal and upper airway mucosa, gastric juice may also interfere with mucociliary clearance, potentially affecting bacterial clearance and adherence and compromising local immunity, thereby contributing to an increased risk for opportunistic airway infections. Brief (60 seconds) instillation of the rabbit trachea with solutions of HCl and pepsin at different pH had a direct inhibitory effect on mucociliary flow (MCF) with a gradual slowing of MCF from pH 5 to pH 3 and complete cessation of MCF at pH 2 (61). Similar effects on mucociliary clearance in the middle ear and eustachian tube dysfunction were found in rats after 7 days of repeated nasopharyngeal infusions with HCl and pepsin (242).

The larynx, pharynx and airways are not protected by the clearance mechanisms and intrinsic mucosal properties present in the distal esophagus. Because of this work in experimental animals, many gastroenterologists, ORL specialists and pulmonologists assume that even a single episode of acid reflux beyond the esophagus may be sufficient to cause substantial laryngeal and tracheal injury and inflammation and may complicate or delay subsequent healing (114). A single supraesophageal acid reflux episode may also activate reflexes including swallowing, cough, glottic closure and laryngospasm (123).

Using combined esophago-pharyngeal pH monitoring, acid GEPR has been demonstrated in numerous patients with reflux-related supraesophageal manifestations (114, 145, 186, 188, 221). In an ambulatory 24-hour simultaneous three-site pharyngo-esophageal pH monitoring study by Shaker et al, 14 reflux laryngitis patients were studied and compared to 3 different control groups (healthy volunteers; esophagitis patients without laryngeal symptoms; patients with laryngopharyngeal symptoms but without laryngoscopic abnormalities). Distal acid reflux parameters were similar in all groups but laryngitis patients had a significantly higher percentage of distal reflux episodes reaching the proximal esophagus, more pharyngeal reflux episodes and a significantly higher time of pharyngeal acid exposure. Significantly more pharyngeal reflux occurred in the upright position than in the supine position. These findings indicate that daytime, upright pharyngeal reflux is the most prevalent reflux pattern in reflux laryngitis patients and that pathological distal esophageal reflux parameters are not a prerequisite for the development of reflux laryngitis (188).

Results of combined esophago-oropharyngeal (186), esophago-nasopharyngeal (163) and of esophago-tracheal (84) pH monitoring have shown that acid GEPR may further extend into

the oropharynx, the nasopharynx and the trachea. The recent finding of high concentrations of pepsin/pepsinogen in middle ear effusion samples from children with otitis media with effusion (OME), led the authors to conclude that gastric juice refluxes from the nasopharynx, through the eustachian tube, into the middle ear and may be the primary factor in the initiation of OME (212).

Other motility and pH studies in humans may also contribute to better understanding the pathophysiology of reflux-related ORL symptoms and disorders. Kahrilas et al demonstrated that UES pressure in healthy volunteers may decrease dramatically during sleep to values below 10 mm Hg. This UES relaxation, together with a sleep-related decrease in salivation and a 25-fold decrease in the swallowing rate, potentially leaves the laryngopharynx less protected to reflux-episodes during sleep and may help to explain the occurrence of nocturnal reflux-related supraesophageal symptoms in some patients, as well as the frequently reported phenomenon of these symptoms being worse early in the morning (96). In 40 patients with a GERD-diagnosis, based on the finding of pathological distal esophageal acid exposure, the same investigators performed dual channel esophageal pH monitoring (85). While none of the control subjects had abnormal proximal reflux, 13 of 25 patients (52%) with laryngeal symptoms, regardless of laryngoscopic findings, had pathological proximal acid reflux at night. Results from this study suggest that intermittent nocturnal proximal reflux may be an important cause of reflux-related ORL manifestations. On the other hand, periods of transient low UES resting pressure during which acid reflux may overcome the UES and reach the laryngopharynx, also occur during the day. The UES may relax spontaneously, with fatigue, during belching, at the initial stage of deglutition, during coughing and during changes in position (96, 188).

Esophageal motility disorders with impaired acid clearance may also contribute to GER-related ORL disorders.

A second mechanism may consist of reflexes, elicited from the esophagus by stimulation of vagal afferent nerves through acid contact or esophageal distension during reflux-episodes (169). A potential role for this mechanism in causation of ORL symptoms such as hoarseness, throat clearing or globus remains to be established. In a pig model, esophageal acid perfusion and balloon distension evoked an increased electromyographic (EMG) contractile activity in the thyroarytenoid (TA) muscle, the most powerful laryngeal adductor muscle that causes glottal closure. The authors suggested that this mechanism might contribute to hoarseness in patients with apparently normal larynges on laryngeal examination (64).

Both mechanisms, direct acid contact with the airway mucosa or reflexes elicited from the esophagus through stimulation of vagal afferent nerves, may cause or contribute to cough or bronchial constriction. Animal experiments have demonstrated the deleterious effects of acid on the bronchopulmonary tree by both mechanisms (125, 219). Gastroesophageal reflux episodes may elicit cough or bronchial constriction by stimulating a vagal reflex arc that extends from the esophagus to the bronchopulmonary tree (126).

C. DIAGNOSTIC TESTING

Reflux may be assessed by a variety of diagnostic tests. Currently, the laryngoscopic examination, 24-hour pH monitoring and an empiric trial with a PPI are considered the most important tests for diagnosing GERD in patients with suspected reflux-related ORL disorders. Upper gastrointestinal (g.i.) endoscopy and esophageal manometry are less commonly used in the initial diagnostic work up of ORL patients with suspected GERD.

1. Laryngoscopic evaluation

The most common reflux-related laryngeal abnormalities are confined to the posterior larynx and include edema 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). When severe, the edema and erythema may extend over the entire larynx. Mild, diffuse, non-specific laryngitis is also commonly present. Other, less common findings include laryngeal contact ulcers and granulomas (178).

However, the laryngoscopic evaluation is normal in many patients with reflux-related laryngopharyngeal symptoms. Although some early studies reported no laryngeal abnormalities in a majority of patients (4, 155), later studies found that 50% or more of the patients have laryngoscopic signs suggestive for GERD (114).

Most studies on the effects of antireflux treatment for suspected reflux-related ORL disorders reported a substantial reduction or disappearance of symptoms together with or followed by a marked reduction or disappearance of posterior laryngeal edema and erythema. These laryngeal signs are presently regarded to as clinical signs suggestive of reflux laryngitis.

Several authors, using different laryngeal visualisation techniques and laryngeal reflux scoring systems (7, 101) have attempted to develop guidelines for the diagnosis and

monitoring of reflux laryngitis. Still, controversy persists regarding sensitivity, specificity and inter- and intra-observer reliability of laryngoscopic findings.

The specificity of the above described and other laryngoscopic findings have been recently challenged. In 105 normal, healthy volunteers, Hicks et al found that the majority of subjects (86%) had laryngoscopic findings associated with reflux and certain signs reached a prevalence of 70%; a need for improved diagnostic specificity was highlighted (75). In a study by the same investigators, laryngoscopic findings of posterior cricoid wall erythema, true/false vocal fold erythema and edema and arytenoid medial wall erythema/edema were significantly more frequently detected in patients suspected of reflux injury than in normal controls. Importantly, these signs improved or resolved on acid suppressive therapy (223). These findings highlight the existing confusion on the role of the laryngeal findings in the diagnosis of supraesophageal reflux.

2. 24-hour ambulatory esophageal pH monitoring

Ambulatory 24-hour pH monitoring with a double or dual channel pH probe (one probe in the distal esophagus and a second probe in the proximal esophagus just below the UES, in the UES or in the hypopharynx) is considered the most sensitive test for the diagnosis of supraesophageal reflux in patients with suspected GERD-related ORL disorders (178, 188).

The distal esophageal pH probe is placed 5 cm above the upper level of the LES, as determined by esophageal manometry. Distal acid exposure times, for which normal values are available, can be quantified (90, 210). When pathological distal acid reflux is found, a GERD diagnosis is established.

Several investigators have placed a proximal probe above the UES in the hypopharynx, thus increasing the likelihood of supraesophageal reflux as the cause of ORL disorders (103, 114). Up to 30% of patients with suspected reflux-related ORL disorders have normal distal esophageal acid exposure but show reflux into the hypopharynx. Katz found one or more hypopharyngeal reflux-episodes in 7 of 10 patients with suspected reflux-related hoarseness. Three of these 7 patients had normal esophageal acid exposure and reflux frequency, but hypopharyngeal reflux was associated with these few esophageal reflux episodes (103). Koufman found pathological esophageal acid exposure in 62% of 197 patients with suspected reflux-related ORL disorders. Hypopharyngeal reflux was found in 30% of 160 patients; 11%

of this group had normal distal esophageal acid exposure. It was concluded from this study that a considerable day-to-day variation in acid laryngopharyngeal reflux exists and that the patients with the most severe mucosal damage (i.e. laryngeal carcinoma and laryngeal stenosis) also had the highest prevalence of hypopharyngeal reflux (114). Although initial studies suggested that hypopharyngeal monitoring for acid reflux is the most sensitive test for identifying patients with GERD-related ORL disorders (114), there are several difficulties with pH monitoring in the pharynx. The placement renders standardizing the distance between the proximal and distal probes more difficult, and unless two separate pH electrodes are used, causes variability in placement of the distal esophageal probe 5 cm above the LES, the standard position for developing normal values. Probes in the hypopharynx can be uncomfortable and may be occasionally subject to interpretation errors, including incorrect diagnosis of reflux due to probe drying resulting in a drop of pH <4 that is referred to as "pseudoreflux" (18, 98, 244). In contrast, a "true" pharyngeal reflux episode will always occur simultaneously with a reflux episode in the distal esophagus. In addition, the relatively large volume of the hypopharynx may also increase the potential for a small volume of reflux to be missed, leading to a false negative reading (66, 98). Esophageal pH criteria are validated criteria for establishing a diagnosis of GERD as endoscopic esophagitis correlates well with acid exposure and typical symptoms have a high specificity and an acceptable sensitivity for GERD (107). Validation of pharyngeal pH criteria in diagnosing acid reflux-related supraesophageal disorders seems much more problematical as posterior laryngitis is non-specific for acid injury and laryngopharyngeal symptoms may have several causes. While the true prevalence of gastro-esophago-pharyngeal reflux (GEPR) in patients with chronic laryngitis remains unknown, the frequency of GEPR-episodes that may be considered pathological remains to be established. A single pharyngeal acid reflux episode may not be interpreted as pathogenetic evidence. The mere entry of gastric contents into the pharynx does not implicate contact with the laryngeal mucosa as laryngeal protective reflexes i.e. the esophagoglottal and pharyngoglottal closure reflex and pharyngeal swallowing may prevent this from happening (166, 187-189).

In order to evaluate proximal reflux, several investigators prefer placement of the proximal pH probe in the upper esophagus, 20 cm above the LES (85, 178). With this technique, however, the proximal probe has a variable distance to the UES. Placement of the proximal pH electrode under laryngoscopic vision, as described by Smit et al., may help standardize the

proximal recording site and the pH data obtained at this location without the need of a preceding mapping of the UES by manometry (200).

As supraesophageal reflux is frequently intermittent in nature, a negative pH study does not rule out supraesophageal reflux as a cause of suspected reflux-related ORL disorders (114, 169). Vaezi et al. assessed the reproducibility of proximal esophageal pH monitoring and performed dual channel pH probe studies on 2 separate days in 11 patients with suspected GERD-related ORL disorders. The diagnosis based on distal reflux parameters was reproducible in 9 of 11 patients (82%), whereas only 6 of 11 patients (55%) had reproducible proximal pH values (230). These results further underscore that proximal reflux in patients with suspected GERD-related ORL disorders is often intermittent, contributing to a considerable day-to-day variability of proximal pH monitoring.

During pH metry, the patient may be asked to indicate the occurrence of symptoms by pressing an event marker button on the pH-data collector device. This allows correlation of acid reflux events with symptoms; when a close temporal relationship is found, this provides strong evidence for causation. Symptom correlation is considered a valuable diagnostic tool in patients with heartburn, chest pain, cough and asthma. The ORL patient, however, may frequently have chronic symptoms, such as sore throat and hoarseness which are continuous and not produced by a single reflux event. Other symptoms such as throat clearing, cough or laryngospasm may be correlated with single reflux episodes.

3. Empirical treatment trial

A therapeutic trial of antireflux therapy consisting of a high dosed PPI combined with lifestyle and dietary modifications for 8 to 12 weeks has been proposed as an initial diagnostic test in patients with suspected reflux-related ORL symptoms (178). A trial with empiric omeprazole 40 mg at bedtime for 8 weeks found a favourable response in laryngeal symptoms in 14 of 21 patients (67%) with posterior laryngitis (252). In a trial with empiric omeprazole 20 mg b.i.d for 1 month, laryngeal symptom resolution occurred in 6 of 10 patients with reflux laryngitis (132). A trial with esomeprazole 40 mg daily for 8 weeks was conducted in 30 patients diagnosed with laryngopharyngeal reflux and patients were re-evaluated for their laryngeal and esophageal symptoms after 4 weeks and 8 weeks. After 4 weeks of treatment, 8 of 30 patients had significant improvement in laryngeal symptoms while 11 of 18 patients

improved on esophageal symptoms. After 8 weeks of treatment, 18 of 30 patients improved on laryngeal symptoms and 13 of 18 patients had significant improvement on esophageal symptoms. Five of 7 non-responders who were tested had positive findings on pH studies (on medication regimen) at 1 cm above the UES. Four of 10 non-responders improved further after increasing their dosage to 40 mg b.i.d.. Laryngeal examination scores were statistically improved in responders after 8 weeks of treatment. The authors concluded that a treatment period of at least 8 weeks is required for significant improvement in laryngopharyngeal reflux symptoms in the majority of patients; esophageal symptoms improved sooner (28).

4. Upper gastrointestinal endoscopy

Existing data on the use of upper g.i. endoscopy in ORL patients are limited and the results are conflicting. This will be further addressed in Chapter 5.

5. Esophageal manometry

Esophageal manometry is currently considered of limited usefulness in the initial diagnostic work up of ORL patients with suspected GERD. Esophageal manometry quantifies LES pressure and may detect abnormalities in primary esophageal peristalsis.

Manometry may not only demonstrate a too low LES resting pressure, allowing "free" reflux to occur, but may also detect esophageal motility abnormalities. The most common finding in patients with GERD appears to be ineffective esophageal motility (IEM) (amplitude of contraction in the distal esophagus less than 30 mm Hg occurring with 30% or more of water swallows) and may be found in approximately 35 % of patients with esophagitis (117). IEM is frequently associated with delayed acid clearance and may in this way contribute to esophagitis and reflux-related supraesophageal manifestations. While some investigators found a higher prevalence of IEM in supraesophageal reflux disease and suggested that IEM may be a marker for GERD and for supraesophageal reflux disease in particular (55, 109), other investigators found no significant difference in the prevalence of IEM in patients with classical GERD or with supraesophageal reflux disease and concluded that IEM does not stand alone as a significant marker for the presence of GERD in general or supraesophageal reflux disease in particular (34, 234).

When antireflux surgery is considered, manometry is often performed to evaluate contraction amplitude in the esophageal body. In patients with normal peristalsis, the surgeon will usually

perform a Nissen-fundoplication (360° wrap) while a Toupet procedure (240° wrap) may be preferred in patients with IEM.

D. ANTIREFLUX THERAPY

Most studies on therapy in patients with suspected reflux-related ORL symptoms and disorders to date are not placebo-controlled and not randomized.

McNally et al. treated 11 patients with chronic hoarseness with ranitidine 150 mg b.i.d. during 12 weeks. Esophagitis, initially present in six patients, improved in all but hoarseness improved in only one patient (131). Other studies reported better results. Koufman treated 123 ORL patients with an escalating dose of ranitidine up to 300 mg t.i.d. for 6 months; symptoms resolved in 104 patients (85%) (114).

Kamel et al. treated 16 patients with chronic laryngitis, refractory to H_2 blockers, with omeprazole 40 mg/day for 6 to 24 weeks (4 patients with persisting laryngitis after 6 weeks were subsequently treated with omeprazole 40 mg b.i.d.). Laryngeal inflammatory signs and symptoms disappeared or were markedly reduced on omeprazole therapy but recurred following cessation of acid suppressive therapy. At the onset of omeprazole therapy, only 3 patients also had esophagitis and typical reflux symptoms; these esophageal symptoms responded faster and more completely to omeprazole than the laryngeal symptoms (101). Jaspersen et al. found chronic laryngitis in 32 of 89 consecutive patients (36 %) with esophagitis (grades 1 and 2). These patients were treated with omeprazole 20 mg/day. After 2 weeks, esophagitis healed in 19 patients (59%) while chronic laryngitis had disappeared in only 12 patients (37%). After 4 weeks, both esophagitis and laryngitis had disappeared in all patients (88). Both studies indicate that, on omeprazole therapy, laryngitis heals more slowly than esophagitis. Treating chronic laryngitis may therefore require longer duration of therapy and in some patients also higher dosing of PPI's than is needed for the treatment of esophagitis.

Hanson et al. performed the most exhaustive study on the treatment of suspected reflux-related chronic laryngitis in 182 consecutive patients (67). Symptoms most frequently associated with chronic laryngitis included chronic or recurring sore throat, frequent throat clearing, feelings of postnasal drip, hoarseness and cough. In these patients, a gradual ("step-up") therapeutic approach was used which started with nocturnal antireflux measures including the avoidance of meals and drinks for 3 hours before going to sleep and elevation of

the head end of the bed with 8 to 10 inches. The outcome measures were resolution of symptoms and improvement of laryngitis. After 6 to 12 weeks, symptoms resolved on nocturnal antireflux lifestyle measures alone in 93 patients (51%). In the other patients, famotidine 20 mg at bedtime was added to these lifestyle measures; symptoms resolved within 6 weeks in an additional 48 patients (77% incremental therapy response; in % of the total group). Thirty-four of the remaining 41 patients experienced symptom relief with omeprazole (20 mg at bedtime; 4 patients required 40-80 mg/day) (98% incremental therapy response; in % of the total group). In the other 5 patients symptoms eventually resolved following fundoplication surgery. In general, the ORL symptoms responded more slowly than the typical esophageal reflux symptoms and frequently required 6 to 12 weeks for improvement. In most patients, a relationship existed between the severity of their laryngeal signs and the response to therapy. While patients with mild findings on laryngeal examination (erythema) most frequently responded to nocturnal antireflux lifestyle measures and famotidine, patients with moderate to severe findings (marked erythema, stasis of secretions, ulceration, granuloma, hyperkeratosis) tended to require more aggressive treatment with omeprazole or antireflux surgery in some of them. Patients in need of omeprazole more frequently had recurrence of symptoms following cessation of therapy; symptoms only disappeared again with renewed omeprazole-intake. These findings also indicate a dose-response relationship which in addition to the favourable outcome of antireflux therapy, further supports a causal relation between GERD and chronic laryngitis (67). Shaw et al. evaluated videolaryngostroboscopy and acoustic voice-analysis in 68 patients with suspected reflux laryngitis before and after treatment with omeprazole during 12 weeks. While symptoms disappeared or were markedly reduced in 85% of these patients, a significant improvement in the laryngoscopic findings of edema, erythema, granular mucositis and ulceration (but not granuloma) was also noted (190). While omeprazole appears effective and superior to H_2 blockers in the treatment of moderate to severe reflux laryngitis in most patients, some patients have been reported with laryngitis refractory to high doses (80 mg) of omeprazole due to "omeprazole resistance" and ongoing acid reflux (11).

A recent study in patients with laryngoscopic abnormalities suggestive for acid reflux and respiratory symptoms indicated that pharyngeal pH monitoring seemed more relevant in confirming a suspected diagnosis of supraesophageal reflux in patients with severe laryngoscopic abnormalities than in patients with less severe or no laryngeal abnormalities (147).

Very few randomized placebo-controlled studies evaluated the efficacy of antireflux medical treatment on reflux laryngitis. In a study by El-Serag et al., 6 of 12 patients (50%) receiving lansoprazole 30 mg b.i.d. during 3 months had complete resolution of laryngeal symptoms compared to only 1 of 10 patients (10%) in the placebo group ($p = 0.04$). The authors concluded that empirical PPI treatment can be considered a first line option in the management of patients with idiopathic chronic laryngitis (45). In two other randomized placebo-controlled studies patients with reflux laryngitis symptoms were selected on the basis of pharyngeal pH monitoring criteria. In 14 patients who participated in all parts of a crossover trial, Eherer et al. found marked improvement in symptoms and laryngitis scores in both treatment groups (placebo or pantoprazole 40 mg b.i.d., each during 3 months separated by a 2-week wash out period) and concluded that the self-limited nature of reflux-associated laryngitis in non-smokers is largely underestimated. Laryngitis symptoms improved despite the persistence of reflux and the advantage of long term PPI treatment over placebo appears to be largely overestimated (42). Over a 2 months period, Noordzij et al. treated 30 patients with one or more reflux laryngitis symptoms and more than 4 pharyngeal reflux episodes. Most symptom scores improved over time for both the omeprazole (40 mg bid) and placebo group. Although a placebo effect appears to exist in the treatment of reflux laryngitis, throat clearing and hoarseness, when initially scored low, improved significantly more in patients on omeprazole. Endoscopic laryngeal signs did not change significantly over the course of the study for either patient group (146).

Antireflux surgery may be considered in some patients with reflux-related ORL disorders, especially in those with severe GERD in which continuous PPI therapy is needed to control symptoms. Waring et al agressively treated 27 patients with severe typical GERD and associated cough and hoarseness. Six patients took omeprazole 20 to 40 mg daily and 21 patients underwent laparoscopic antireflux surgery, most frequently the Nissen fundoplication. Cough or hoarseness improved in 20 of the 25 patients (80%) and resolved completely in 9 patients (36%). The response of heartburn to therapy was strongly predictive of successful therapy for cough and hoarseness. Both symptoms improved in only 2 of the 5 patients with residual heartburn symptoms compared to 18 of 20 patients with no heartburn (240). Two prospective uncontrolled studies evaluated the efficacy of Nissen fundoplication in patients with GERD-related laryngeal disorders. Deveney et al. evaluated 13 consecutive patients with symptomatic chronic laryngitis including 6 patients with leukoplakia of the vocal cords and 5 patients previously treated for laryngeal carcinoma. All patients had

objective evidence for GERD and were refractory to previous treatment with H_2 blockers. Symptoms and laryngeal abnormalities resolved in 8 of 11 patients (73%) available for follow up after 11 months (32). So et al. studied 35 consecutive patients with predominant atypical GERD (i.e. pulmonary and laryngopharyngeal symptoms and non-cardiac chest pain) who underwent Nissen fundoplication. Most of these patients had pharyngeal reflux on pH metry. Most patients (86%) also had heartburn requiring antacids and 36% had evidence of esophagitis. Over a follow up period of at least 12 months, 93% of the patients were relieved of heartburn, and symptom improvement, although to a lesser degree than for heartburn, was reported for 78% of laryngeal symptoms, 58% of pulmonary symptoms and 48% of epigastric/chest pain symptoms. A symptom response to pre-operative acid suppressive therapy appeared an important predictor for post-operative symptom improvement (203).

CHAPTER 3: GENERAL OUTLINE AND AIMS OF THE STUDY

Gastroesophageal reflux disease (GERD) and ORL disorders both commonly occur in the general population. These disorders therefore may simply coexist without a direct relationship. Although a possible causal association between GERD and several ORL disorders is increasingly suspected, many aspects of the relationship between both remain incompletely understood. The clinical spectrum of reflux-related ORL disorders is likely to be incompletely determined, and a possible role of GERD in several ORL disorders has not been explored. Multiple aspects of the pathophysiology of GERD-related ORL disorders remain unclear. Finally, the role of diagnostic testing and several management aspects in these patients remain to be established.

In a series of studies in patients with suspected GERD-related ORL symptoms, we aimed at answering the following issues:

1. It is often stated that erosive esophagitis is a rare finding in ORL patients with suspected underlying GERD. However, critical evidence is lacking in the literature.
2. In patients with suspected reflux-related ORL disorders a high dosed proton pump inhibitor trial is frequently advocated during at least 3 months prior to re-evaluating the patient's therapeutic response. It is incompletely established whether such a long duration of PPI therapy is really required in the majority of ORL patients with suspected reflux-related disorders, and shorter treatment intervals have insufficiently been evaluated.
3. It is unclear whether patients with reflux-related ORL disorders have a more delayed acid clearance function of the esophagus, which might contribute to proximal extension of the reflux and ORL disorders.
4. As the reported prevalence of heartburn is low in patients with suspected reflux-related ORL disorders, it has been suggested that these patients may have decreased acid sensitivity of the esophageal mucosa.
5. The role for prolonged pH monitoring in the proximal esophagus as a diagnostic test in patients with suspected GERD-related ORL symptoms has not been established.
6. A possible contribution of duodeno-gastro-esophageal reflux (also called "bile reflux") in the pathophysiology of reflux related ORL disorders has not been studied.
7. A possible role for gastroesophageal reflux in chronic ear complaints and chronic secretory otitis media in adults has not been demonstrated.

8. Animal experiments indicate that laryngeal acid exposure evokes laryngospasm. It has been suggested, but not established, that paroxysmal laryngospasm in man is a GERD-related disorder.

More specifically, we want to address the following questions:

1. What is the true prevalence of esophagitis, Barrett's esophagus and upper g.i. abnormalities at endoscopy in consecutive ORL patients with chronic unexplained refractory symptoms compared to endoscopic findings in heartburn patients?
2. What is the response to medical antireflux therapy with a PPI in these patients?
3. Is ambulatory proximal esophageal pH monitoring a clinical useful tool in the diagnosis of suspected reflux-related supraesophageal symptoms? To determine whether abnormal proximal reflux is more prevalent in patients with suspected reflux-related supraesophageal symptoms, characteristics of patients with and without abnormal proximal reflux in dual pH monitoring studies will be compared.
4. Which parameters of distal esophageal reflux and esophageal motility will determine the presence of abnormal proximal reflux? Do patients with more distal acid reflux also have more proximal esophageal reflux? Do patients with pathological distal esophageal DGER have more proximal esophageal reflux?
5. Do patients with suspected reflux-related ORL symptoms have normal esophageal sensitivity to acid perfusion and what is their proximal and distal esophageal acid clearance function compared to healthy controls and heartburn patients?
6. What is the prevalence of GER, assessed with upper g.i. endoscopy and pH monitoring, in consecutive patients with a chronic refractory feeling of pressure in the ear(s)? What is their response to antireflux therapy with a PPI?
7. What is the prevalence of GER, assessed with upper g.i. endoscopy and pH monitoring, and of DGER, assessed with fiberoptic bilirubin monitoring, in consecutive patients with chronic refractory complaints of excessive throat phlegm? Is the colour spectrum of throat phlegm related to GER and DGER? May DGER also occur in the proximal esophagus and what is the composition of throat phlegm? What is the response of these complaints to antireflux therapy with a PPI?
8. What is the prevalence of GER, assessed with upper g.i. endoscopy and pH monitoring, and of DGER, assessed with fiberoptic bilirubin monitoring, in consecutive patients with paroxysmal laryngospasm. Are laryngospasm episodes associated with simultaneous esophageal acid reflux episodes? What is the response of paroxysmal laryngospasm to antireflux therapy with a PPI?

CHAPTER 4: MATERIALS AND METHODS

The methods described in this section have been applied in several clinical studies. Materials and details specific to a study are described in their respective chapters.

A. Clinical studies

1. Patient selection

Consecutive patients with chronic "refractory" unexplained ORL symptoms and/or disorders, considered to be possible manifestations of EER, were referred from the ORL outpatient clinic to the department of Gastroenterology. Before referral, other apparent causes of their ORL symptoms had been ruled out (i.e. allergy, chronic upper respiratory tract infection, tumour, bronchopulmonary, cardiovascular and neurological disease). Even though these patients had not been treated for GERD, they are called "refractory" from a strict (ORL) point of view, as previous "conventional" medical therapies (i.e. antihistamines, antibiotics and corticoids) and/or surgical treatments (i.e. tonsillectomy, middle ear surgery, nasal and sinus surgery) had only led to short term or incomplete improvement or no improvement at all. None of the patients were on acid suppressive medication during at least 6 months before the first ORL consultation and before referral to the department of Gastroenterology.

2. ORL assessment

All ORL patients were seen by one of the authors (JP) and had a careful history taking including an extensive symptom questionnaire covering most classical, atypical and suspected reflux-related supraesophageal symptoms to assess symptom frequency and severity. The severity of 60 different ORL and reflux symptoms was graded as absent (0), mild (1), moderate (2) or severe (3) by the patient. Patients were also asked to identify their predominant symptom. The frequency of symptoms was scored as absent (0), less than monthly (1), weekly (2) or daily (3). They also underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy.

3. Upper gastrointestinal endoscopy

All patients underwent upper g.i. endoscopy during which the presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the modified classification of Savary-Miller, which served as a basis for antisecretory drug reimbursement in Belgium (149, see also Chapter 1, section **D.***1*). The mucosa was graded as esophagitis if one or more mucosal breaks with erosions and/or ulcerations were present and as Barrett's esophagus when at least 1 cm of columnar epithelium was present in the distal esophagus and confirmed by biopsies. A hiatal hernia was diagnosed if >2 cm of gastric mucosa appeared above the diaphragm during endoscopy. In addition, the presence of peptic ulcers in the stomach or duodenum was also noted.

4. 24-hour ambulatory dual channel esophageal pH monitoring

Ambulatory esophageal pH monitoring was performed using dual channel antimony pH electrodes located 5 and 20 cm above the upper level of the LES, with a separate skin reference electrode (Synectics Medical, Stockholm, Sweden). The data were stored on a portable digital recorder (Digitrapper Mk III, Synectics Medical, Stockholm, Sweden). Before each study, the pH probe was calibrated in buffer solutions of pH 7 and 1. An episode of acid reflux was defined as a decrease in esophageal pH to less than 4 during more than 10 seconds (210).

5. Esophageal manometry

Most patients also had esophageal manometry by a stationary pull-through technique to quantify LES-pressure and to detect abnormalities in primary esophageal peristalsis. Esophageal manometry was performed using an eight lumen manometric assembly incorporating a sleeve sensor. Intragastric pressure was recorded by a side-hole located 1 cm beyond the distal margin of the sleeve. Side-holes at the proximal sleeve margin and 4, 8, 12 and 16 cm more proximally recorded motility in the esophageal body and a side-hole in the pharynx monitored swallowing. The sleeve, gastric and esophageal side-holes were perfused with distilled water at a rate of 0.6 ml/min using a low compliance pneumohydraulic capillary infusion system. The pharyngeal side-hole was perfused at a rate of 0.3 ml/min, in order to obtain an accurate indication of swallowing but minimise the effect of the assembly on the

swallow rate. Each lumen was connected to external pressure transducers (pvb, Medizintechnik GMBH, Germany). With the sleeve adequately positioned across the gastroesophageal junction, 10 wet swallows (5 ml water) were administered at 30 seconds intervals.

6. 24-hour esophageal Bilitec® 2000 monitoring

The fiberoptic spectrophotometer Bilitec® 2000 (Synectics Medical) was used to quantify DGER 5cm above the upper level of the LES. The system consists of a miniaturized probe of 2.5 mm diameter that carries light signals into the esophagus and back via a plastic fiberoptic bundle. Before each study the probe was calibrated in water. An episode of DGER is defined as an increase in esophageal bilirubin absorbance > 0.14 for more than 10 seconds (210).

7. Antireflux therapy

Regardless of endoscopic, pH metric and Bilitec® monitoring findings, all ORL patients received antireflux therapy consisting of PPI intake. In addition, they were instructed to apply antireflux lifestyle measures (raising the head end of the bed with 20 to 25 cm, avoiding meals and drinks 3 hours before going to sleep and other classical dietary and lifestyle modifications) (see also Chapter 1, section **D.***1*). All patients were followed at 2 weeks intervals until their predominant symptoms had resolved or were markedly improved. At each follow up visit, response to therapy was scored as change of the predominant symptom since the onset of treatment (0 = no response, unchanged or worse, 1 = mild response, up to 50% improvement, 2 = clear response, 50 to 75% improvement and 3 = excellent response, more than 75% improvement or disappearance). The PPI therapy was gradually decreased if the patient had a clear or excellent response for at least 4 weeks on a given dose. This allowed determining the lowest effective maintenance dose, if any.

8. Study protocol

In these ORL patients, we performed upper g.i. endoscopy, followed by stationary esophageal manometry and 24-hour ambulatory dual channel esophageal pH metry on one of the next 4 days. In a subset of ORL patients, Bilitec® monitoring was performed simultaneously with pH metry.

On the day of the ambulatory monitoring, probes for assessing acid GER and DGER were introduced via a nasal orifice into the esophagus to the distance previously determined by manometry as 5 cm proximal to the LES. The probes were then attached with adhesive tape to the subject's nose and cheek. In addition, appropriate positioning in the esophagus was confirmed by fluoroscopy. Data collection devices were connected to the probes and worn in a belt on the patient's waist. Registration of acid reflux or DGER lasted for approximately 22 hours after which the probes were removed and the data transferred to a personal computer for analysis with the aid of commercially available software (Gastrosoft Inc., Synectics Medical, Irvine, Texas, USA). Patients recorded the time of meal or fluid consumption and posture changes on a diary card.

During the Bilitec® recording time, only liquid meals (200 ml of Nutridrink; 300 kcal: 13% proteins, 48% carbohydrates, 39% lipids, Nutricia, Bornem, Belgium), not interfering with Bilitec® monitoring were used (210). The amount of kcal ingested during the study ranged from 1200-1800. Patients were asked to preferably drink water and to avoid coffee, tea, and fruit juices during the recording.

Subsequently, regardless of the outcome of investigations, all ORL patients received standard antireflux therapy consisting of PPI intake and lifestyle measures.

B. Data and statistical analysis

Using commercially available software (Gastrosoft), acid reflux and DGER were quantified separately as fraction of time of acid reflux (pH < 4) or DGER exposure (absorbance > 0.14). Distal acid exposure time (percentage of total time pH was <4) was considered pathological when it exceeded 4% of the time (210). Proximal acid exposure time was judged abnormal when it exceeded 0.8% (36). Pathological DGER is present when intra-esophageal bilirubin absorbance is above 0.14 for more than 4.6% of the time (210).

A diagnosis of GERD was based on the presence of esophagitis and/or a pathological distal acid exposure time.

Continuous variables were compared using two-tailed Student's t-test or Mann-Whitney U-test. Categorical data were compared using chi-square testing. Differences were considered to be significant at the 5% level. Data are given as mean ± SEM or as median and interquartile ranges (IQR).

CHAPTER 5: THE YIELD OF UPPER GASTROINTESTINAL ENDOSCOPY IN PATIENTS WITH SUSPECTED REFLUX-RELATED CHRONIC ORL SYMPTOMS

A. Introduction

Gastroesophageal reflux disease (GERD), defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the esophagus, is one of the most common disorders affecting the gastrointestinal tract (120). When effects of refluxed gastric contents extend beyond the esophagus itself, this is referred to as extra-esophageal reflux (EER). These effects may be caused by the direct noxious effects of gastric juice on the mucosal surfaces of the tracheobronchopulmonary tree, the laryngopharynx, the middle ear and the nasosinusal complex. A second mechanism responsible for EER is the activation of reflexes by the reflux of gastric contents into the esophagus.

Extra-esophageal manifestations of GER include a variety of pulmonary and ORL symptoms and disorders. These pulmonary and ORL manifestations related to EER may also be referred to as supraesophageal complications of GERD. Pulmonary manifestations that have been related to EER include asthma, chronic bronchitis, cough, idiopathic pulmonary fibrosis and pneumonia. ORL disorders related to EER include not only laryngeal abnormalities (i.e. reflux laryngitis or posterior laryngitis, laryngospasm, contact-ulcerations, laryngeal granulomas, laryngeal and subglottic stenosis and laryngeal carcinoma) (21, 27, 67, 101, 114, 119, 123, 133, 148, 178, 238, 239), but also pharyngitis (237), chronic rhinosinusitis (10, 33, 35, 221) and glue ear (212). ORL symptoms related to EER include hoarseness, frequent throat clearing, sore throat, excessive or sticky throat mucus, feelings of postnasal drip, halitosis, globus, nonproductive cough and stridor (10, 21, 27, 33, 35, 67, 101, 114, 119, 123, 133, 148, 178, 221, 237-239). The majority of patients with reflux-related ORL manifestations do not report classical reflux symptoms like heartburn and regurgitation (114, 148, 155).

At present, upper g.i. endoscopy is not recommended in the diagnostic work up of suspected GER in ORL patients, as the prevalence of pathological findings is considered low (76, 154, 170, 178). However, the studies on which this recommendation was based are hampered by low number of patients or less accurate assessments of esophagitis, such as radiology (114, 155, 243). The endoscopic finding of erosive esophagitis not only establishes a diagnosis of

GERD in ORL patients but may also reveal severe reflux disease with lesions that require long term potent acid inhibition or endoscopic follow up (178).

An initial therapeutic trial is considered a favourable strategy in patients with classical reflux symptoms because of the high specificity of heartburn and acid regurgitation in indicating acid reflux disease (50, 107). There is currently little or no knowledge about the sensitivity or specificity of supraesophageal symptoms, but this is likely to be considerably lower. Furthermore, these supraesophageal symptoms and disorders usually respond less quickly and often less completely on potent acid suppression than typical reflux symptoms (88, 101, 131), which might make an initial therapeutic trial a less favourable strategy in ORL patients.

The aim of the present study therefore was to prospectively assess the prevalence of erosive esophagitis, Barrett's esophagus and other upper g.i. abnormalities at endoscopy in consecutive ORL patients with chronic unexplained refractory symptoms. A group of heartburn patients seen in the same period served as comparative population. Furthermore, we evaluated the response to medical antireflux therapy.

B. Materials and methods

1. Patient selection

Four hundred and five consecutive patients with chronic refractory "unexplained" ORL symptoms, considered to be possible manifestations of EER, were referred to the department of Gastroenterology. All patients had chronic ORL symptoms for at least 3 months and were selected for the present study, as described above (Chapter 4, section **A.***1*). None of the patients were on acid suppressive medication during at least 6 months before the first ORL consultation and before referral to the department of Gastroenterology.

A group of 554 consecutive new patients with heartburn without prior acid suppressive treatment, seen in the same time period, served as controls for the endoscopic findings. At the time of the study, PPI's and even H_2 blockers were only reimbursable in Belgium after upper g.i. endoscopy, which provided a large reflux patient population naïve to acid suppressive drugs.

2. ORL assessment

All ORL patients were seen by one of the authors (JP) and had a careful history taking including an extensive symptom questionnaire covering most classical, atypical and supraesophageal reflux symptoms to assess symptom frequency and severity. All patients had symptoms on a daily basis. The severity of 60 different ORL and reflux symptoms was graded as absent, mild, moderate or severe by the patient. Patients were also asked to identify their predominant symptom and, on this basis, could be classified in one of the following symptom categories: throat complaints (sore throat with pain, burning or irritation; excessive or sticky throat mucus, feelings of postnasal drip, frequent throat clearing); hoarseness (dysphonia and/or aphonia, including prolonged voice warm up and worsening of voice quality with voice use); non productive cough; globus; miscellaneous complaints (halitosis; laryngospasm, cervical dysphagia; feelings of fullness in the ear(s); nasal congestion). They also underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy.

All patients with typical reflux symptoms received an abbreviated version of the questionnaire including 14 symptoms (heartburn, acid regurgitation, food regurgitation, chest pain, dysphagia, odynophagia, nausea, vomiting, choking, sore throat, hoarseness, nocturnal cough, nocturnal dyspnea, wheezing) which they scored for severity (absent, mild, moderate or severe) (111).

3. Upper gastrointestinal endoscopy

As part of investigations to establish a diagnosis of GERD, all patients underwent upper g.i. endoscopy during which the presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the classification of Savary-Miller, which served as a basis for reimbursement in Belgium (149; see also Chapter 4, section **A.***3* and Chapter 1, section **D.***1*).

4. Acid suppressive therapy in ORL patients

Subsequently, all ORL patients received antireflux therapy consisting of omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d., regardless of endoscopic findings, to which the prescribing physician (JP) was blinded. In addition, they were instructed to apply conservative antireflux

measures, as described above (Chapter 4, section **A.***7*). All patients were followed at 2 weeks intervals until their predominant symptoms had resolved or were markedly improved. At each follow up visit, response to therapy was scored as change of the predominant symptom since the onset of treatment (0 = no response, unchanged or worse, 1 = mild response, up to 50% improvement, 2 = clear response, 50 to 75% improvement and 3 = excellent response, more than 75% improvement or disappearance). The PPI therapy was gradually decreased if the patient had a clear or excellent response for at least 4 weeks on a given dose. This allowed determining the lowest effective maintenance dose, if any.

5. Statistical methods

Continuous variables were compared using two-tailed Student's t-test or Mann-Whitney's U-test. Categorical data were compared using chi-square testing. Differences were considered to be significant at the 5 % level. All data are given as mean ± SEM.

C. Results

1. Patient characteristics

Over a 30 month period, 405 consecutive ORL patients with chronic, unexplained, "refractory", suspected reflux related ORL symptoms and/or disorders (204 men and 201 women; age range 14 - 86 years; mean age 48.4 ± 0.7 years) were recruited for the study. Their mean weight was 74.0 ± 0.8 kg, and the mean length 170 ± 0.6 cm. Nineteen percent were smoking cigarettes and 25% drank alcohol on a regular basis. In the first 230 patients, biopsies were taken from the antrum and the corpus to stain with cresyl violet for the presence of Helicobacter pylori (Hp). Clinical examination revealed signs of posterior laryngitis (edema and erythema of the arytenoids and the interarytenoidal mucosa) in 280 patients (69%).

Five hundred and forty five consecutive new patients with heartburn or regurgitation without acid suppressive treatment, seen in the same time period, were also studied. The demographic properties of these patients did not differ from those with chronic ORL symptoms. There were 245 men and 300 women, and the mean age was 46.7 ± 0.6 years, with a mean body weight of

71.8 ± 0.7 kg and a mean length of 169 ± 0.4 cm. Twenty five percent were smokers and 21% drank alcohol on a regular basis. A questionnaire revealed the presence of hoarseness, throat ache and nonproductive cough in respectively 37%, 31%, and 29% of the patients with heartburn or regurgitation.

2. Symptom pattern

According to their most predominant symptom, ORL patients were classified into the following categories: throat complaints (48.9 %), nonproductive cough (16.5 %), hoarseness (13.3 %), globus (7.1 %), and miscellaneous complaints like halitosis, pharyngeal dysphagia, laryngospasm, feelings of fullness in the ear(s), nasal congestion, etc. (14 %). All patients had at least moderate symptom intensity for the predominant symptom. Beside their predominant symptom, most patients also had one or more additional ORL symptoms in other symptom categories.

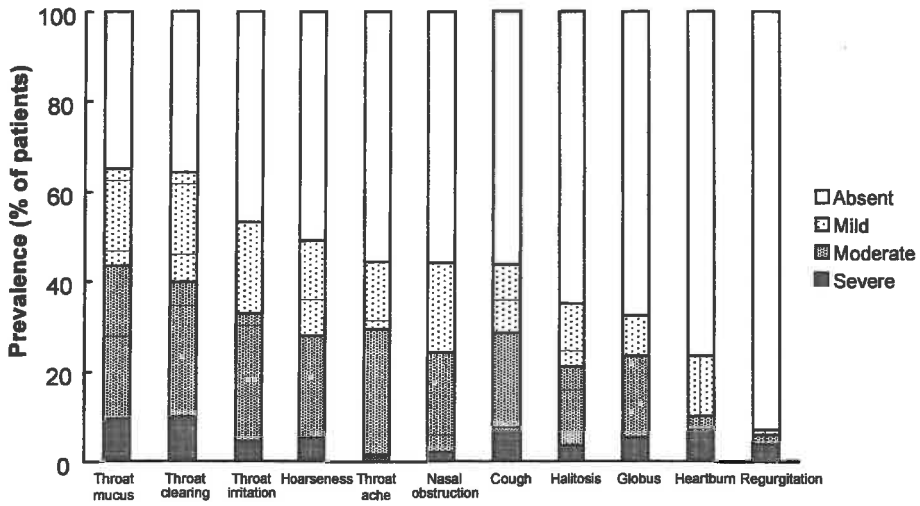

Figure 1. Prevalence at different severity levels of main ORL symptoms and typical reflux symptoms in 405 patients with suspected reflux-related chronic ORL symptoms.

The most prevalent symptoms in all patients were throat complaints (frequent throat clearing, feelings of excessive or sticky throat mucus, a sense of throat irritation or throat ache). Hoarseness, nasal obstruction, nonproductive cough, globus and halitosis were also frequently reported (Figure 1). Heartburn and regurgitation were each present on a weekly basis in respectively 78 (19.3 %) and 77 (19.0 %) of the patients (Figure 1). All typical GERD patients presented with heartburn or acid regurgitation (respectively 70.8% and 78.7% of the patients).

3. Endoscopic findings

Of the ORL patients, upper g.i. endoscopy revealed erosive esophagitis in 212 patients (52.3 %): 129 had grade 1 esophagitis (31.9%), 51 grade 2 (12.6%), 7 grade 3 (1.7%) and 5 grade 4 esophagitis (esophageal peptic ulcer, 1.2%). Barrett's esophagus was present in 20 patients (4.9 %). A hiatus hernia was found in 105 patients (25.9%) (Figure 2). The prevalence of erosive esophagitis did not differ in ORL patients with or without heartburn or regurgitation (respectively 54% and 44%, NS).

In the heartburn patients, upper g.i. endoscopy revealed erosive esophagitis in 38.4% of the patients (grade 1 in 22.7%, grade 2 in 8.4%, grade 3 in 1.7% and grade 4 in 2.5%), Barrett's esophagus in 25 patients (4.5%) and hiatal hernia in 208 patients (37.5%) (Figure 2). The prevalence of reflux associated lesions (esophagitis or Barrett's esophagus) was significantly higher in ORL patients (52.3 vs. 42.6%, $p < 0.05$) and the prevalence of negative endoscopies was significantly lower in ORL patients compared to heartburn patients (43.9% vs. 55.1%, $p < 0.001$). The prevalence of grade I esophagitis was significantly higher in ORL patients ($p < 0.005$), but the presence of higher grades of esophagitis and the presence of Barrett's esophagus did not differ between both patient populations. GERD patients were more likely to have a hiatal hernia (37.5%, $p < 0.0005$) and less likely to have a peptic ulcer (2.3%, $p < 0.05$) than ORL patients.

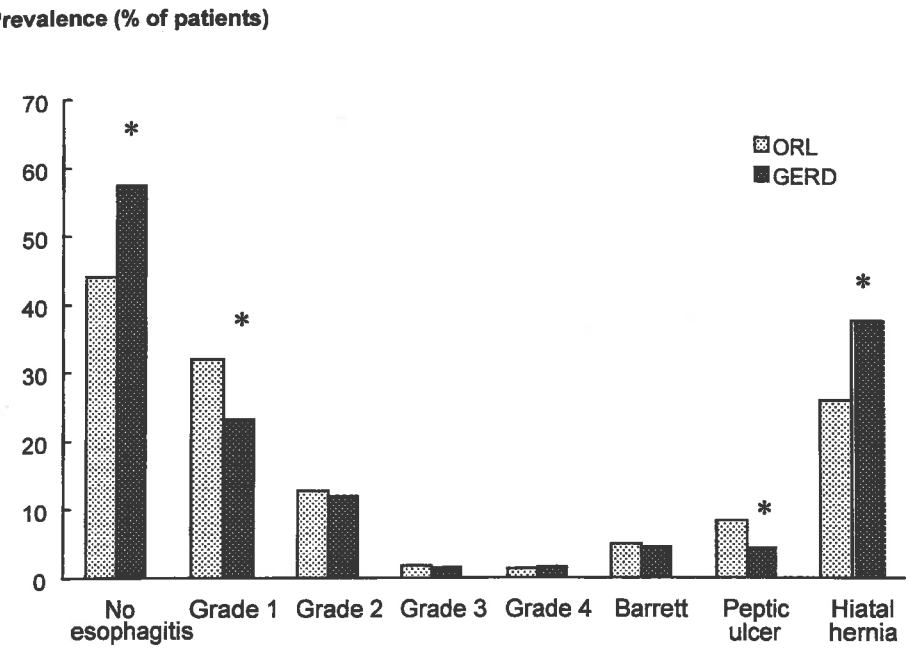

Figure 2. Endoscopic findings (esophagitis grades, peptic ulcer, Barrett's, hiatal hernia) in 405 patients with suspected reflux-related chronic ORL symptoms and in 554 heartburn patients. *$p < 0.05$ compared to ORL patients.

Esophagitis was most prevalent in patients with predominant cough (65.7 %), and significantly higher than in patients with throat symptoms (47.0 %, $p = 0.01$) and patients with globus (37.9, $p = 0.01$).

Helicobacter pylori (Hp) was demonstrated on gastric biopsies in 22.5% of 230 ORL patients. Peptic ulcers were found in 34 patients (8.4 %, 25 gastric and 9 duodenal; 14 Hp positive and 4 NSAID related). In 19 patients, peptic ulcers occurred in the presence of esophagitis or Barrett's esophagus. In typical GERD patients, 24 peptic ulcers were found (4.3%, 17 gastric and 7 duodenal; 9 Hp positive and 5 NSAID related). The prevalence of peptic ulcers was significantly lower in GERD patients compared to ORL patients ($p < 0.05$). "Severe" lesions

on upper g.i. endoscopy (esophagitis 3 or 4; Barrett's esophagus; gastric or duodenal ulcers) were detected in 47 ORL patients (11.6 %) and in 55 GERD patients (9.9%).

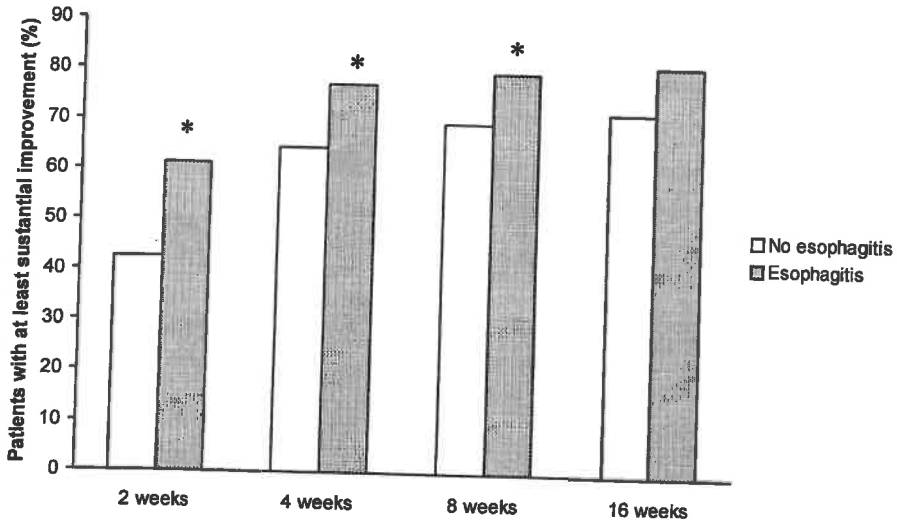

Figure 3. Symptomatic relief during PPI therapy according to the presence or absence of reflux-associated lesions (esophagitis or Barrett's esophagus). * $p < 0.05$ compared to patients without reflux-associated lesions.

4. Response to therapy

Following antireflux therapy with omeprazole (20 mg b.i.d.) or lansoprazole (30 mg o.i.d.) most patients had a substantial improvement of their predominant symptom (score 2 or 3, clear response or excellent response) after 2 weeks (51.1%), 4 weeks (71.9%), 8 weeks (75.3%) or 16 weeks (77.2%). Associated symptoms also responded to therapy and laryngeal erythema, if present, diminished or disappeared. Response rates to PPI therapy did not differ between patients with or without heartburn. Patients with esophagitis had significantly higher rates of symptom relief at 2, 4 and 8 weeks compared to those without esophagitis (Figure 3). The highest symptom relief occurred in patients with non productive cough and the lowest relief was seen in globus and in the miscellaneous group (Figure 4).

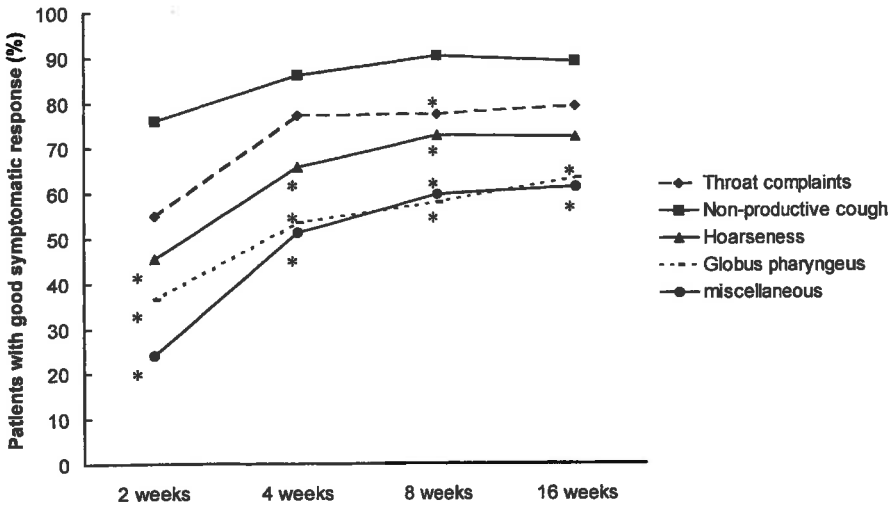

Figure 4. Prevalence of clear or excellent response to PPI therapy according to the predominant symptom type in patients with suspected reflux-related chronic ORL symptoms. * $p < 0.05$ compared to patients with non productive cough as a predominant symptom.

At the follow up visits of 8, 12 and 16 weeks, PPI was lowered to half dose (omeprazole 20 mg or lansoprazole 15 mg o.i.d.) in respectively 14, 20 and 24% of the patients, and PPI's were stopped, maintaining only lifestyle measures, in respectively 12, 18 and 19% of the patients.

D. Discussion

It is well known that GERD may cause a number of pulmonary and ORL complications, and this has been referred to as extra-esophageal reflux (EER). The vast majority of studies examining EER complications of GERD have focused on asthma because of its frequent occurrence. Several retrospective and more recent prospective studies consistently demonstrate that GERD is a prevalent finding, occurring in 30 to 90% of adults with asthma (116, 204, 205). Studies in asthma patients reported erosive esophagitis at endoscopy in 33–

39% (116, 204) and a large case control study of U.S. military veterans demonstrated an elevated odds ratio of 1.51 for asthma in patients with esophagitis (47).

More recently, ORL manifestations of GERD have received increasing attention. Using barium esophagography, a method that would now be considered insufficiently sensitive, Koufman found esophagitis in only 18% of 182 ORL patients (114). Using endoscopy, the same group reported only a 19% prevalence of esophagitis in 58 patients with abnormal pharyngeal pH monitoring (115). However, less than half of these patients had pathological distal esophageal acid exposure (115). A similarly low prevalence of endoscopic esophagitis was reported in two relatively small studies. An esophagitis prevalence of approximately 10% was found in 63 ORL patients with chronic unexplained throat symptoms (155), and a prevalence of approximately 27% was reported in 11 patients with laryngoscopic findings suggestive of reflux disease (243). Based on these findings, it has been postulated that erosive esophagitis is a rare finding in ORL patients, and upper g.i. endoscopy is not recommended as an initial test for GER in these patients (76, 154, 170, 178). However, a number of small studies in selected ORL patients suggested a higher prevalence of esophageal lesions (4, 131, 144, 213). Batch et al. reported endoscopic esophagitis in 63% of 104 patients with globus (4). Mc Nally et al. found endoscopic esophagitis in 55% of 11 patients with chronic "unexplained" hoarseness (131) while Ness et al. found endoscopic esophagitis in 54% of 22 consecutive ORL patients with hoarseness (144). Tauber et al. reported a 43% prevalence of esophagitis in 30 patients with non-specific laryngopharyngeal symptoms (213).
In the present study, we investigated the presence of abnormalities during upper g.i. endoscopy in consecutive patients with suspected GERD-related ORL symptoms and compared this to a control group of patients with typical GERD symptoms. In 43% of the GERD population esophageal lesions were seen during endoscopy, which is comparable to previous reports (15, 59, 233). Contrary to what has been suggested in the literature (76, 154, 170, 178), the prevalence of lesions suggestive of reflux disease was significantly higher in ORL patients. In 52.3% of the ORL patients, the presence of erosive esophagitis or of Barrett's esophagus confirmed the suspected diagnosis of GERD.

After 4 weeks of PPI therapy (omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d.), the predominant ORL complaints were markedly reduced in the majority of these prospectively studied patients. The response rates to PPI therapy in the present study are high compared to a number of publications (45, 146). We suspect that this is mainly reflecting patient selection.

We recruited consecutive patients with suspected reflux-related symptoms or disorders from the ORL clinic for a full reflux investigation, while we suspect that previous studies dealt with selected ORL patients referred to the gastroenterologist because of particularly difficult and refractory symptoms. The response rate was significantly higher in patients with erosive esophagitis at endoscopy, especially during the first two months of treatment. In some patients a longer treatment period or higher PPI dosing were required to obtain symptom relief. A subset of patients experienced no or insufficient symptom relief. In these patients their persisting symptoms could be related to insufficient acid inhibition and ongoing acid reflux, to non-acid reflux or to other causes unrelated to GER (11, 210, 232). As can be derived from Figure 1, most patients had multiple symptoms. However, these additional symptoms generally responded similarly to therapy as the predominant symptom. The presence of ORL symptoms in different categories in the same patient suggests that, when EER occurs, it is likely to induce multiple symptoms rather than a single complaint.

Several authors have reported a low prevalence of heartburn and/or regurgitation (6-43%) in patients with EER-related ORL manifestations (114, 148, 155), and this is confirmed in the present study. One possible explanation for this could be an esophageal mucosal insensitivity to acid in ORL patients (155). This conclusion was suggested based on the finding of a high incidence of acid reflux on pH monitoring and a low incidence of positive acid perfusion tests (5%) in ORL patients, which is lower than the rate of positive acid perfusion tests for patients with classical reflux symptoms (range 32-100%; mean 78%) (86). Patients who are not sensitive to experience heartburn and who acquire supraesophageal complications of GERD might have major esophageal acid exposure, thereby increasing the likelihood of erosive lesions in the distal esophagus, which may be clinically silent. On the other hand, it has been reported that distal esophageal acid exposure is similar in patients with posterior laryngitis and patients with typical GERD, and that a higher percentage of reflux episodes reaches the proximal esophagus in patients with reflux laryngitis compared to patients with typical GERD symptoms (115, 188).

It has been suggested that esophagitis patients are more susceptible to supraesophageal reflux (47). One possible explanation for this could be given by the finding that esophagitis patients, when compared to normal volunteers, not only have more reflux episodes reaching the middle and upper esophagus but also have a shorter duration of upper esophageal sphincter (UES) contraction in response to reflux episodes. This may enhance the possibility that gastric contents overcome the UES and reach the laryngopharynx (218), especially when the

esophagus is entirely filled with refluxate during "common cavity events" and as the intraesophageal pressure exceeds the pressure within the UES or within parts of the UES (the pressure-profile within the UES is asymmetrical with the lowest pressures in the lateral parts). This may possibly occur when UES pressure is low with values below 10 mm Hg, like during sleep (96) or when the UES relaxes during belching and in the initial phase of deglutition (96, 188). On the other hand, as most supraesophageal reflux occurs during the daytime (188), the occurrence of low UES pressure during fatigue, belching, coughing, changes in position and in the initial phase of deglutition may be more relevant (96, 188). In the feline model a negative influence of acute esophagitis on the esophagoglottal closure reflex, which is considered one of the protective reflexes against the aspiration of gastric contents, has been shown (167).

The most important finding of the present study, to our knowledge the largest to address this issue, is that the majority of patients with chronic, refractory, unexplained, suspected reflux-related ORL symptoms have abnormal findings, suggestive of GERD, on upper g.i. endoscopy. The finding of erosive esophagitis not only establishes a diagnosis of GERD with an supraesophageal symptomatic manifestation, but is also associated with a better response to PPI therapy and is helpful in assessing severity of GERD in these patients. Erosive esophagitis suggests a more serious form of GERD in which patients often require continuous medical therapy with a PPI for effective symptom relief and healing (178). Based on these findings, the use of upper g.i. endoscopy as an initial investigation in suspected reflux-related ORL symptoms might be advocated, especially when the cost of upper g.i. endoscopy is low and when risk factors for Barrett's esophagus or for complicated forms of GERD are present.

CHAPTER 6: CHARACTERISTICS AND CLINICAL RELEVANCE OF PROXIMAL ESOPHAGEAL PH MONITORING

A. Introduction

Ambulatory esophageal pH monitoring of the distal esophagus is currently the most reliable method for detecting gastroesophageal reflux (31, 99). Suspected reflux-related supraesophageal symptoms and disorders such as choking, sore throat, hoarseness, asthma, nocturnal cough and nocturnal dyspnea, may result from reflux of gastric contents into the distal and proximal esophagus and into the pharynx (18, 43, 60, 85, 160, 169, 188, 240). Therefore, measuring proximal esophageal acid reflux may be useful in the evaluation of patients with suspected reflux-related supraesophageal manifestations (18, 85, 169). However, the limited available data are conflicting. Some studies have documented prominent proximal reflux (PR) in patients with laryngitis (85, 188), chest pain (60) and respiratory symptoms (160). Other studies have found no such association in asthma (43, 60), chronic cough (60), and hoarseness (240). The clinical usefulness of proximal esophageal pH monitoring therefore remains unproven.

In addition, it is unclear which factors will determine the proximal extent of gastroesophageal reflux. Theoretically, several elements may be important: frequency of reflux in the distal esophagus, volume of the refluxate, esophageal body resistance and esophageal clearance function. The fiberoptic spectrophotometer Bilitec® 2000 (Synectics Medical), is used to quantify duodeno-gastro-esophageal reflux (DGER) in an ambulatory fashion, (see also Chapter 1 section C.5). Several recent studies, using simultaneous pH and DGER (Bilitec®) monitoring, have demonstrated that both acid reflux and DGER show a graded increase in severity from controls to esophagitis patients with the highest values observed in patients with Barrett's esophagus (14, 19, 105, 227). It remains unclear whether patients with DGER also have higher volume of gastroesophageal refluxate and therefore also might demonstrate more acid reflux in the proximal esophagus.

The aim of the present study was: (a) to evaluate the clinical usefulness of ambulatory proximal pH monitoring by comparing the characteristics of patients with and without abnormal PR in dual pH monitoring studies and (b) to evaluate which parameters of distal esophageal acid reflux and esophageal motility will determine the presence of PR.

More specifically, we wanted to test the following hypotheses: 1) proximal esophageal acid reflux is more prevalent in patients with suspected reflux-related supraesophageal (respiratory or ORL) symptoms. 2) Patients with more distal esophageal acid reflux also have more proximal esophageal acid reflux. 3) Patients with pathological distal esophageal DGER have more proximal esophageal acid reflux.

B. Materials and methods

1. Study subjects

Twenty healthy controls and 400 consecutive patients who underwent ambulatory pH monitoring within a 24-month period participated in this study. The patients were referred by gastroenterologists, ORL specialists, pulmonologists and esophageal surgeons for suspected GERD. The healthy controls took no medication and had no history of gastrointestinal disease. Patients with a history of gastric or esophageal surgery were excluded from the study. All drugs potentially affecting gastrointestinal motility and gastrointestinal secretion were discontinued at least one week prior to the pH monitoring.

In all patients, weight and length was measured and body mass index (BMI) was calculated. Prior to the ambulatory monitoring studies, each patient completed a symptom questionnaire. The patient was asked to grade the intensity (0-3; 0=absent, 1=mild, 2=moderate and 3=severe, interfering with daily activities) of 14 potentially reflux-related symptoms. These symptoms were acid reflux, food reflux, chest pain, heartburn, vomiting, dysphagia, odynophagia, nausea, choking, sore throat, hoarseness, wheezing, nocturnal cough and nocturnal dyspnea. Smoking habits, alcohol intake and a history of cholecystectomy were recorded.

2. Upper gastrointestinal endoscopy

All subjects underwent conventional upper g.i. endoscopy during which the presence of erosive esophagitis was noted and graded according to the modified classification of Savary-Miller which was the basis for antisecretory drug reimbursement in Belgium (149; see also

Chapter 4, section **A.***4* and Chapter 1, section **D.***1*).

3. Ambulatory distal and proximal pH monitoring

Ambulatory esophageal pH monitoring was performed using a dual channel antimony pH electrode, as described above (Chapter 4, section **A.***4*).

4. Measurement of duodeno-gastro-esophageal reflux

The fiberoptic spectrophotometer Bilitec® 2000 (Synectics, Stockholm, Sweden) was used to quantify DGER, as described above (Chapter 4, section **A.***6*).

5. Esophageal manometry

We performed standard intra-esophageal manometry using a sleeve catheter that was positioned so that pressures could be recorded from proximal stomach (side hole 2 cm below the sleeve), the LES (sleeve), esophageal body (side holes 4, 7, and 10 cm proximal to the sleeve), and pharynx (side hole 28 cm proximal to the sleeve, to detect swallows). The esophageal catheter was infused at a flow rate of 0.5 mL/min with distilled water using a low-compliance pneumohydraulic capillary infusion system (Arndorfer Medical Specialties, Milwaukee, Wisconsin, USA). Pressure of the LES, peristalsis (normal peristalsis, intermittent peristalsis, segmentary aperistalsis or absent peristalsis) and amplitude (normal amplitude, low amplitude (<30 mmHg) or no measurable amplitude) of the contractions were determined.

6. Study protocol

The Ethics Committee of the hospital approved the study protocol. Patients were asked to fill out a detailed questionnaire about symptoms and frequency, smoking and drinking habits, weight and height. In all patients, we subsequently performed an upper g.i endoscopy, followed by stationary esophageal manometry and ambulatory 24-hour esophageal pH and

Bilitec® monitoring on one of the next 4 days, as described above (Chapter 4, section A.*8*).

7. Data analysis

Acid reflux and DGER were quantified separately with the following variables obtained from computerised analysis: number of reflux episodes per hour, number of reflux episodes lasting longer than 5 minutes per hour, longest reflux episode (minutes), fraction of time of acid reflux or DGER. An episode of acid reflux was defined as a decrease in esophageal pH to less than 4 during more than 10 seconds. An episode of DGER was defined as an increase in esophageal bilirubin absorbance > 0.14 for more than 10 seconds. Analysis was done for the total recording time, upright time and supine time.

The upper limit of the normal (95th percentile) for distal acid reflux and the upper limit of the normal (95th percentile) for DGER were determined from previous studies in our laboratory . The upper limit of the normal (95th percentile) for proximal acid reflux was calculated from the data in 20 healthy volunteers. Based on the results of pH monitoring, we classified patients as patients with normal PR and patients with abnormal PR.

Patients with normal PR and patients with abnormal PR were compared for the following characteristics: age, gender, length, weight, BMI, prevalence of cholecystectomy, prevalence of different grades of esophagitis, prevalence of abnormal manometry results, abnormal distal acid reflux, abnormal DGER and the prevalence of 14 symptoms scored by the patient on a questionnaire (acid reflux, food reflux, chest pain, heartburn, vomiting, dysphagia, odynophagia, nausea, choking, sore throat, hoarseness, wheezing, nocturnal cough and nocturnal dyspnea). We tested whether proximal acid reflux correlated with distal acid reflux and whether proximal acid reflux correlated with DGER.

We used the factors identified to be associated with pathological proximal acid exposure in univariate analysis, to perform a multivariate analysis of risk factors for pathological proximal acid exposure. P values of 0.05 and 0.1 were chosen as cut-off points to enter and exit a stepwise multiple logistic regression analysis. Odds ratios (OR) with 95% confidence interval (CI) were computed.

Values are presented as means ± SEM for parametric data and median (interquartile range) for non-parametric data. Normally distributed data were compared by Student's t test. Linear regression analysis was used to test correlations. Chi-square test was used to compare the prevalence of symptoms, the prevalence of previous cholecystectomy, the prevalence of daily alcohol or nicotine use, the prevalence of different grades of esophagitis and the prevalence of abnormal manometry results between patients with and patients without abnormal proximal reflux. P-values < 0.05 were considered to be significant.

C. Results

1. Healthy controls

20 healthy controls (13 men and 7 women; age 19-27; mean age 22 ± 0.9 years) underwent ambulatory dual channel distal and proximal pH monitoring as well as distal Bilitec® monitoring to establish the upper limit of the normal proximal esophageal acid exposure (95th percentile). The results are summarized in Table 1. The mean registration time was 22 h 39 ± 8 min. The upper limit of normal (95th percentile) for distal esophageal acid exposure was 4.7 % of the time. The upper limit of normal (95th percentile) for DGER was 4.6 % of the time. The upper limit of normal (95th percentile) for proximal acid exposure was 1.4 % of the time.

2. Patient characteristics

A total of 400 eligible patients were recruited, of which 54 were excluded because of previous upper gastrointestinal tract surgery (n = 47) or because of technically inadequate recordings (n = 7). Thus, a total of 346 patients with symptoms suggestive of GERD (167 men and 179 women; age 15-81 years; mean age 47.2 ± 0.8 years) were included in the study. Their mean body weight was 71.9 ± 0.8 kg, the mean length 169.1 ± 0.5 cm and the mean BMI 25.0 ± 0.3 kg/m^2. The patients were significantly older than the healthy subjects ($p<0.01$). A cholecystectomy had been performed in 8 patients (2%). The questionnaire showed that 25.8% of the patients were smokers and 18% drank alcohol on a daily basis.

Table 1: Results of dual pH monitoring and duodeno-gastro-esophageal reflux monitoring in twenty healthy controls.

	Percentage of time with reflux			*Reflux episodes (n)*	
	Distal pH monitoring	Proximal pH monitoring	DGER monitoring	pH-monitoring	DGER
Total	4.7	1.4	4.6	72.2	24.4
Upright	5.1	1.9	7.8	71.2	23.4
Supine	5.2	1.3	0.0	11.2	1.0
Postprandial	7.0	4.5	11.8	16.7	6.1

The symptom pattern is summarized in Figure 1. The most frequently reported symptoms were acid regurgitation, heartburn, chest pain and throat ache. Upper g.i. endoscopy revealed no erosive esophageal lesions in 202 patients (58.4%), and grade 1, 2, 3 en 4 esophagitis in respectively 80 (23.1%), 36 (10.4%), 4 (1.2%) and 6 (1.7%) patients. Barrett's esophagus was found in 18 patients (5.2%).

Distal esophageal pH monitoring was pathological in 124 patients (36%); 183 patients (53%) had pathological DGER and 57 patients (16%) had pathological proximal acid reflux. Figure 2 summarizes the various combinations of pathological acid reflux (distal or proximal) and DGER exposure that were found. Poor but significant correlations were found between distal and proximal esophageal acid exposure ($r = 0.2160$, $p < 0.0001$) and between distal esophageal acid exposure and esophageal DGER exposure ($r = 0.3479$, $p < 0.0001$). No significant correlation was found between proximal esophageal acid exposure and esophageal DGER exposure.

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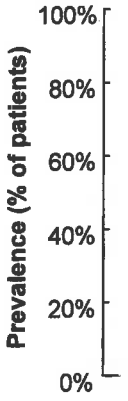

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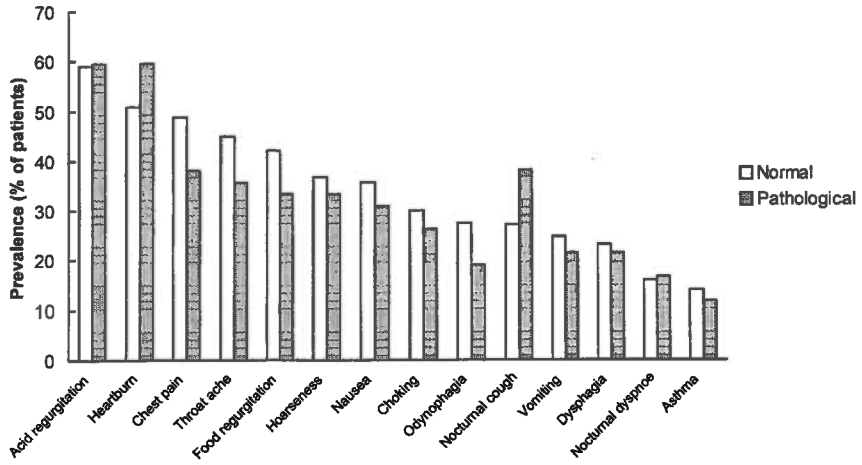

Figure 1: Prevalence of 14 typical and atypical reflux symptoms compared between patients with abnormal proximal reflux and without abnormal proximal reflux.

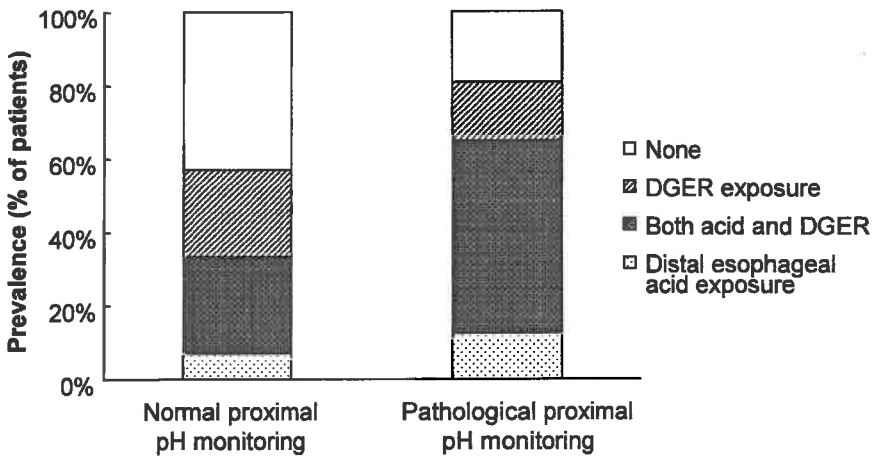

Figure 2: Distribution of findings in simultaneous dual pH and Bilitec® monitoring in 347 patients. The figure depicts the prevalence of pathological distal acid exposure, pathological DGER exposure or both in patients with or without pathological proximal esophageal acid exposure.

Manometry revealed normal peristalsis in 288 patients (83%), ineffective esophageal motility in 26 patients (8%), segmentary aperistalsis in 29 patients (8%) and absence of peristaltic contractions in 4 patients (1%). The mean resting pressure of the LES was 17 ± 0.4 mm Hg. The amplitude of the contractions was normal in 294 patients (85%), below 30 mm Hg in 48 patients (14%) and absent in 4 patients (1%).

Table 2: Comparison of demographic, endoscopic and manometric characteristics between patients with normal proximal reflux and with abnormal proximal reflux.

	Normal proximal esophageal acid exposure	**Pathological proximal esophageal acid exposure**	**p**
Number of patients	289	57	/
Men/women	134 / 155	33 / 24	NS
Mean age	47.3 ± 0.9	46.6 ± 1.8	NS
Mean BMI (kg/m^2)	25.0 ± 0.3	24.8 ± 0.7	NS
Cholecystectomy	5	3	NS
Daily use of nicotine	72	17	NS
Daily use of alcohol	45	17	0.01
Esophagitis grades 0/1/2/3/4/Barrett	172/68/27/3/3/16	30/12/9/1/3/2	NS
LES pressure	17.0 ± 0.5	17.0 ± 1.0	NS
Peristalsis (normal/segmental aperistalsis/intermittent/absent)	176/20/16/2	47/3/6/1	NS
Amplitude (normal/low/absent)	180/32/3	51/5/1	NS

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3. Characteristics of patients with abnormal proximal esophageal acid exposure

Fifty seven patients (16%) (33 men and 24 women; mean age 47 ± 2 years) had abnormal proximal esophageal acid exposure. The demographic features and endoscopic findings in patients with pathological proximal esophageal acid exposure are summarized in Table 2.

In patients with abnormal proximal acid exposure, the mean fraction of total time of proximal acid reflux was 8.5 ± 1.6 %. The total number of proximal acid reflux episodes was 78.4 ± 3.7 and the number of reflux episodes lasting longer than 5 minutes 3.6 ± 0.2. The longest proximal reflux episode lasted on average 32.4 ± 0.2 minutes. In patients with abnormal proximal acid exposure, this occurred both in upright and supine positions (respectively 7.5 ± 0.6 and 9.4 ± 0.4 % of time; respectively 57.7 ± 4.6 and 20.9 ± 2.4 reflux episodes).

Manometry revealed normal peristalsis in 47 patients (82%), in 3 patients (5%) intermittent peristalsis, in 6 patients (11%) segmentary aperistalsis and in 1 patient (2%) absent peristalsis. The mean pressure of the LES was 17 ± 1 mmHg. The amplitude of the contractions was normal in 51 patients (89%), below 30 mm Hg in 5 patients (9%) and absent in 1 patient (2%).

In patients with pathological proximal esophageal acid exposure, the most prevalent symptoms were acid regurgitation, heartburn and nocturnal coughing in respectively 57%, 57% and 38% of the patients.

4. Comparison between patients with normal and abnormal proximal esophageal acid exposure

No major demographic differences were found between both groups, except for a higher prevalence of daily use of alcohol in those with pathological proximal esophageal acid exposure (15 vs. 30%, p = 0.01). Endoscopic findings and the prevalence of a history of cholecystectomy did not differ significantly between both groups (Table 2).

Patients with abnormal proximal esophageal acid exposure had significantly higher distal

esophageal acid exposure as well as esophageal exposure to DGER. The number of distal reflux episodes, both acid and DGER, as well as longstanding reflux episodes, were all higher in patients with abnormal proximal esophageal acid exposure (Table 3). The prevalence of pathological distal esophageal acid exposure was significantly higher in patients with pathological proximal esophageal acid exposure (29% vs. 65%, $p < 0.0001$). Similarly, the prevalence of pathological DGER was also significantly higher in patients with pathological proximal esophageal acid exposure (50% vs. 68%, $p = 0.01$).

Table 3: Results of distal esophageal pH monitoring and Bilitec® monitoring in patients with and without pathological proximal esophageal acid exposure.

	Normal proximal acid exposure	**Pathological proximal acid exposure**	**P**
Distal esophageal acid exposure			
Number of reflux episodes	62.5 ± 4.4	104.1 ± 10.1	< 0.001
Number episodes > 5 minutes	2.1 ± 0.2	4.6 ± 0.8	< 0.001
Longest reflux episode (min)	19 ± 3	46 ± 14	< 0.001
% of time pH < 4	5.8 ± 0.7	13.0 ± 2.6	< 0.001
Esophageal DGER exposure			
Number of DGER episodes	25.6 ± 1.8	22.5 ± 3.3	0.03
Number episodes > 5 minutes	3.8 ± 0.3	5.8 ± 0.8	< 0.01
Longest DGER episode (min)	99 ± 12	142 ± 25	NS
% of time DGER	14.2 ± 1.2	22.5 ± 3.3	< 0.01

The pressure of the LES did not differ significantly between patients with and without abnormal proximal esophageal acid exposure. The prevalence of abnormal peristalsis or abnormal contractile amplitude in the esophagus did not differ between both groups (Table 2). The prevalence of typical and atypical reflux symptoms and of suspected reflux-related supraesophageal symptoms did not differ between patients with and without abnormal

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proximal esophageal acid exposure, regardless of which cut-off level was used. The multivariate analysis identified only pathological distal esophageal acid exposure as an independent risk factor for the presence of pathological proximal esophageal acid exposure (OR 4.515, 95% CI 2.477 – 8.229, $p < 0.0001$).

D. Discussion

Several investigators have advocated the use of a proximal esophageal pH probe or even a pH probe above the UES in the hypopharynx, when investigating supraesophageal reflux as a cause of pulmonary and ORL disorders (103, 114). Although initial studies suggested that hypopharyngeal monitoring for acid reflux is the most sensitive test for identifying patients with GERD-related ORL disorders, there are considerable technical difficulties with pH monitoring in the pharynx, and this technique has so far not gained widespread acceptance (Katz 1990, Koufman 1991, Kahrilas and Ergun 1997, Champion and Richter 1993, Wiener et al 1987). Several investigators prefer placement of the proximal pH probe in the upper esophagus, 20 cm above the LES (85, 178). However, the reproducibility of proximal esophageal pH monitoring was shown to be poor and there is no convincing evidence that proximal esophageal pH monitoring predicts the response to acid suppressive therapy in ORL patients (228).

In the present study, we systematically assessed distal and proximal esophageal acid exposure in patients referred for reflux testing. We observed that acid reflux to the proximal esophagus is rather common in patients with GERD: one quarter of our patients with abnormal distal reflux and nearly one fifth of our patients with abnormal DGER had abnormal proximal reflux too. We systematically studied factors associated with pathological proximal esophageal acid exposure.

Patients with abnormal proximal reflux had significantly greater and more frequent DR and DGER than patients without abnormal PR. We found a poor but statistically significant correlation between PR and DR, but not between PR and DGER. In the literature, a correlation between PR and DR has already been reported (253). The correlation between DGER and proximal esophageal acid exposure suggest a possible role of higher volume reflux in inducing proximal spread of the acid refluxate. Demographic, endoscopic and manometric findings did not differ between patients with or without pathological PR. The

symptom pattern also did not differ in patients with normal or pathological PR. We did observe a higher prevalence of pathological DR and pathological DGER in patients with pathological PR. However, in the multivariate analysis, only distal esophageal acid exposure was an independent risk factor for the presence of pathological PR.

These observations question the clinical usefulness of ambulatory proximal pH monitoring. First of all, proximal pH monitoring was only rarely pathological when distal pH monitoring was normal, which limits the diagnostic gain of a second, proximal, acid sensor. Only 20 patients (5%) had abnormal proximal reflux without abnormal distal acid reflux. Furthermore, proximal esophageal acid exposure did not correlate with the presence of atypical (respiratory or ORL) GERD symptoms, which limits its ability to provide relevant pathophysiological information. Putatively GERD-related respiratory and ORL symptoms such as choking, odynophagia, sore throat, hoarseness, wheezing, and nocturnal coughing or dyspnea did not occur more frequent in patients with abnormal PR.

GERD may cause or worsen respiratory symptoms (asthma, cough, dyspnea) by promoting a vagally mediated bronchospasm that does not require proximal reflux. This may explain the poor correlation of the respiratory GER symptoms with abnormal proximal reflux (125, 126). Microaspiration of gastric acid may also precipitate respiratory symptoms (20, 38). This may not register as an abnormal amount. So far, a similar role for acid in triggering ORL symptoms has not been established, but cannot be excluded. The observation that distal esophageal acid perfusion was able to induce some ORL symptoms in patients with suspected GERD-related ORL symptoms is supportive of such a mechanism (see Chapter 7), but further studies are required.

E. Conclusion

Our data do not support routine proximal esophageal pH monitoring as a clinical tool. This does not preclude its use in selected patients with difficult-to-manage suspected supraesophageal reflux. Proximal pH monitoring rarely identifies patients who would be considered normal based on distal pH monitoring alone. Furthermore, proximal pH monitoring does not differentiate patients with typical or atypical GERD manifestations. Finally, distal esophageal DGER exposure was not an independent risk factor for pathological

CHAPTER 7: ESOPHAGEAL SENSORIMOTOR FUNCTION IN PATIENTS WITH SUSPECTED REFLUX-RELATED CHRONIC ORL SYMPTOMS.

A. Introduction

Gastroesophageal reflux disease (GERD), defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the esophagus, is one of the most common disorders affecting the gastrointestinal tract. Heartburn and/or regurgitation are the typical or classical symptoms of GERD. In addition, a number of less typical symptoms, including a variety of pulmonary and ORL disorders, have been increasingly recognized to be associated with GERD. The most common clinical presentations of reflux-related ORL disorders or chronic symptoms include chronic laryngitis, hoarseness, cough, globus, sore throat, excessive throat phlegm and frequent throat clearing. The common interpretation is that these are manifestations of supraesophageal reflux, i.e. the effect of the exposure of areas proximal to the upper esophageal sphincter to gastric contents.

Although distal esophageal acid exposure is a prerequisite for proximal acid exposure to occur, several authors have reported a low prevalence of the classical reflux symptoms of heartburn and regurgitation in patients with suspected reflux-related ORL disorders (114, 148, 155). It has been suggested that decreased distal esophageal acid sensitivity might contribute to the low prevalence of typical GERD symptoms in ORL patients with suspected reflux-related supraesophageal manifestations (155). Furthermore, although a statistically significant correlation between the presence of GERD and the occurrence of several ORL and pulmonological diagnoses has been established (47), the majority of GERD patients do not have ORL or respiratory symptoms. It has been suggested that impaired esophageal clearance function might contribute to the proximal spread of reflux events (155). However, an alternative explanation might be the volume of the refluxate, which is also a likely contributor to proximal spread of the refluxate.

The aim of the present study was to evaluate distal esophageal sensitivity to acid perfusion and the proximal and distal esophageal acid clearance function in patients with suspected reflux-related ORL symptoms.

B. Materials and methods

1. Patient selection

Consecutive patients with chronic refractory "unexplained" suspected reflux-related ORL symptoms were referred to the department of Gastroenterology. All patients had chronic ORL symptoms for at least three months and were selected for the present study as described above (Chapter 4, section A.*1*). None of the patients were on acid suppressive medication during at least six months before the first ORL consultation and before referral to the department of Gastroenterology.

All patients were seen by one of the authors (JP) and had a careful history taking including an extensive symptom questionnaire covering most classical, atypical and supraesophageal reflux symptoms to assess symptom frequency and severity. They also underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy. Subsequently, based upon their predominant chronic symptoms, patients could be classified in one of the following symptom categories: throat complaints (sore throat with pain, burning or irritation; excessive or sticky throat mucus, feelings of postnasal drip, frequent throat clearing); hoarseness (dysphonia and/or aphonia, including prolonged voice warm up and worsening of voice quality with voice use); nonproductive cough; globus; miscellaneous complaints (halitosis, laryngospasm, cervical dysphagia, feelings of pressure in the ear(s), nasal congestion).
A group of healthy volunteers and a group of consecutive heartburn patients without prior acid suppressive treatment, seen in the same time period, served as controls. None of the healthy subjects had symptoms or a history of gastrointestinal disease nor were taking any medication. Subjects with a history of gastric or esophageal surgery were excluded from this study. All drugs potentially affecting gastrointestinal motility and

gastrointestinal secretion were discontinued at least one week prior to the pH monitoring. At the time of the study, PPI's and even H_2 blockers were only reimbursable in Belgium after upper gastrointestinal (g.i.) endoscopy, which provided a large reflux patient population naïve to acid suppressive drugs.

2. Upper gastrointestinal endoscopy

As part of investigations to establish a diagnosis of GERD, all patients underwent upper g.i. endoscopy. The presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the classification of Savary-Miller, which served as a basis for reimbursement in Belgium (149; see also Chapter 4, section **A.***3* and Chapter 1, section **D.***1*).

3. Ambulatory distal and proximal pH monitoring

Ambulatory dual channel esophageal pH monitoring was performed, as described above (Chapter 4, section **A.***4*).

4. Manometry and esophageal acid sensitivity testing

A standard esophageal manometric catheter with a 6 cm Dent sleeve (Arndorfer, Milwaukee, WI) was used to record intraluminal pressure in four esophageal sites at 3 cm intervals, lower esophageal sphincter (LES) and gastric fundus simultaneously. The catheters were constantly perfused with bubble-free distilled water by a low compliance pressure-driven perfusion pump at a rate of 0.4 ml/min. Intraluminal pressure changes were transmitted to external pressure transducers (Siemens Elema 746, Siemens, Iselin N.J.) which were connected to a computer, allowing the continuous recording of pressure changes. The catheter served to identify the location of the LES. During the acid

perfusion test 0.1 N hydrochlorid acid was infused 10 cm proximal to the LES. The time of onset and of worsening of heartburn and any other spontaneous or swallow-induced esophageal or thoracic sensations during the acid perfusion test were registered. As soon as the subject felt worsening heartburn or pain, bicarbonate 0.1N was infused to neutralize the acid. The maximal total duration of the acid perfusion was 30 minutes.

5. Esophageal acid clearance testing

The subjects were put in a supine position with a dual pH monitoring probe in place as described above. A 10 ml bolus of 0.1 N hydrochlorid acid was instilled 15 cm proximal to the LES. The subjects were asked to swallow at 30 second intervals.

6. Data analysis

Comparisons were made between healthy controls, patients with established classical GERD and patients with suspected reflux-related ORL symptoms, with or without pathological acid exposure. Acid reflux was quantified as the fraction of time of acid reflux. For the esophageal acid sensitivity studies, the time of onset and of worsening of heartburn and any other spontaneous or swallow-induced esophageal or thoracic sensations during the acid perfusion test were registrated. During the acid clearance studies, the acid clearance time (ACT) was defined as the time needed to reach a pH > 4 after the pH drop below 4 induced by instillation of the acidic fluid bolus. Using both the proximal and distal sensor, ACT was calculated both for the proximal and distal esophagus.

Values are presented as means ± SEM for normally distributed data and median (interquartile range) for not-normally distributed data. Data were compared by Student's t test or by Mann-Whitney U-test. P-values < 0.05 were considered to be significant.

C. Results

1. Patient characteristics

Twenty-six patients (11 men and 15 women, mean age 48 ± 3 years) with suspected reflux-related ORL symptoms participated in the study. Predominant symptoms were sore throat (n = 11), nonproductive cough (n = 6), globus (n = 5), excessive throat phlegm (n = 3) and halitosis (n = 1). Six patients had grade I erosive esophagitis, one had grade II esophagitis and 2 had Barrett's metaplasia. Distal and proximal esophageal acid exposure were respectively 5.7 ± 1.0% and 2.2 ± 0.8 % of time pH < 4. Distal esophageal pH monitoring was pathological (> 4.7 % of time pH < 4) in twelve patients. In these, distal and proximal esophageal acid exposure were respectively 10.5 ± 1.6% and 3.3 ± 1.7 % of time pH < 4.

Thirteen patients with established GERD (pathological pH monitoring) with typical symptoms (heartburn and/or regurgitation) served as classical GERD controls. There were 10 female and 3 male patients, and the mean age was 51 ± 10 years. Two patients had grade I erosive esophagitis, whereas all others were endoscopy negative. On pH monitoring, distal and proximal esophageal pH were below 4 during respectively 13 ± 4 % and 1.9 ± 0.5% of time.

Twelve healthy subjects (4 men, mean age years 31 ± 4 years) served as controls. Endoscopy and pH monitoring were performed to rule out reflux. Distal and proximal esophageal acid exposure were respectively 3.8 ± 2.4% and 0.7 ± 0.4 % of time pH < 4.

2. Esophageal acid sensitivity testing

Esophageal acid sensitivity was tested in 16 ORL patients (5 men, mean age 45.5 ± 4.6). A 30 minute acid perfusion failed to induce heartburn in 12 patients (75%). In the 4 remaining patients (25%), an initial sensation of heartburn occurred after 7.3 ± 1.5 min

and worsened after 14.7 ± 0.9 min. In 5 patients (31%), esophageal acid perfusion induced a sensation of throat ache after 11.2 ± 2.9 min. Esophageal acid exposure was pathological in 8 patients (50%), but only two of these had a positive heartburn acid perfusion test.

Esophageal acid perfusion caused a sensation of heartburn in all patients with established typical GERD, on average after 8.9 ± 1.5 minutes, which was significantly earlier than in ORL patients ($p < 0.0001$).

In healthy controls, a 30 minute acid perfusion failed to induce heartburn in 4 subjects. In the other subjects, an initial sensation of heartburn occurred after 6.7 ± 1.7 minutes and worsening occurred after 10.8 ± 3.0 minutes (Figure 1).

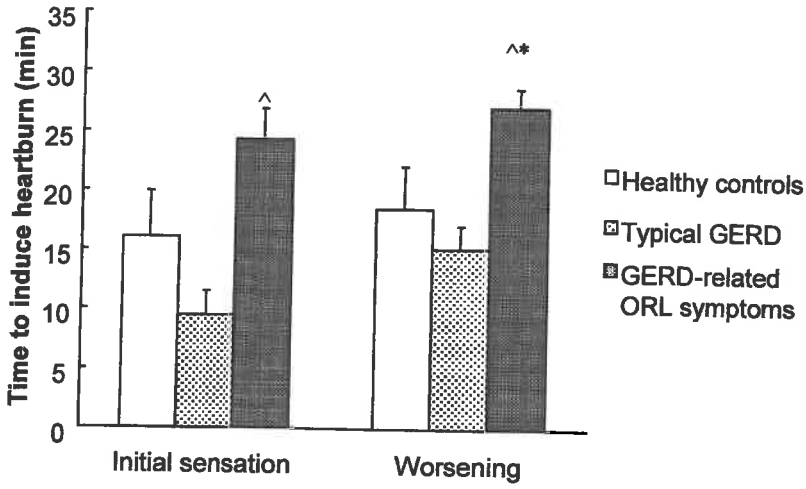

Figure 1: Sensitivity to esophageal acid perfusion in controls, typical GERD and suspected GERD-related ORL symptoms. In case of absence of symptom induction during 30 minutes of acid perfusion, the time was arbitrarily set at 31 minutes. * $p < 0.05$ compared to controls, ^ $p < 0.05$ compared to typical GERD.

3. Esophageal acid clearance testing

Esophageal acid clearance time was tested in all subjects. In healthy controls, acid clearance required 0 ± 0 swallows in the proximal esophagus and 7.5 ± 1.6 swallows in the distal esophagus. In patients with established typical GERD, proximal and distal esophageal acid clearance required respectively 2.2 ± 0.9 ($p < 0.05$ compared to controls) and 13.4 ± 2.6 ($p = 0.06$ compared to controls) swallows. In patients with suspected GERD-related ORL symptoms, proximal and distal esophageal acid clearance required respectively 3.1 ± 0.5 and 14.7 ± 1.8 swallows. These numbers did not differ significantly from values in typical GERD, but were significantly higher than in controls ($p < 0.001$ for proximal acid clearance and $p = 0.01$ for distal esophageal acid clearance) (Figure 2).

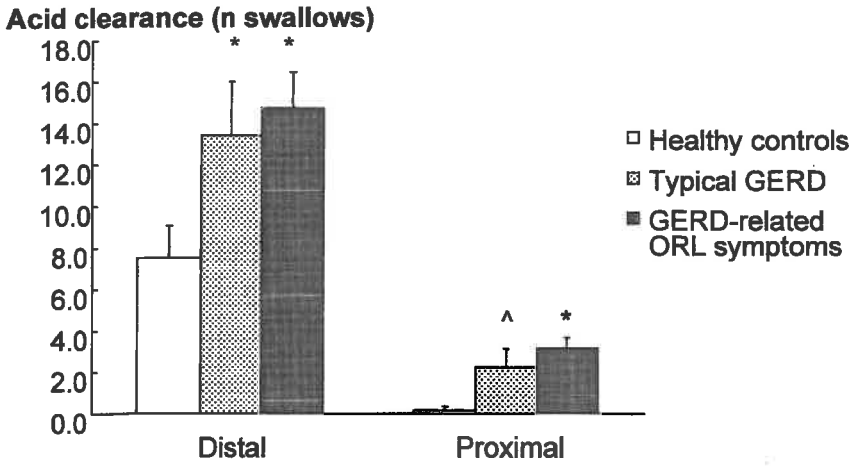

Figure 2: Acid clearance in the distal and proximal esophagus in controls, typical GERD and suspected GERD-related ORL symptoms. * $p < 0.05$ compared to controls, ^ $p = 0.06$ compared to controls.

D. Discussion

Although it is now well accepted that a number of ORL symptoms may be presenting symptoms for GERD, the features that distinguish typical GERD patients from patients with atypical GERD manifestations have not been completely elucidated. In the present study, we observed that patients with suspected GERD-related ORL symptoms have a decreased sensitivity of the distal esophagus to acid exposure, and in the majority of these, esophageal acid perfusion actually failed to induce symptoms of heartburn. Even when only ORL patients with pathological esophageal acid exposure were selected, the finding of esophageal hyposensitivity to acid perfusion was confirmed. This observation is in keeping with a previous study (155) and may at least in part explain the low prevalence of typical reflux symptoms in patients with supraesophageal manifestations of GERD.

Factors underlying esophageal acid sensitivity have only partially been studied. It has been proposed that intra-epithelial free nerve endings act as acid-sensitive nociceptors. These nerve endings do not seem to be located at the epithelial surface, as topical anesthetics fail to alter the symptom response to acid infusion. In case of erosive esophagitis, luminal acid has free access to these intra-epithelial nerve endings. However, the prevalence of erosive esophagitis does not explain the difference in acid sensitivity in typical and atypical GERD patients in the present study. An increased intercellular space, which may allow access of luminal acid to intra-epithelial nerve endings, has been reported in heartburn patients without erosive esophagitis (216). So far, intercellular spaces or esophageal mucosal permeability have not been studied in patients with GERD-related supraesophageal symptoms without heartburn.

Proximal spread of the refluxate is considered a major factor in the pathogenesis of supra-esophageal manifestations of GERD. Studies using hypopharyngeal pH monitoring (103, 114) and proximal esophageal pH monitoring (178) have shown increased proximal acid reflux in patients with suspected supraesophageal manifestations of GERD as a group. Several factors may contribute to the proximal extent of gastroesophageal reflux

episodes. The volume and physicochemical characteristics of the refluxate are likely to be major factors in the proximal extent of reflux events. This aspect is further addressed in the chapter on proximal pH monitoring (Chapter 6). During reflux events in healthy subjects, an increased resistance of the esophageal body prevents the acid bolus to move upwards (192). In typical GERD patients, entrance of acid often induces inhibition of tone in the esophageal body (193). So far, esophageal body tone has not been studied in patients with atypical GERD manifestations. Finally, once reflux has occurred, esophageal peristaltic activity clears the bolus from the esophagus. We studied proximal and distal esophageal clearance in controls, patients with typical GERD and patients with suspected GERD-related ORL symptoms. Controls were younger than patients. Therefore, we cannot exclude that this different age-distribution might have contributed in some way to different findings between controls and patients. We observed impaired clearance both in the proximal and distal esophagus, in the typical as well as the atypical GERD groups. These data confirm impaired clearance in GERD patients as a group, but fail to explain the difference between typical and atypical GERD.

In summary, we have shown decreased sensitivity to esophageal acid infusion and impaired esophageal clearance in patients with suspected GERD-related ORL symptoms. These observations may help to explain the low prevalence of heartburn in patients with supraesophageal manifestations of GERD.

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A. Introd

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CHAPTER 8: UNEXPLAINED CHRONIC EAR COMPLAINTS: THE INCIDENCE OF GASTROESOPHAGEAL REFLUX AND THE OUTCOME OF ANTIREFLUX THERAPY.

A. Introduction

Gastroesophageal reflux (GER) has been defined as the occurrence of lesions or signs and symptoms secondary to the reflux of gastric contents into the esophagus or beyond into the oral cavity or airways. Lesions attributed to GER include esophagitis, inflammation of the larynx and oropharynx, and acute or chronic pulmonary injury (178). For the ORL specialist, GER presents itself with suspected reflux-related signs and symptoms such as reflux laryngitis and posterior laryngitis with hoarseness, frequent throat clearing, sore throat, globus pharyngeus, and chronic cough (67, 101, 114). Other possible reflux-related supraesophageal ORL manifestations include laryngospasm (123), contact ulcers (21, 148), laryngeal and subglottic stenosis (114, 119) and even laryngeal carcinoma (114, 238).

Studies using combined esophageal and pharyngeal pH probes demonstrated acid reflux into the pharynx in many of these patients (114, 188). The important contribution of GER in pediatric inflammatory upper airway disorders has been shown (12). The term gastronasal reflux has been used to indicate a possible relation between reflux and pediatric chronic sinusitis (10).

Recently, we encountered a patient with a chronic therapy-resistant ear problem that only resolved after his coexisting GER was diagnosed to be the cause and consequently was treated successfully as such. This observation suggested to us that some cases of middle ear disease might be considered as another extraesophageal manifestation of GER. In order to learn the prevalence of this association and its clinical properties, we undertook a prospective study to investigate the relationship between chronic middle ear problems and GER. We studied the prevalence of GER in these patients by endoscopy and pH metry. We also assessed short- and long-term responses to medical antireflux therapy.

B. Materials and methods

From November 1997 to November 1999, all consecutive patients with predominant complaints of a chronic refractory discharging middle ear (chronic refractory secretory otitis media; CSOM) were referred to our department of Gastroenterology. Also referred were all patients with a chronic refractory feeling of pressure (CRFP) in one or both ears thought to be related to eustachian tube dysfunction, with or without manifest changes on tympanometry, but with short-term alleviation of the feeling of pressure after a Politzer or Valsalva maneuver.

Both, CSOM patients and CRFP patients were some of the 217 ORL patients with chronic complaints, thought to be reflux-related supraesophageal manifestations, who were referred to the department of gastroenterology within this same 2-year period.

The CSOM group consisted of 5 patients with longstanding complaints of a chronic discharging middle ear, unilaterally or bilaterally with tympanic membrane perforations, atelectatic middle ears, and granulations or polyps in the middle ear(s), but without evidence of active cholesteatoma. The cases are called refractory because previous conventional topical and systemic medical therapy and/or surgical treatment(s), including tympanoplasty, mastoidectomy, and nasal and endoscopic sinus surgery, had been of no avail (Table 1). The CRFP group consisted of 16 consecutive patients with chronic refractory complaints of pressure or fullness in one or both ears, thought to be related to concomitant eustachian tube dysfunction (Table 2). All of them had intact ear drums without signs of middle ear effusion. Most of them had no or only minor changes on tympanometry or pure tone audiometry. All of these patients could alleviate their continuous feeling of ear pressure with a repetitive and forceful Valsalva maneuver, but only for some minutes. Other causes for their complaints had been ruled out. Previous conventional medical treatments including antihistamines, nose and ear drops, antibiotics and topical or systemic corticosteroids had only led to short-term or incomplete improvement or no improvement at all.

In order to establish a diagnosis of GER, we submitted all patients to upper gastrointestinal (g.i.) endoscopy during which the presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the classification of Savary-Miller (149; see also Chapter 4, section **A.***3* and Chapter 1, section **D.***1*). In addition, ambulatory 24-hour dual channel

esophageal pH monitoring was performed to quantify esophageal acid exposure, as described above (Chapter 4, section **A.***4*). Finally, most patients also had esophageal manometry in order to quantify LES pressure and detect abnormalities in primary esophageal peristalsis (see also Chapter 4, section **A.***5*).

The diagnosis of GER was made on the basis of the presence of esophagitis and/or a distal exposure time (percentage of total time pH was <4) exceeding 4% of the time. Proximal acid exposure time was judged abnormal when it exceeded 0.8% (36). All patients were screened for other possible reflux-related symptoms and underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy.

All patients received antireflux therapy consisting of omeprazole 20 mg twice per day (2 patients initially took 40 mg twice per day; patients 1 and 4 on Table 1) regardless of endoscopic and pH-metric findings. In addition, they were instructed to apply antireflux lifestyle measures, as described above (Chapter 4, section **A.7**). All patients were followed at 2-week intervals until their ear symptoms had resolved completely. The omeprazole therapy was gradually decreased if the patient was asymptomatic for at least 4 weeks on a given dose. This reduction allowed determination of the lowest maintenance dose, if any (Tables 1 and 2). Subsequently, the patients entered long term follow up (range, 4 months to 2 years; mean, 11 months).

C. Results

From November 1997 to November 1999, all 217 consecutive ORL patients with suspected reflux-related supraesophageal symptoms were referred to the department of Gastroenterology for investigation and subsequently received antireflux treatment. The predominant complaints were chronic sore throat, unproductive cough, hoarseness, globus pharyngeus and laryngospasm.

Among the patients were 21 with predominant chronic ear complaints; 5 of them had CSOM and 16 had CRFP. All patients with CSOM (Table 1) and 12 patients of the 16 with CRFP (Table 2) received a diagnosis of GER.

Erosive esophagitis was found in 100% of the CSOM patients - usually to a more severe degree in them than in the CRFP patients, of whom 50% had erosive esophagitis. Hiatus

hernia was found in 7 patients (33%). We also found 2 patients with Barrett's esophagus and another patient with a gastric ulcer (Helicobacter pylori-negative).

TABLE 1. GROUP WITH CHRONIC REFRACTORY SECRETORY OTITIS MEDIA

Patient No.	Age (y)	Sex	Surgical History	Ear Complaints	Ear Signs	Additional Complaints	Additional Signs	UGIT Endoscopy: Esophagitis Grade	UGIT Endoscopy: HH	24-h Double pH Probe: Distal*	24-h Double pH Probe: Proximal†	Esophageal Manometry: LESP	Esophageal Manometry: Mot	Omeprazole Maintenance (mg/d)
1	72	M	Ty L	CD L	Gr	None	Ph	3	None	18.9	11.6	Nl	DS	80
2	34	M		CD bilat	Gr, At	None	Ph, PL	1	None	17.5	13.4	Nl	Nl	20
3	71	F	Ty L, Rad L	CD L	Rad, At	Hr, ST, UC, Ho, GP	Ph	2	None	18.0	19.8	Nl	Nl	40
4	29	M	NS, ESS	CD bilat	Gr, At	ST, Ho, FO	Ph, PL	2	3 cm	5.6	2.4	7 mm Hg	PP	40
5	57	F	Ty R	CD bilat	Gr	None	Ph, PL	2	None	PF	PF	Nl	Nl	40

UGIT — upper gastrointestinal tract, HH — hiatus hernia, LESP — lower esophageal sphincter pressure (normal, <10 mm Hg), Mot — esophageal motility, Ty — tympanoplasty, CD — chronic middle ear discharge, Gr — ear granulation(s) and/or polyps, Ph — pharyngitis, Nl — normal, DS — diffuse esophageal spasm, bilat — bilateral, At — atelectasis of middle ear, PL — posterior laryngitis, Rad — radical cavity, Hr — heartburn or regurgitation (see text), ST — sore throat, UC — unproductive cough, Ho — hoarseness, GP — globus pharyngeus, NS — nasal septal surgery, ESS — endoscopic sinus surgery, FO — fetor ex ore, PP — poor peristaltic amplitudes (<30 mm Hg), PF — probe failure.

*For distal probe, result of 24-hour dual-probe measurements in percentage of time pH was <4 (see text).

†For proximal probe, result of 24-hour dual-probe measurements in percentage of time pH was <0.8 (see text).

Distal acid exposure was pathological in 12 patients (64%); proximal acid exposure was pathological in 11 patients (58%). The CSOM patients had highly pathological values of distal acid exposure (mean, 15%; range, 5.6% to 18.9%) and of proximal acid exposure (mean, 11.8%; range, 2.4% to 19.8%). In the CRFP group, distal acid exposure (mean, 6%; range, 0.1% to 21%) was pathological in 8 patients (53%), and proximal exposure (mean, 1.5%; range, 0% to 3.7%) was pathological in 7 patients (47%).

Esophageal manometry showed poor peristaltic amplitudes (<30 mm Hg) in 2 patients and intermittent high-amplitude simultaneous contractions indicative of diffuse esophageal spasm in 4 other patients. Four patients had a low resting LES pressure of <10 mm Hg. Thus, overall, an esophageal motility disorder and/or a too-low LES pressure (<10 mm Hg) was found in 8 patients (40%).

Other reflux-related ORL symptoms were a sore throat (13 patients or 62%), hoarseness (9 or 43%), unproductive cough (7 or 33%), and laryngospasm (5 or 24%). Only 5 patients (24%) experienced heartburn or regurgitation.

The chronic reflux-related ORL signs were marked erythema of the pharynx (pharyngitis) in 18 patients (86%) and marked edema and erythema of the posterior larynx (posterior laryngitis) in 16 patients (76%). There were no significant differences between the CSOM and

the CRFP groups in the occurrence of additional symptoms neither in the findings of posterior laryngitis and pharyngitis. Of the CSOM group, 3 of the 5 patients had bilateral ear disease, and of the CRFP group, 11 did (69%). Of the CSOM patients, 3 had a history of ear surgery. Of the CRFP patients, only 1 had a history of a failed tympanoplasty.

TABLE 2. GROUP WITH CHRONIC REFRACTORY FEELING OF PRESSURE IN EAR

Patient No.	Age (y)	Sex	Surgical History	Ear Complaints	Ear Signs	Additional Complaints	Additional Signs	UGIT Endoscopy: Esophagitis Grade	UGIT Endoscopy: HH	24-h Double pH Probe: Distal*	24-h Double pH Probe: Proximal†	Esophageal Manometry: LESP	Esophageal Manometry: Mot	Omeprazole Maintenance (mg/d)
1	67	F		FP bilat		None	Ph, PL	0	None	6.9	3.1	Nl	Nl	20
2	75	F		FP bilat		UC, Ho	Ph	0	2 cm	5.7	0.5	Nl	Nl	20
3	55	M	Ty 2x L, VT	FP L	RP	None	PL	1	None	3.0	0.0	Nl	Nl	20
4	56	M		FP bilat		Hr, LS, ST, UC, Ho	Ph, PL	2, Ba	4 cm	21.0	2.6	0 mm Hg	PP	40
5	29	F	ESS, CC	FP bilat		Hr, ST, UC, Ho, FO	Ph, PL	1	None	0.4	0.0	Nl	Nl	20
6	70	F		FP bilat		LS, ST, UC, Ho	PL	0	None	13.2	3.0	Nl	Nl	20
7	39	F		FP bilat		ST, Ho	Ph, PL	0	None	3.0	0.3	Nl	Nl	None
8	54	F		FP L		ST	Ph, PL	0	None	2.3	1.7	Nl	DS	None
9	27	M		FP bilat		ST, GP	PL	0	None	0.1	0.0	Nl	Nl	None
10	31	F	ESS	FP L		ST	Ph, PL	1, GU	3 cm	1.8	0.8	NR	NR	20
11	58	M	CC	FP bilat		LS, ST, FO	Ph, PL	2	3 cm	12.0	2.4	Nl	DS	40
12	68	M		FP bilat		Hr, LS, UC, Ho	Ph, PL	2	3 cm	PF	PF	Nl	Nl	20
13	42	M	VT	FP bilat		None	Ph	0	None	0.6	0.0	8 mm Hg	Nl	20
14	68	F		FP L		ST	Ph	0	None	4.3	3.7	Nl	Nl	None
15	47	M	CL	FP R, EP		Hr, LS, ST, UC, Ho, FO	Ph, PL	1	3 cm	8.1	3.3	Nl	DS	40
16	66	M		FP bilat		ST, FO	Ph, PL	2, Ba	None	9.0	0.7	8 mm Hg	Nl	20

UGIT — upper gastrointestinal tract, HH — hiatus hernia, LESP — lower esophageal sphincter pressure (normal, <10 mm Hg), Mot — esophageal motility, FP — feeling of fullness and/or pressure, bilat — bilateral; Ph — pharyngitis, PL — posterior laryngitis, Nl — normal, UC — unproductive cough, Ho — hoarseness, Ty — tympanoplasty, VT — ventilation tube, RP — retraction pocket, Hr — heartburn, LS — laryngeal spasm, ST — sore throat, UC — unproductive cough, Ba — Barrett's esophagus, PP — poor peristaltic amplitudes (<30 mm Hg), ESS — endoscopic sinus surgery, CC — conchal cauterization, FO — fetor ex ore, DS — diffuse esophageal spasm, GP — globus pharyngeus, GU — gastric ulcer, NR — no results, PF — probe failure, CL — Caldwell Luc procedure, EP — ear pain.

*For distal probe, result of 24-hour dual-probe measurements in percentage of time pH was <4 (see text).

†For proximal probe, result of 24-hour dual-probe measurements in percentage of time pH was <0.8 (see text).

On antireflux therapy with omeprazole 20 mg twice per day (2 patients took 40 mg twice per day: patients 1 and 4 on Table 1), the middle ear discharge completely ceased in all CSOM patients, and the middle ear granulations and/or polyps disappeared, leading to a residual dry perforation or a dry atelectatic middle ear. The average time this resolution took was 11 weeks (range, 6 to 16 weeks). One patient (patient 4 on Table 1) discontinued his treatment on his own initiative; his original problems reappeared, to heal again only when his therapy was restarted. At the end of follow up, the CSOM patients remained on a median dose of 40 mg of omeprazole per day. All CRFP patients became asymptomatic after an average time of 4 weeks (range, 2 to 6 weeks) with antireflux therapy and omeprazole 20 mg twice per day. This reaction to therapy was also noted in the 4 patients who did not have GER according to

the above-mentioned criteria (patients 7, 8, 9, and 13 on Table 2); they were nevertheless included in this series because of their complaints and the signs found on clinical examination. The tympanograms that were available on follow up (6 patients, of whom 3 initially had type C curves) normalized simultaneously with the disappearance of the symptoms.

At the end of follow up, the CRFP patients remained on a median maintenance dose of 20 mg of omeprazole per day ($p<.01$ as compared to CSOM patients). The ORL examination revealed that after the patients became asymptomatic, the erythema of the pharynx and the posterior larynx disappeared as well. The additional symptoms, if present, also responded to therapy.

D. Discussion

Reflux may be assessed by a variety of diagnostic tests. If, on upper g.i. endoscopy erosive esophagitis or Barrett's esophagus is found, a GER diagnosis is established. The use of upper g.i. endoscopy has not been routinely advocated in ORL patients, because they usually do not experience heartburn or regurgitation (less than half of patients in most studies) and because erosive esophagitis is considered to be a rare finding. Large prospective studies underscoring this policy, however, are lacking.

Ambulatory 24-hour pH monitoring is considered to be ideal in ORL patients suspected of having GER. Dual channel pH monitoring with one electrode in the distal esophagus, 5 cm above the LES, and a second probe 20 cm above the LES in the proximal esophagus just below the UES is considered preferable (178). The major advantage is the possibility of quantifying distal and proximal acid exposure times on which normal values are available, making this a useful standard (36, 90). If abnormal distal esophageal acid exposure is found, the diagnosis of GER is established.

Documentation of abnormal proximal esophageal acid exposure suggests a higher potential for acid reflux to reach the laryngopharynx and the upper airways, and therefore the probability becomes higher that the ORL symptom or sign is due to GER (178). Furthermore, abnormal proximal reflux may predict the response to medical therapy in patients with pulmonary disease (69), but this correlation is less clear in ORL patients. Probes placed in the

hypopharynx can document reflux above the UES, giving more certainty to laryngopharyngeal reflux as the cause of ORL symptoms or signs. This placement of the probe above the UES would be ideal if there were not a number of technical problems (including possible interpretation errors due to probe drying and other artifacts resulting in a drop in pH to <4 that is not a true reflux episode). At present, normal values are not available (178). Esophageal manometry can demonstrate an esophageal motility disorder, including a resting pressure in the LES that is too low, which may also contribute to ORL problems due to GER. The results of our first 75 patients were reported previously. In the majority of that group (77%), GER could be demonstrated, and treatment with a PPI induced relief of symptoms within 4 weeks in most of them (82%).

Our data suggest that GER sometimes may be diagnosed in patients with chronic ear complaints thought to be related to eustachian tube dysfunction and in patients with CSOM. Reflux of gastric contents (i.e. acid and pepsin) into and beyond the esophagus and into the pharynx and nasopharynx might lead to eustachian tube dysfunction, tubotympanitis, and CSOM through an inflammatory reaction and possibly secondary infection. Erosive esophagitis and abnormal distal and proximal esophageal acid exposure on 24-hour pH monitoring were not only more prevalent, but usually also more serious, in the CSOM patients than in the CRFP patients - a finding suggesting a direct relationship between the severity of ear problems and of GER in some of the CSOM patients. This seems to be confirmed by the longer treatment period required to obtain symptom relief in CSOM patients (11 weeks) than in CRFP patients (4 weeks). It is also supported by the higher dose of omeprazole needed to keep the CSOM symptoms under control after the initial treatment. It might be reasoned that most CRFP patients have no real ear disease since no abnormalities were found on otoscopy, pure tone audiometry or tympanometry. In that case, the ear complaints might be explained as a referred feeling from the irritated pharyngeal wall.

An interesting subgroup within the CRFP patients are the 4 patients (patients 7, 8, 9, and 13 on Table 2) who had no GER according to the criteria we used, but who nevertheless were included on the basis of their complaints and the signs found on clinical examination. These patients also responded favourably to their treatment. One possible explanation might be a placebo response. A second explanation, and the most plausible, is related to the established norms of the 24-hour pH monitoring, especially regarding proximal acid exposure. The larynx and pharynx are not protected by the clearing mechanisms and intrinsic mucosal properties

present in the distal esophagus. It is conceivable that a single episode of acid reflux may be sufficient to cause laryngeal (and most likely also pharyngeal) symptoms and signs. Delahunty and Cherry, who produced vocal fold granulomas experimentally in 1968, did so within 4 weeks by placing gastric juice on the vocal processes of dogs for only 30 min/d, 5d/wk, with no exposure over the weekends. They produced erythema within the first week that did not resolve over the weekend at the end of the second week, and granulomas thereafter (27). If one were to accept a zero-exposure threshold for proximal acid reflux, 2 of the 4 patients had evidence of proximal acid reflux (patients 7 and 8 on Table 2). Also, the normal pH monitoring results could reflect a day-to-day variability and the possibility of a false-negative finding on this basis. Therefore, these 4 patients may have responded favourably because they had (intermittent) reflux-induced laryngopharyngeal symptoms and signs even though they did not meet current diagnostic criteria on the day they were studied. On the other hand, this response could reflect a day-to-day variability of the 24-hour pH measurement and thus indicate a false-negative finding. If CSOM or CRFP persists in spite of antireflux therapy, additional (antibacterial) therapy might be prescribed or repeated pH monitoring might be performed to exclude ongoing acid reflux.

E. Conclusions

This is to date the largest and, to our knowledge, also the first study of groups of adult patients with reflux-related CSOM and with reflux-related CRFP. It documents the diagnostic work up and the results of antireflux therapy with omeprazole. Ambulatory 24-hour dual channel esophageal pH monitoring and upper g.i. endoscopy are considered highly useful (certainly in CSOM patients) in establishing a GER diagnosis and in indicating the severity of GER. Additional information may be obtained by esophageal manometry. The results of our reflux investigations indicate a higher prevalence of GER and usually more serious forms of GER in patients with CSOM than in patients with CRFP. Antireflux treatment combining omeprazole and conservative antireflux measures appears to be highly successful in GER-related CSOM and CRFP. The longer duration of antireflux therapy needed for CSOM patients to become asymptomatic and the higher maintenance dose required for them to remain symptomfree are also indicative of more serious forms of GER in CSOM patients than in CRFP patients. In reflux-related ear problems, GER should be thought of as supraesophageal reflux that may cause nasopharyngitis leading to eustachian tube dysfunction and/or middle ear disease.

CHAPTER 9: THE ROLE OF (DUODENO)-GASTRO-ESOPHAGEAL REFLUX IN UNEXPLAINED EXCESSIVE THROAT PHLEGM.

A. Introduction

Chronic throat clearing, excessive throat phlegm and feelings of postnasal drip are reported to be almost invariably present in patients with suspected supraesophageal reflux (67, 146, 151, 217). It has been suggested that, whether transparent, white, yellow or green, the coloration of excessive throat phlegm and postnasal drip represents gastric content in many cases (151, 217). However, formal evidence for this is lacking up to date.

Duodeno-gastro-esophageal reflux (DGER) refers to the reflux of duodenal contents i.e. bile into the esophagus. Esophageal exposure to both acid and DGER is not only the most prevalent reflux pattern but both acid reflux and DGER also show a graded increase in severity from controls to esophagitis patients with the highest values observed in patients with Barrett's esophagus (227). Whether, similar to GER, DGER may also extend into the proximal esophagus and whether, similar to gastric contents (acid and pepsin/pepsinogen), bile may actually reach the pharynx, thereby potentially causing or contributing to reflux-related supraesophageal manifestations, remains to be established.

The aim of this study was to prospectively investigate the role of GER as well as DGER in consecutive patients with chronic complaints of excessive throat phlegm. We used upper gastrointestinal (g.i.) endoscopy and pH monitoring to study the prevalence of GERD and we used fiberoptic bilirubin monitoring to study the prevalence of DGER. Furthermore, as throat phlegm may have a spectrum of colours of which the pathophysiological significance is unknown, we investigated a putative role for supraesophageal reflux of duodenal contents by studying the correlation of the colour spectrum of throat phlegm with the presence of acid GER and DGER, by investigating the presence of DGER in the proximal esophagus and by analysing throat phlegm composition. Finally, we assessed the response of excessive throat phlegm to antireflux therapy.

B. Materials and methods

1. Patient selection

Over a 30 month period, 59 consecutive adult patients with chronic refractory unexplained complaints of excessive throat phlegm, seen at the ORL outpatient clinic, were referred to the department of Gastroenterology. We refer to these patients as throat phlegm patients. All patients had chronic complaints of excessive throat phlegm for at least three months, some of them for up to more than 30 years (median: 3 years; IQR: 6 months to 7.5 years). Before referral, other apparent causes of their symptoms (i.e. allergy, upper airway infection, abscess, tumour, anatomical obstructive intranasal abnormalities) had been ruled out. None of the patients had a history of bronchopulmonary, neurological, cardiovascular or systemic disease, and all patients had normal plasma bilirubin levels. Even though these patients had not been treated for GERD, they are called "refractory" from a strict (ORL) point of view, as previous "conventional" medical therapies (i.e. mucolytics, antihistamines, antibiotics and corticoids) and/or surgical treatments, including nasal and sinus surgery had only led to short term or incomplete improvement or no improvement at all. None of the patients were on acid suppressive medication during at least six months before the first ORL consultation and before referral to the department of Gastroenterology.

2. Throat phlegm symptoms

The patients reported that troublesome throat phlegm could be felt adherent to the entire length of the pharyngeal wall or to the laryngopharynx, oropharynx and/or nasopharynx. Feelings of phlegm-adherence to the nasopharyngeal wall were frequently interpreted as postnasal drip. All throat phlegm patients had the ability to evacuate their throat phlegm, thereby obtaining some temporary symptom relief. While in some patients this evacuation of phlegm was felt to happen relatively easy, requiring only some minor throat clearing efforts, others experienced greater difficulties in doing so, evacuating their throat phlegm only after repetitive and forceful throat clearing and/or vigorous coughing.

All patients reported the evacuation of transparent throat phlegm several times daily. Some patients reported on the evacuation of varying amounts of exclusively transparant throat phlegm on a daily basis; these patients are referred to as transparant throat phlegm (TTP)-

patients. In addition to daily evacuation of transparent throat phlegm, some patients also reported the evacuation of varying amounts of yellow stained throat phlegm on a regular basis with a frequency varying from at least once a week to several times daily. We refer to these patients as yellow throat phlegm (YTP)-patients.

3. ORL and GERD examinations

All patients were seen by one of the authors (JP) and had a careful history taking, completed with an extensive symptom questionnaire, as described above (Chapter 4, section **A.***2*). They also underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy.

In order to establish a diagnosis of GERD, all patients subsequently underwent an upper g.i. endoscopy and 24-hour ambulatory dual channel esophageal pH monitoring, preceded by esophageal manometry. In order to quantify DGER, all patients also underwent 24-hour ambulatory Bilitec® monitoring. Subsequently, regardless of the outcome of investigations, all patients received standard antireflux therapy consisting of PPI intake and lifestyle measures.

4. Endoscopy

All patients underwent upper g.i. endoscopy during which the presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the classification of Savary-Miller, which served as a basis for reimbursement in Belgium (149; see also Chapter 4, section **A.***3* and Chapter 1, section **D.***1*).

5. *Ambulatory pH Monitoring*

Ambulatory dual channel esophageal pH monitoring was performed to quantify esophageal acid exposure, as described above (Chapter 4, section **A.***4*).

A diagnosis of GERD was based on the presence of esophagitis and/or a distal acid exposure time (percent of total time pH was <4) exceeding 4% of the time (210). Proximal acid exposure time was judged abnormal when it exceeded 0.8% (36).

6. Esophageal manometry

All patients also had esophageal manometry in order to quantify LES pressure and detect abnormalities in primary esophageal peristalsis (Chapter 4, section A.*5*).

7. Ambulatory DGER monitoring

The fiberoptic spectrophotometer Bilitec 2000 (Synectics Medical) was used to quantify DGER in the distal esophagus, 5 cm above the upper level of the LES, as described above (Chapter 4, section A.*6*). Pathological DGER is present when intra-esophageal bilirubin absorbance is above 0.14 for more than 4.6% of the time (210).
In seven YTP-patients, in addition to the Bilitec® probe in the distal esophagus, a second Bilitec® probe was placed in the proximal esophagus 20 cm above the LES.

8. Bile acid dosage in throat phlegm

From throat phlegm patients, one or more samples of throat phlegm were collected and were subsequently analysed for the presence of bile acids using the 3-alfa-hydroxysteroid dehydrogenase enzymatic assay (220).

9. Antireflux therapy

Regardless of endoscopic, pH-metric and Bilitec® monitoring findings, to which the prescribing physician was blinded, all patients received antireflux therapy consisting of omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d. In addition, they were instructed to apply antireflux lifestyle measures, as described above (Chapter 4, section A.*7*). All patients were followed at two weeks intervals until their complaints of excessive throat phlegm had

resolved or were markedly improved. The PPI therapy was gradually decreased if the patient was asymptomatic for at least 4 weeks on a given dose. This allowed determining the lowest effective maintenance dose, if any. Subsequently, most patients entered long term follow up.

10. Study protocol

In 59 consecutive patients with chronic complaints of excessive throat phlegm, we performed upper g.i. endoscopy, followed by a 24-hour ambulatory dual channel esophageal pH-metry and Bilitec® monitoring on one of the next four days, as described above (Chapter 4, section A.*8*).

11. Data and Statistical Analysis

Using commercially available software (Gastrosoft), acid reflux and DGER were quantified separately as fraction of time of acid reflux (pH < 4) or DGER exposure (absorbance > 0.14). All values are expressed as median and interquartile ranges (IQR). t-test or chi-square test compared results (mean ± SEM) wherever appropriate. p-values were considered to be significant if < 0.05.

C. Results

1. Patient characteristics

The median age of the 32 men and 27 women was 46 yr (range 14 to 78 yr); their mean body weight was 75 kg. Eleven (19%) patients were smoking cigarettes and nineteen (32%) patients drank alcohol daily. Thirty three patients (56%) were classified as TTP-patients and 26 patients (44%) as YTP-patients. Demographic characteristics did not differ between TTP- and YTP-patients. Smoking (31% vs. 9%; p = 0.03) and daily alcohol use (46% vs. 21%; p = 0.04) were more prevalent in YTP-patients than in TTP-patients. Eleven patients (17%) had a history of sinus surgery, which tended to be more prevalent in YTP-patients than in TTP-patients (27% vs. 9%; p = 0.07).

2. Symptom pattern and clinical signs

Other potentially reflux-related chronic symptoms like frequent throat clearing (80%), sore throat (68%), nasal congestion (53%), feelings of postnasal drip (49%), dysphonia (49%), cough (44%), halitosis (41%), globus pharyngeus (36%) were also frequently found in throat phlegm patients. In contrast, the classical reflux symptoms of heartburn or regurgitation were experienced on a weekly basis by only 20 (34%) patients and were never a predominant symptom. Feelings of postnasal drip (73% vs. 30%; $p = 0.001$) and nasal congestion (69% vs. 39%; $p = 0.02$) were more prevalent in YTP-patients than in TTP-patients. Sore throat was less prevalent in YTP-patients than in TTP-patients (46% vs. 85%; $p = 0.002$). When all patients who smoked or were daily using alcohol were excluded from the statistical analysis, there was no significant difference in the prevalence of sore throat between both patient groups.

On clinical ORL examination, yellow stained or transparent phlegm-clumps, -strains or -fragments, adherent to the larynx and/or to the entire length or parts of the pharyngeal wall could be seen in several throat phlegm patients. Reflux-related ORL signs were edema and erythema of the posterior larynx (posterior laryngitis) in 31(53%) patients and erythema of the pharynx in 27(46%) patients. There were no significant differences in the prevalence of posterior laryngitis and pharyngeal erythema between YTP- and TTP-patients.

3. Classical GERD investigation

Erosive esophagitis was found in 33 (56%) patients (grade 1: 14 patients; grade 2: 11 patients; grade 3: 2 patients; grade 4: 6 patients of which 1 patient with esophageal ulcer, 3 patients with Barrett's esophagus and 2 patients with Barret's esophagus and esophageal ulcer). A hiatal hernia was present in 23 patients (39%). Peptic ulcers were found in 4 patients (7%, 2 gastric and 2 duodenal), of whom 2 had Helicobacter pylori (Hp) on gastric biopsies and 1 patient reported regular use of NSAID's. In 3 patients, peptic ulcers occurred in the presence of esophagitis or Barrett's esophagus.

Table 1 summarizes endoscopic findings in TTP-patients and YTP-patients. The prevalence of esophagitis did not differ significantly between both patients groups, but a hiatal hernia was found more frequently in YTP-patients. The prevalence of "severe" lesions on upper g.i.

endoscopy (esophagitis grades 3 and 4, Barrett's esophagus, gastric or duodenal ulcers) was not significantly different between both patients groups (6/26 vs. 4/33; NS).

Table 1. Results of esophageal investigations in transparent throat phlegm (TTP-) patients or yellow throat phlegm (YTP-) patients.

	TTP (n = 33)	YTP (n = 26)	P value
Presence of esophagitis (n (%))	17 (52%)	16 (62%)	NS
Presence of hiatal hernia (n (%))	7 (21%)	16 (62%)	0.002
Distal acid exposure (% of time)	2.6% (0.7;6.5)	5.4% (3.5; 11.6)	NS
Proximal acid exposure (% of time; IQR)	0.1% (0.0; 0.3)	1.3% (0.3; 2.5)	0.02
Pathological distal acid exposure (n (%))	13 (39%)	19 (73%)	0.01
Pathological proximal acid exposure (n (%))	4 (12%)	13 (54%)	< 0.001
Prevalence of LES pressure below 10 mm Hg (n (%))	2 (8%)	5 (16%)	NS
Prevalence of peristaltic amplitude below 30 mm Hg (n (%))	9 (27%)	5 (19%)	NS
Distal esophageal DGER exposure (% of time; IQR)	2.2% (0.3; 6.9)	18.6% (13.0; 25.8)	< 0.001
Pathological distal esophageal DGER exposure (n (%))	9 (27%)	23 (92%)	< 0.001

Distal acid exposure was pathological in 32 (54%) patients while proximal acid exposure was pathological in 17 (30%) patients. In 3 patients, proximal pH monitoring data were not available due to technical failure. Table 1 summarizes the data on acid exposure and on esophageal manometry in TTP- and YTP-patients. Proximal esophageal acid exposure and the

prevalence of distal and proximal pathological acid exposure were significantly higher in YTP-patients compared to TTP-patients. According to the prevalence of esophagitis or of pathological distal acid exposure, a diagnosis of GERD was established in 44 patients (75%), and significantly more YTP-patients (24/26; 92%) than TTP-patients (20/33; 61%) were diagnosed with GERD ($p = 0.01$). Abnormalities on esophageal manometry were found in 11 TTP-patients (33%) and in 7 YTP-patients (27%).

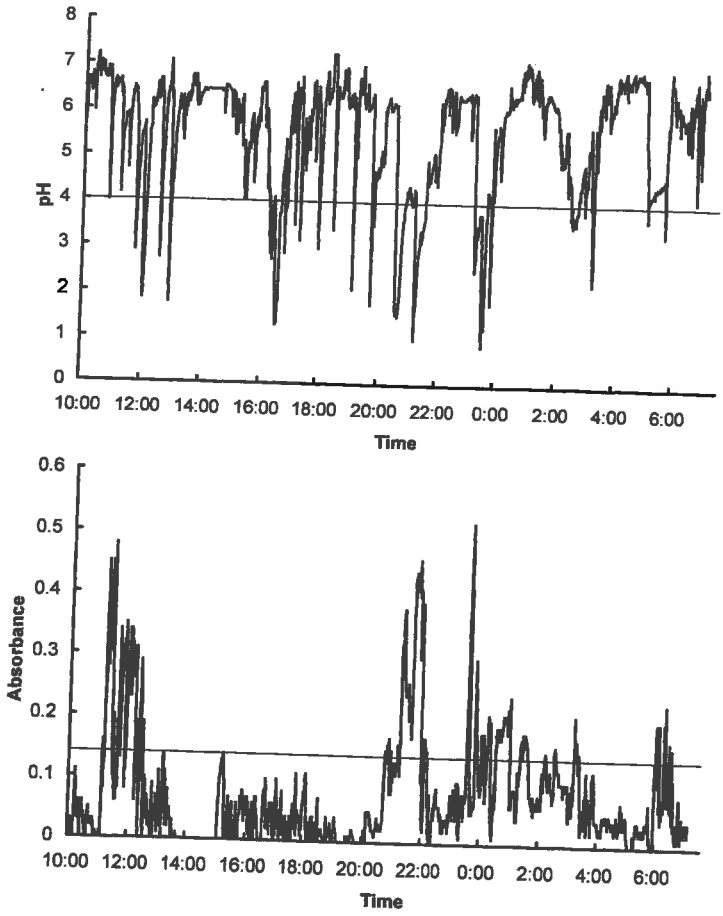

Figure 1. Representative tracing of combined pathological pH and Bilitec® monitoring in a patient with chronic unexplained excessive throat phlegm. X-axis depicts time, left Y-axis in the upper panel depicts intra-esophageal pH and left Y-axis in the lower panel depicts bilirubin absorbance. Cut-offs of normal ranges are indicated (pH < 4 and absorbance > 0.14).

4. DGER investigation

Due to technical failure, DGER results were not available in one patient. DGER exposure was pathological in 32 patients (55 %). YTP-patients had significantly higher distal esophageal DGER exposure and a higher prevalence of pathological DGER exposure (Figure 1) (Table 1).

All seven YTP-patients who underwent double probe esophageal DGER monitoring with one probe in the distal esophagus and a second probe in the proximal esophagus had elevated DGER, not only in the distal esophagus (median: 13%; IQR: 9.5% to 19.6%) but also in the proximal esophagus (median: 7.4%; IQR: 1.8% to 20.8%)(Figure 2). Because of the considerable discomfort associated with repeat/proximal Bilitec® monitoring, this was not performed in TTP-patients.

In 9 samples, obtained from 8 patients, consisting of predominantly yellow stained throat phlegm or containing clearly visible yellow stained phlegm within a rather watery solution, the presence of bile acids was demonstrated (total bile acid concentration median: 0.06 µmol/ml; range: 0.02 to 0.319 µmol/ml). In 7 other samples, obtained from 6 patients, containing no clearly visible yellow stained phlegm, no bile acids were detected (below threshold for detection).

5. Response to antireflux therapy

On antireflux therapy with omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d., the evacuation of TTP ceased in most (61%) throat phlegm patients and was reduced, no longer being troublesome, in the others. The evacuation of YTP ceased in all YTP-patients. Additional reflux-related symptoms, if present, also responded to therapy. The sensation of postnasal drip disappeared in most (69%) and improved in the other throat phlegm patients. Nasal congestion ceased in a majority (77%) of throat phlegm patients, and improved (13%) or remained unchanged (10%) in the others. There were no significant differences in the response of these symptoms to antireflux therapy between YTP- and TTP-patients.

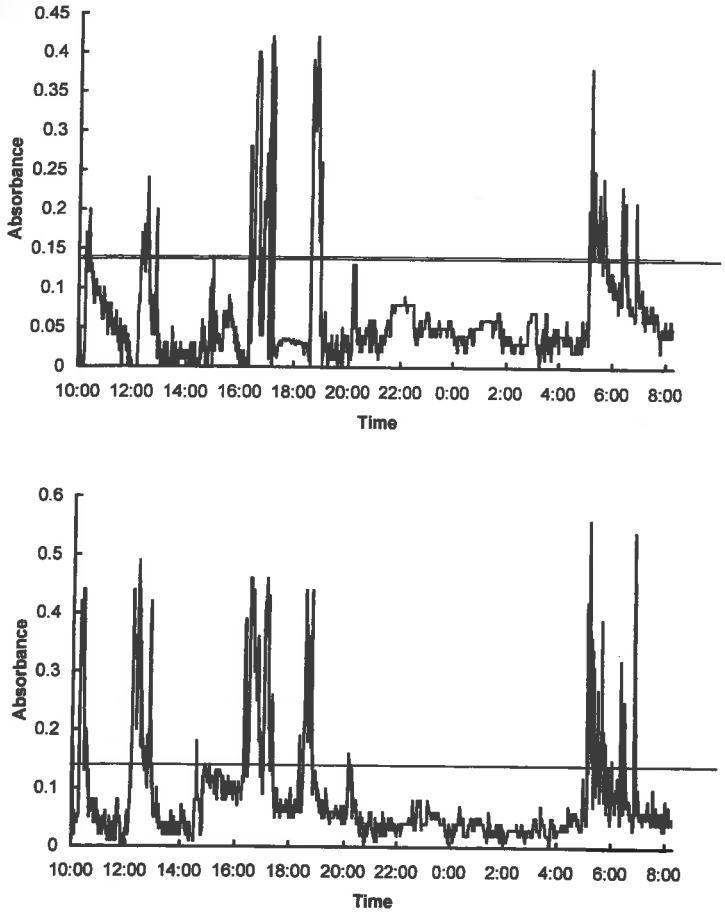

Figure 2. Representative tracing of dual Bilitec® monitoring in a patient with unexplained excessive yellow-stained throat phlegm. X-axis depicts time, Y-axis depicts bilirubin absorbance. The upper panel shows Bilitec® monitoring 20 cm proximal to the lower esophageal sphincter. The lower panel shows pathological Bilitec® monitoring 5 cm proximal to the lower esophageal sphincter. Cut-offs of normal ranges are indicated (absorbance > 0.14).

The time needed to become asymptomatic was on average 4 weeks (IQR: 2 to 16 weeks). During the first week of treatment, the 2 patients with Hp positive gastric or duodenal ulcers received eradication therapy (amoxicilline 1g b.i.d., clarithromycine 500 mg b.i.d. and omeprazole 20 mg b.i.d. for 1 week).

Fifty-one (86%) patients entered long term follow up (mean: 10 months; range: 3 months to 3 years). At the end of follow up, more YTP-patients (21/23; 91%) than TTP-patients (19/28; 68%) were in need of a PPI maintenance therapy to remain asymptomatic (p = 0.04). In addition, of those in need of a PPI maintenance dose, more YTP-patients (15/21; 71%) than TTP-patients (7/19; 37%) (p = 0.03) needed a full PPI maintenance dose (omeprazole 20 mg b.i.d.; lansoprazole 30 mg o.i.d. vs. omeprazole 20 mg o.i.d. or lansoprazole 15 mg o.i.d). In 11 patients (19%), PPI therapy could be stopped while maintaining lifestyle measures, without recurrence of excessive throat phlegm or other reflux-related symptoms. The ORL examination revealed that after patients became symptomfree, the erythema of the posterior larynx and pharynx and, to a lesser degree, also the edema of the posterior larynx were reduced or had disappeared in most patients; yellow stained throat phlegm- clumps, -strains or -fragments were no longer observed. Because of gradually recurring symptoms after an excellent initial therapy response, two YTP-patients eventually underwent a laparoscopic Nissen-fundoplication while one YTP-patient and one TTP-patient underwent an endoscopic antireflux-procedure. These patients are presently asymptomatic.

D. Discussion

Excessive throat phlegm is a common symptom and unexplained excessive throat phlegm is a frequently occurring clinical condition. Although it has been suggested that excessive throat phlegm and postnasal drip may represent supraesophageal reflux of gastric content in many cases (151, 217), this has not been formally proven. In the present study, we investigated the association of unexplained excessive throat phlegm and GER and, using endoscopy and pH monitoring, we could demonstrate pathological GER in the vast majority of patients. In keeping with the hypothesis that supraesophageal reflux is involved in the pathogenesis of unexplained excessive throat phlegm, the majority of patients became asymptomatic during treatment with standard doses of acid suppressive therapy. Studies in esophageal manifestations of reflux disease have established that DGER, assessed by fiberoptic bilirubin monitoring, is an important co-factor related to extent of the reflux, the presence of lesions and the response to proton pump inhibitor therapy in GERD (210, 211, 229; see also Chapter 6). In the present study, approximately half of the patients had also pathological DGER.

Given the high prevalence of GERD and the good to excellent response to medical antireflux therapy with disappearance or marked reduction of excessive throat phlegm in the vast majority of patients, we might hypothetize that GER plays an important role in the origin of these chronic complaints. Theoretically, the origin of excessive throat phlegm may involve different etiological mechanisms, including direct supraesophageal reflux of gastric contents, altered biophysical properties of pharyngeal mucus or altered mucus clearance mechanisms. It is conceivable, and in our opinion even likely, that mucus of gastric origin, as well as other constituents of gastric contents, might reflux into the esophagus and subsequently into the pharynx. Mucus from swallowed saliva may follow a similar reflux pattern back into the pharynx. Alternatively, throat phlegm may originate from the mucous blanket that under physiological conditions covers the surface of the pharyngeal wall and mainly consists of salivary mucoproteins, repleted with mucoproteins secreted by airway mucosa that are continuously drained towards the pharynx through the mucociliary clearance process. This mucous blanket is moving aborally from the pharynx towards the esophagus and the stomach by regular swallowing acts. Normally, this aboral movement of the pharyngeal mucous blanket as well as of the airway mucociliary clearance process is unperceived. However, under pathological conditions, the physical properties of the pharyngeal mucous blanket might change and throat mucus might become more abundant and/or more viscous, thereby inducing a sensation of excessive and/or more difficult to clear throat phlegm. Similar to pH-related changes in rheological properties of gastric (91), biliary (143) and respiratory mucus (78), we can postulate a potential for refluxed acid to render the pharyngeal mucus more viscous and therefore more difficult to clear by swallowing only. When a drop in pharyngeal pH due to acid reflux spreads from the pharynx to the larynx and into the trachea, this may potentially not only increase viscosity of local surface mucus but may also slow or even impede airway mucociliary clearance, resulting in stasis of secretions. Brief (60 seconds) instillation of the rabbit trachea with solutions of HCl and pepsin at different pH had a direct inhibitory effect on mucociliary flow (MCF) with a gradual slowing of MCF from pH 5 to pH 3 and complete cessation of MCF at pH 2 (61). In addition, the enzymatic activity of pepsin may directly affect the underlying cilia (61). Similar effects on viscosity of surface mucus and on mucociliary clearance may occur in the middle ear (242) and potentially also in the nasosinusal complex when acid reflux extends into the nasopharynx and reaches the eustachian tube and the posterior nose (212). Impaired pharyngo-esophageal clearance mechanisms including pharyngeal hypocontractility and esophageal motility disorders may play an additional role in some patients with symptoms of excessive throat phlegm. Finally, as

animal experiments have shown that gastric juice causes mucosal injury and induces inflammation in the larynx and trachea (27, 255), changes in secretion and/or in the physical properties of airway mucus may occur secondarily to inflammation. Antireflux therapy with PPI eliminates or reduces GER and GEPR and might, by acting directly or indirectly upon the above described pathophysiological mechanisms, eliminate or reduce excessive throat phlegm and, if present, also other associated reflux-related symptoms and signs.

We found that YTP-patients had a higher prevalence of GERD, as defined in the above mentioned criteria, and of hiatus hernia. Moreover, YTP-patients not only had more severe DGER and more frequently a pathological DGER, they also showed a higher prevalence of pathological distal and proximal acid reflux as well as more severe proximal acid exposure. As throat phlegm occurs within or extends into the nasopharynx, this may be perceived as postnasal drip. Initially, prior to medical antireflux therapy, YTP-patients had a higher prevalence of associated feelings of postnasal drip and nasal congestion than TTP-patients. These findings may reflect a different duodeno-gastro-esophageal reflux (DGEPR) distribution pattern in YTP-patients compared to TTP-patients indicating more severe reflux, higher volume of reflux (192; see also Chapter 6) and possibly reflux extending more frequently into the nasopharynx. The observation that more YTP-patients than TTP-patients were in need of a PPI-maintenance dose to remain asymptomatic is also compatible with more severe reflux in YTP-patients, which could be related to the nature of the refluxate, or the refluxate volume, or both. Although studies have shown that DGER responds to PPI therapy, presumably indirectly through a decrease of intragastric fluid volume, the effect of acid suppression on DGER is less complete compared to the effect on acid reflux (19, 211, 229). Smoking and daily alcohol-intake were more prevalent in YTP-patients than in TTP-patients. It is well known that smoking cigarettes and regular alcohol intake enhance GER (198); whether these habits also stimulate DGER is actually unknown and requires further investigation. Sore throat was less prevalent in YTP-patients than in TTP-patients, but this difference was no longer present when all smoking and alcohol drinking subjects were excluded from the statistical analysis. Cigarette smoke acts as a sensory depressant in the upper aerodigestive tract (250). This mechanism may also explain the adverse effects of smoking on the protective reflex activity of the laryngopharynx, potentially facilitating a further spread of refluxed (duodeno)-gastric contents into the pharynx, larynx and airways (39, 40, 250). Alcohol intake may have similar effects.

The invariable association of YTP with DGER as well as the almost invariable association of YTP with pathological DGER (and with GERD, as defined in the above mentioned criteria,) together with the disappearance of YTP in all patients following medical antireflux therapy with a PPI indicates that YTP in these patients was the result of DGER and probably subsequent DGEPR. This is further supported by the observation that all seven YTP-patients who underwent double probe esophageal DGER monitoring had high DGER exposure both in the distal and in the proximal esophagus. Distal DGER was pathological in all of these patients and, although no established normal values are available regarding proximal DGER exposure, the median value of proximal DGER exposure in these patients was higher than the upper limit of normal for distal DGER exposure, making it very likely that these values reflect abnormal proximal DGER exposure.

The finding in these patients of a proximal extent of DGER implicates the potential of subsequent DGEPR especially when pressure in the upper esophageal sphincter (UES) is low, like during sleep or on UES relaxation (96). Monitoring DGEPR with the Bilitec 2000 probe in the pharynx is technically not feasible. In order to evaluate DGEPR, we therefore used an enzymatic assay to investigate the presence of bile acids in nine yellow stained and in seven transparent throat phlegm samples. The invariable presence of bile acids, exclusively found in YTP-samples at concentrations comparable to those found in esophageal and gastric aspirates of GERD patients (223) further supports the conclusion that YTP in these patients resulted from DGEPR.

In summary, to our knowledge, this is the first study that demonstrates a role of GERD and of DGER in patients with chronic unexplained, "refractory" complaints of excessive throat phlegm. We have demonstrated a high prevalence of GERD and a favourable response to antireflux therapy in these patients. Furthermore, we have shown that DGER may extend into the proximal esophagus and into the pharynx. As this is associated with yellow stained throat phlegm, DGER and supraesophageal bile reflux is a contributing factor to reflux-related supraesophageal symptoms and clinical signs in ORL patients. Patients with yellow throat phlegm, which is almost invariably associated with pathological DGER, have a higher prevalence of pathological distal and proximal esophageal acid exposure and are more frequently in need of a PPI maintenance dose compared to patients with transparent throat phlegm. In light of the findings of this study we might consider unexplained excessive throat phlegm a sign suggestive of GER and GEPR, and unexplained yellow throat phlegm a sign suggestive of proximal esophageal and supraesophageal DGER.

CHAPTER 10: SUMMARY OF ADDITIONAL STUDIES ON CLINICAL PRESENTATION AND MANAGEMENT OF REFLUX-RELATED ORL DISORDERS.

A. PAROXYSMAL LARYNGOSPASM : A TYPICAL BUT UNRECOGNIZED SUPRAESOPHAGEAL MANIFESTATION OF GASTROESOPHAGEAL REFLUX. Submitted for publication 2004.

Over a 30 months period, 35 consecutive adult patients with paroxysmal laryngospasm (LS) and with unimpaired vocal fold mobility were prospectively studied for co-existing gastroesophageal reflux disease (GERD). 19 patients reported frequent (>3 episodes a week) LS-episodes (FLS-patients) and 16 patients reported occasional LS-episodes (OLS-patients). All patients underwent an extensive otorhinolaryngological (ORL) examination, upper gastrointestinal endoscopy, ambulatory 24-hour dual channel esophageal pH monitoring and esophageal manometry. In addition, a subset of LS-patients also underwent ambulatory duodeno-gastro-esophageal reflux (DGER) monitoring. Patients with daily LS used the symptom marker during pH monitoring indicating separate LS-episodes. All FLS-patients and 14 OLS-patients (87%) had a diagnosis of GERD. Only 10 patients (29%) experienced heartburn and/or regurgitation. Compared to OLS-patients, FLS-patients generally had more severe GERD as is indicated by a higher prevalence of a hiatal hernia, higher distal and proximal esophageal acid exposure times and higher values of DGER. In 6 FLS-patients, 21 LS-episodes (91%) occurred simultaneous with acid reflux indicating a causal association between LS and GER. On antireflux therapy consisting of omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d. and lifestyle measures, LS ceased completely in all patients within 6 weeks. The present study not only demonstrates the role of GER in the pathogenesis of LS and the effectiveness of antireflux therapy, but also suggests that LS in adult patients with unimpaired vocal fold mobility might be considered a typical, although most frequently unrecognized, supraesophageal manifestation of GER.

B. CHRONIC MIDDLE EAR DISEASE AND GASTROESOPHAGEAL REFLUX DISEASE: A CAUSAL RELATION? Otol Neurotol. 2001 Jul; 22(4): 447-50.

OBJECTIVE: To describe one patient with a puzzling therapy-resistant unilateral chronic otitis media, analyse his diagnosis, and describe three similar patients with the same symptoms and signs, i.e. a chronic ear problem together with gastroesophageal reflux disease (GERD). STUDY DESIGN: Thorough analysis of one patient with a chronic ear problem and GERD, both of which responded favourably after antireflux therapy consisting of omeprazole and conservative antireflux measures (raising the head of the bed by 20 to 25 cm, avoiding meals and drinks 3 hours before retiring, and other dietary and lifestyle modifications), and a search for more patients with similar co-existing conditions. SETTING: Tertiary referral center. METHODS: Patients with chronic ear problems and GERD were thoroughly analysed by the otorhinolaryngologist and the gastroenterologist. The latter used endoscopy and Savary-Miller's classification of esophagitis, a 24-hour ambulatory dual esophageal pH monitoring, and esophageal manometry. RESULTS: Four patients were identified who had a chronic ear problem and simultaneous GERD. It is reasoned that GERD leads to nasopharyngitis and this to a chronic ear problem. All patients responded favourably to antireflux therapy. CONCLUSIONS: GERD may manifest itself as an extraesophageal manifestation, such as nasopharyngitis, leading to ear disease. Therapy-resistant chronic middle ear disease may be caused by GERD.

C. DETERMINANTS OF LONG-TERM OUTCOME OF PATIENTS WITH REFLUX-RELATED ORL SYMPTOMS. Presented at DDW 2000.

Gastro-esophageal reflux disease (GERD) is present in up to 75% of patients with chronic refractory ORL symptoms, and proton pump inhibitor therapy during 4 weeks induces symptom relief in the majority of these patients (Poelmans et al, DDW 1999). It has been suggested that endoscopic findings and quantification of esophageal acid exposure may help to predict the long-term outcome of medical therapy (Sataloff & Castell 1999). However, prospective studies that confirm this hypothesis are lacking. The *aim* of the present study was to investigate the relationship of endoscopic

findings and quantification of reflux with long-term outcome in patients with reflux-related ORL symptoms. *Methods:* Consecutive patients with chronic refractory unexplained ORL symptoms underwent upper gastrointestinal (g.i.) endoscopy, 24-hour dual esophageal pH and Bilitec® monitoring and esophageal manometry. Subsequently, all were treated with omeprazole 20 mg b.i.d. and patients with complete symptom relief at 4 weeks entered long-term follow-up for up to 2 years. After a treatment period of at least 8 weeks, omeprazole therapy was gradually decreased and the lowest effective omeprazole maintenance dose, if any, was determined. *Results:* 81 patients (50 men; mean age: 50) experienced complete symptom relief after 4 weeks of omeprazole 20 mg b.i.d. In 36 patients (44%, group A), PPI treatment could be stopped completely. 27 patients (33%, group B) required a maintenance dose of omeprazole 20 mg/day and 18 patients (22%, group C) required maintenance with omeprazole 40 mg/day. The prevalence of reflux esophagitis (11%, 85% and 78%, $p<0.001$) and of hiatal hernia (25%, 58% and 56%, $p<0.05$) were significantly lower in group A patients compared to groups B and C. Distal esophageal acid exposure (1.3±0.8;16.6±3.2 and 16.7±2.4%, $p<0.01$) and proximal esophageal acid exposure (0.1±0.1;5.0±3.4 and 1.0±1.0%, $p<0.05$) but not Bilitec® values (7.6±2.6;5.5±3.2 and 5.7±5.7%, NS) were significantly lower in group A compared to B and C. Predictive values for need of maintenance therapy were as follows: presence of esophagitis, 85%; distal acid exposure >7.5%, 86%; proximal acid exposure >1.8%, 75%; Bilitec® >12%, 77%. *Conclusion*: In patients with reflux-related ORL symptoms, initial findings on upper g.i. endoscopy, on 24-hour pH metry and on Bilitec® monitoring are not only useful in assessing the presence and severity of underlying reflux disease, they also help to predict the need for maintenance therapy in these patients.

D. EVALUATION OF A DISPOSABLE ACID EXPOSURE SENSOR IN THE MANAGEMENT OF PATIENTS WITH SUSPECTED GERD-RELATED ORL SYMPTOMS

Background/aims: Esophageal pH monitoring is considered the most appropriate investigation in patients with putative atypical manifestations of GERD, but diagnostic application of pH monitoring is hampered by its costs, invasive nature and technical requirements. Recently, we developed a cheap, disposable and easily

applicable miniature acid exposure sensor and we demonstrated that the sensor response (SR) is strongly correlated with the results of simultaneous esophageal pH monitoring (Tack et al., 2003). The aim of the present study was to investigate the use of the sensor in the evaluation of patients with suspected GERD-related ORL symptoms. Methods: 24 patients (14 men, mean age 46±2 years) with suspected GERD-related ORL symptoms underwent 24 hour ambulatory dual pH monitoring and SR monitoring at 5 cm proximal to the LES. Subsequently, all patients received PPI therapy and 21 were followed at two weeks intervals until symptom resolution. PPI therapy was gradually decreased if the patient was asymptomatic for at least 4 weeks on a given dose. Results: Distal acid exposure was pathological in 9 patients (38%). Complete symptom resolution after 8 weeks PPI therapy occurred in 13 patients (62%) and 17 patients (81%) were able to decrease and stop PPI therapy. A significant correlation was found between the exposure of the distal esophagus to acid and SR ($R = 0.42$; $p < 0.05$), and the acid exposure of the proximal esophagus and SR ($R = 0.56$; $p = 0.002$). However, the sensitivity and specificity of the SR to predict pathological distal esophageal acid exposure were poor (sensitivity generally below 50%). At a cut-off of 50, the SR had a sensitivity of 100% and specificity of 47% to predict PPI responsiveness. At the same cut-off, the sensor had 100% sensitivity and specificity in predicting the need for PPI maintenance. Conclusions: In patients with suspected GERD-related ORL symptoms, the acid exposure sensor does not adequately predict pathological acid exposure or short term PPI response. A high sensor response seems to identify a subset of patients who require PPI maintenance therapy.

CHAPTER 11: GENERAL CONCLUSIONS AND FUTURE PROSPECTS

Gastroesophageal reflux disease (GERD) and ORL disorders both commonly occur in the general population. Over the last 40 years, supraesophageal manifestations including a variety of pulmonary and ORL disorders, have been increasingly recognized to be associated with GERD. Although a possible causal association between GERD and several ORL disorders is increasingly suspected, many aspects of the relationship between both remain incompletely understood.

At present, upper g.i. endoscopy is not recommended in the diagnostic work-up of suspected GERD in ORL patients, as the prevalence of pathological findings is considered low. However, the studies on which this recommendation was based are hampered by a small number of patients or less accurate assessments of esophagitis. We prospectively assessed the prevalence of erosive esophagitis, Barrett's esophagus and other upper g.i. abnormalities at endoscopy in 405 consecutive ORL patients with chronic unexplained refractory symptoms. A group of 554 heartburn patients seen in the same period served as comparative population. We also evaluated the response to medical antireflux therapy. The most important finding of this study is that the majority (52%) of patients with chronic, refractory, unexplained ORL symptoms have abnormal endoscopic findings, suggestive of GERD. The finding of erosive esophagitis not only establishes a diagnosis of GERD with a supraesophageal symptomatic manifestation, but is also associated with significantly higher rates of symptom relief during the first 8 weeks of PPI therapy. Endoscopy is also useful in assessing the severity of GERD. Erosive esophagitis suggests a more severe form of GERD in which patients often require continuous PPI therapy for effective symptom relief and healing. Based on the findings of this study, the use of upper g.i. endoscopy as an initial investigation in suspected GERD-related chronic ORL symptoms might be advocated, especially when the cost of upper g.i. endoscopy is low and when risk factors for Barret's esophagus or for complicated forms of GERD are present. On PPI therapy (omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d.), the predominant ORL complaints were markedly reduced in 72% of the patients after 4 weeks and in 75% after 8 weeks. Therefore, an initial PPI treatment trial of 4 to 8 weeks duration seems sufficient to assess symptom response in a majority of ORL patients with suspected reflux-related chronic symptoms.

Suspected reflux-related supraesophageal symptoms and disorders may result from reflux of gastric contents into the distal and proximal esophagus and into the pharynx. Therefore, measuring proximal esophageal acid reflux may be useful in the evaluation of patients with suspected reflux-related supraesophageal manifestations. We intended to evaluate the clinical usefulness of ambulatory proximal pH monitoring by comparing the characteristics of 345 patients with and without abnormal proximal reflux in dual pH monitoring studies. We observed that acid reflux to the proximal esophagus is common in patients with GERD. We systematically studied factors associated with pathological proximal esophageal acid exposure. In only 6% of all the studied patients, proximal pH monitoring identifies pathological reflux in patients who would be considered normal based on distal pH monitoring alone. Furthermore, proximal pH monitoring does not differentiate patients with typical or atypical GERD manifestations. Finally, distal esophageal DGER exposure was not an independent risk factor for pathological proximal esophageal acid exposure. Therefore, our data do not support routine proximal esophageal pH monitoring as a clinical tool.

Compared to healthy controls, 26 patients with suspected reflux-related chronic ORL symptoms and 13 patients with typical GERD show impaired esophageal acid clearance. The ORL patients also have a decreased sensitivity to esophageal acid infusion, a finding that may help to explain the low prevalence of heartburn in patients with suspected reflux-related chronic ORL symptoms. Esophageal clearance function does not explain differences between patients with typical GERD and patients with suspected reflux-related chronic ORL symptoms.

Reflux investigations revealed GERD in 12 of 16 consecutive patients with a chronic unexplained refractory feeling of pressure in the ears (CRFP) and in all 5 consecutive patients with chronic unexplained refractory secretory otitis media (CSOM). In addition, more severe GERD was found in patients with CSOM than in patients with CRFP. This finding indicates a dose-response relationship and suggests causality. All patients responded favourably to antireflux therapy with omeprazole and conservative measures: middle ear drainage ceased in the CSOM patients and symptom relief was obtained in the CRFP patients. These findings suggest that otological symptoms and disorders may also occur as a consequence of GER in adults.

Excessive throat phlegm (TP) is a common symptom and unexplained excessive TP is a frequently occurring clinical condition. It has been suggested that excessive TP may represent supraesophageal reflux of gastric content in many cases, but proof for this hypothesis is lacking. Using endoscopy and pH monitoring in 59 patients with unexplained excessive TP, 33 patients with transparent TP and 26 patients with yellow TP, we could demonstrate GERD in 44 patients (75%). In keeping with the hypothesis that supraesophageal reflux is involved in the pathogenesis of unexplained excessive TP, the majority of patients became asymptomatic during treatment with standard doses of acid suppressive therapy. On 24-hour duodeno-gastro-esophageal reflux (DGER) monitoring, 32 patients (55%) had pathological DGER and this was associated with yellow TP. Proximal esophageal DGER monitoring revealed high DGER exposure in all investigated subjects. Chemical analysis revealed median bile aid concentrations of 0.06 μM in 9 YTP-samples and no detectable bile acids in 7 TTP-samples. We have demonstrated that DGER may extend into the proximal esophagus and into the pharynx, and this is associated with yellow TP. These findings establish DGER and supraesophageal bile reflux as a contributing factor to reflux-related supraesophageal symptoms and clinical signs in ORL patients. Compared to TTP patients, YTP patients had a higher prevalence of pathological DGER (27% and 92% respectively; $p < 0.001$), a higher prevalence of pathological distal (39% and 73% respectively; $p < 0.01$) and pathological proximal (12% and 54% respectively; $p < 0.001$) esophageal acid exposure and were more frequently in need of a PPI maintenance (37% and 71% respectively; $p = 0.03$). This study demonstrates that unexplained excessive TP can be considered a sign suggestive of GER and GEPR, and unexplained yellow TP a sign suggestive of proximal esophageal and supraesophageal DGER.

Paroxysmal laryngospasm (LS) is another condition which was suggested to be reflux-related, but again convincing evidence is lacking. Thirty three of 35 consecutive patients (94%) with paroxysmal LS received a diagnosis of GERD (esophagitis and/or pathological 24-hour pH monitoring). Patients with frequent LS (FLS), compared to those with occasional LS (OLS), had a higher prevalence of hiatal hernia, higher distal and proximal esophageal acid exposure times and higher DGER exposure. In 6 FLS patients the symptom maker was used during 24-hour pH monitoring: 21 of the 23 documented LS episodes occurred simultaneous with acid reflux indicating a causal association between LS and GER. On antireflux therapy with standard doses of PPI's, LS ceased in all patients within 6 weeks. This study not only demonstrates the role of GER in the pathogenesis of LS and the effectiveness of antireflux

therapy, but also suggests that LS in adult patients with unimpaired vocal fold mobility might be considered a typical, although most frequently unrecognized, supraesophageal manifestation of GER.

Finally, in preliminary studies, we demonstrated that the presence of esophagitis, higher esophageal acid exposure and higher esophageal DGER exposure are associated with the need for maintenance PPI therapy in patients with reflux-related ORL symptoms. The response of a disposable and easily applicable miniature acid exposure sensor also seems to identify a subset of patients who require PPI maintenance therapy.

In future studies, the mechanisms underlying supraesophageal manifestations of gastroesophageal reflux need to be established in more detail. Mechanisms underlying bile reflux as well as the potential of bile reflux as a pathogenetic factor should be further addressed in clinical studies and animal experiments. The role of diagnostic testing in patients with suspected reflux-related supraesophageal manifestations remains to be established and clinical studies are needed to address this issue. Additional placebo-controlled studies are required in ORL patents to assess the effectiveness of PPI therapy in various well-described symptom categories and ORL disorders. Large and well-designed multicenter studies are needed to increase evidence on reflux-related ORL disorders and further determine the role of reflux diagnostic testing and antireflux therapy in ORL patients. Additional studies are needed to determine a possible role for baclofen, endoluminal antireflux therapies and antireflux surgery in the treatment of patients with reflux-related supraesophageal symptoms.

CHAPTER 12: SUMMARY

Over the last 40 years, a possible causal association between gastroesophageal reflux disease (GERD) and several ORL symptoms and disorders is increasingly suspected but many aspects of this relationship remain incompletely understood. In the present thesis, several aspects of this association were studied in a series of ORL patients with suspected GERD-related chronic symptoms (i.e. throat symptoms, nonproductive cough, hoarseness, globus).

Current concepts in GERD were addressed in chapter 1. A literature review on suspected reflux-related ORL disorders was provided in chapter 2. In chapter 3, a brief outline of the thesis was provided and aims of the study were summarized. Materials and methods used in the study were described in chapter 4.

In chapter 5, we prospectively assessed the prevalence and severity of erosive esophagitis at endoscopy in 405 consecutive ORL patients with suspected GERD and in 545 typical GERD patients. We also evaluated the response to medical antireflux therapy with a proton pump inhibitor (PPI) (omeprazole 20 mg b.i.d. or lansoprazole 30 mg o.i.d.). The most important finding is that 52% of patients with chronic, refractory, unexplained ORL symptoms have abnormal endoscopic findings, suggestive of GERD. Only 19% of the ORL patients experienced heartburn or regurgitation. The finding of erosive esophagitis not only establishes a diagnosis of GERD with a supraesophageal symptomatic manifestation, but is also associated with significantly higher rates of symptom relief during the first 8 weeks of PPI therapy. On PPI therapy, the predominant ORL complaints were markedly reduced in 72% of the patients after 4 weeks and in 75% of the patients after 8 weeks. Patients with suspected GERD-related ORL symptoms have a high prevalence of esophagitis and this is associated with a better response to PPI-therapy.

In chapter 6, we evaluated the clinical usefulness of proximal esophageal pH monitoring by comparing the characteristics of 346 patients with and without abnormal proximal reflux (PR) in ambulatory dual pH monitoring studies. Fifty seven patients (16%) had pathological PR. We systematically studied factors associated with pathological PR. Only 20 patients (6%) had abnormal PR without abnormal distal acid reflux (DR). Furthermore, proximal pH monitoring did not differentiate patients with typical or atypical (respiratory or ORL) GERD manifestations. The multivariate analysis identified only pathological DR (and not esophageal

duodeno-gastro-esophageal reflux or manometric abnormalities) as independent risk factor for pathological proximal PR. Our data do not support routine proximal esophageal pH monitoring as a clinical tool: PR does not differentiate patients with typical or atypical GERD manifestations and depends mainly on DR.

In chapter 7 we found that 26 patients with suspected GERD-related chronic ORL symptoms and 13 patients with typical GERD showed impaired esophageal acid clearance as compared to healthy controls. In addition, the ORL patients also had a decreased sensitivity to esophageal acid infusion, a finding which might explain the low prevalence of heartburn in patients with suspected GERD-related chronic ORL symptoms. Esophageal clearance function does not explain differences between patients with typical GERD and patients with suspected GERD-related chronic ORL symptoms.

In chapter 8, reflux investigations (upper gastrointestinal endoscopy and 24-hour pH monitoring) revealed GERD in 12 of 16 consecutive patients with a chronic unexplained feeling of pressure in the ear(s) (CRFP) and in all 5 consecutive patients with chronic refractory secretory otitis media (CSOM). More severe GERD, found in CSOM patients, suggested a dose-response relationship and indicated causality. All patients responded favourably to antireflux therapy with omeprazole and conservative antireflux measures: middle ear drainage ceased in the CSOM patients and symptom relief was obtained in the CRFP patients. These findings suggest that otological symptoms or -disorders may occur as a consequence of reflux in adults.

In chapter 9, we addressed the hypothesis that unexplained excessive throat phlegm (TP) may represent supraesophageal reflux of gastric content in many cases. Using endoscopy and 24-hour pH monitoring in 59 patients with unexplained excessive TP (33 patients with transparent TP and 26 patients with yellow TP), we could demonstrate GERD in 44 patients (75%). On 24-hour duodeno-gastro-esophageal reflux (DGER) monitoring, 32 patients (55%) had pathological DGER and this was associated with yellow TP. Proximal DGER exposure was high in all investigated subjects and chemical analysis revealed median bile acid concentrations of 0.06 μM in 9 YTP-samples and no detectable bile acids in 7 TTP-samples. After a median of 4 weeks of PPI therapy, most patients improved and 61% became asymptomatic. Yellow TP-patients were more likely to require maintenance PPI therapy tha transparent TP-patients. Therefore, unexplained excessive TP is a sign suggestive of GER and

gastro-esophago-pharyngeal reflux (GEPR) and unexplained yellow TP a sign suggestive of duodeno-gastro-esophago-pharyngeal reflux (GEPR).

Chapter 10 provided a summary of additional studies on clinical presentation and management of reflux-related ORL disorders.

Paroxysmal laryngospasm (LS) is another condition which was suggested to be reflux-related, but again convincing evidence is lacking. Thirty three of 35 consecutive patients (94%) with a history suggestive of paroxysmal LS, received a diagnosis of GERD (esophagitis and/or pathological 24-hour pH monitoring). Patients with frequent laryngospasm (FLS), compared to those with occasional laryngospasm (OLS), had a higher prevalence of a hiatal hernia, higher distal and proximal esophageal acid exposure times and higher DGER exposure. In 6 FLS-patients the symptom marker was used during 24-hour pH monitoring: 21 of the 23 documented LS-episodes (91%) occurred simultaneous with acid reflux indicating a causal association between LS and GER. On antireflux therapy with standard doses of PPI's, LS ceased in all patients within 6 weeks. This study not only demonstrates the role of GER in the pathogenesis of paroxysmal LS and the effectiveness of antireflux therapy but also suggests that paroxysmal LS in adult patients with unimpaired vocal fold mobility might be considered a typical, although most frequently unrecognized, supraesophageal manifestation of GER.

Finally, in preliminary studies, we demonstrated that the presence of esophagitis, higher esophageal acid exposure and higher esophageal DGER exposure are associated with the need for maintenance PPI therapy in patients with reflux-related ORL symptoms. The response of a disposable and easily applicable miniature acid exposure sensor also seems to identify a subset of patients who require PPI maintenance therapy.

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SAMENVATTING

Zowel gastro-oesofagale refluxziekte (GORZ) als Neus, Keel en Oor (NKO) aandoeningen komen frequent voor in de algemene bevolking. In de loop van de laatste 4 decennia werd in toenemende mate een onderling verband tussen GORZ enerzijds en NKO en pulmonale aandoeningen anderzijds vastgesteld. Over een mogelijk oorzakelijk verband tussen beide type aandoeningen blijven vooralsnog vele onduidelijkheden bestaan.

Momenteel adviseert men geen diagnostische oesofago-gastroscopie bij NKO patiënten wanneer GORZ als een mogelijke oorzaak beschouwd wordt. Men neemt aan dat bij deze patiënten slechts zelden een oesofagitis wordt aangetroffen. Dit advies is echter gebaseerd op de resultaten van enkele studies met een beperkt aantal patiënten waarbij weinig accurate onderzoekstechnieken gebruikt werden voor het vaststellen van oesofagitis. Bij 405 opeenvolgende NKO patiënten met chronische onverklaarde symptomen, welke niet verbeterden met "conventionele" behandelingen, onderzochten wij op een prospectieve wijze de prevalentie van endoscopische afwijkingen zoals erosieve oesofagitis, Barrett's oesofagus en andere afwijkingen zoals peptische ulceraties. Een groep van 554 met zuurbranden als hoofdklacht die in dezelfde periode endoscopisch onderzocht werd vormde de controlegroep. Wij evalueerden bij deze patiënten ook de therapeutische respons van een antireflux behandeling met proton pomp inhibitoren (PPI's). De belangrijkste bevinding van dit onderzoek is dat de meerderheid van deze NKO patiënten (52%) endoscopische letsels vertoonde welke suggestief zijn voor GORZ. Het aantreffen van een erosieve oesofagitis bevestigt niet alleen de diagnose van GORZ maar is eveneens geassocieerd met een significant verhoogde symptoomrespons op PPI therapie gedurende de eerste 8 weken. Bovendien kan met behulp van endoscopie ook de ernst van GORZ bij deze patiënten vastgesteld worden. Een erosieve oesofagitis is doorgaans een ernstige vorm van GORZ, waarbij vaak een continue behandeling met PPI's noodzakelijk is voor symptoomcontrole en genezing van de oesofagitis. Op basis van deze bevindingen kunnen wij een endoscopie aanbevelen als een initieel diagnostisch onderzoek bij patiënten met mogelijke reflux-gerelateerde chronische NKO symptomen. Deze aanbeveling geldt vooral wanneer de kostprijs van de endoscopie niet te hoog is en bij een eventuele aanwezigheid van risicofactoren voor Barrett's oesofagus of van verwikkelingen van GORZ. Aansluitend op een behandeling met PPI's gedurende 4 weken (omeprazole 20 mg twee maal per dag of lansoprazole 30 mg éénmaal per dag) vertoonde 72% van de patiënten een duidelijke

symptomatische verbering na 4 weken en 75% na 8 weken. Een initiële behandeling met PPI's gedurende 4 tot 8 weken lijkt daarom voldoende om de therapie respons te evalueren bij de meerderheid van de NKO patiënten met vermoeden van reflux-gerelateerde chronische symptomen

Mogelijke reflux-gerelateerde supra-oesofagale symptomen en aandoeningen zijn potentieel een gevolg van reflux van maaginhoud in de distale en proximale slokdarm en in de keelholte. Daarom zou het nuttig kunnen zijn om proximale oesofagale reflux te registreren bij patiënten met mogelijke reflux-gerelateerde symptomen of aandoeningen. De evaluatie van proximale pH metingen als een mogelijk diagnostisch onderzoek in de klinische praktijk was het doel van de volgende studie, waarbij de kenmerken van 345 patiënten met en zonder abnormale proximale reflux vergeleken werden. Zure reflux in de proximale slokdarm werd vaak gevonden bij patiënten met GORZ. De met abnormale proximale reflux geassocieerde factoren werden systematisch onderzocht. Bij slechts 6% van al de onderzochte patiënten werd pathologische reflux vastgesteld in afwezigheid van pathologische distale reflux. Bovendien kan de proximale pH meting typische GORZ symptomen niet van atypische atypische GORZ symptomen onderscheiden. Abnormale distale oesofagale galreflux was geen onafhankelijke risicofactor voor pathologische proximale oesofagale zuurexpositie. De bevindingen van dit onderzoek ondersteunen niet het routinematige gebruik van proximale oesofagale pH meting als diagnostische test in de klinische praktijk.

Wij hebben een verminderde sensitiviteit van het slokdarmslijmvlies aangetoond bij zuurinfusie alsook een vertraagde zuurklaring bij 26 patiënten met mogelijke reflux-gerelateerde chronische NKO symptomen. Deze vaststellingen kunnen gedeeltelijk de lage prevalentie van zuurbranden verklaren bij deze patiënten. De oesofagale zuurklaring biedt geen verklaring voor het verschil tussen patiënten met typische GORZ symptomen en reflux-gerelateerde NKO symptomen.

Reflux onderzoeken (endoscopie en pH meting) toonden GORZ aan bij 12 van de 16 opeenvolgende patiënten met chronische onverklaarde, refractaire klachten van drukgevoelens in de oren en bij alle 5 patiënten met een chronische secreterende middenoorontsteking. Bovendien vertoonden deze laatste 5 patiënten meer ernstige vormen van GORZ dan de

patiënten met chronische onverklaarde klachten van drukgevoelens in de oren. Dit suggereert een oorzakelijk verband tussen GORZ enerzijds en deze chronische oorklachten en aandoeningen anderzijds . Alle patiënten reageerden gunstig op antireflux therapie met omeprazole, voedingsadviezen en levensstijlmaatregelen: de oorloop hield op en drukklachten in de oren verdwenen. Deze bevindingen suggereren dat bepaalde ooraandoeningen en symptomen ook bij volwassenen mogelijk een gevolg van GORZ zijn.

Overvloedige slijmvorming in de keel is in de klinische praktijk een frequent voorkomende klacht en kan niet altijd adequaat verklaard worden. Er is gesuggereerd dat overvloedige keelslijmvorming vaak het gevolg zou kunnen zijn van supra-oesofagale reflux van maaginhoud, maar enige vorm van bewijs voor deze hypothese is vooralsnog niet geleverd.
Met behulp van endoscopie en pH metingen bij 59 opeenvolgende patiënten met chronische, onverklaarde, refractaire overvloedige keelslijmvorming, 33 patiënten met transparante slijmen en 26 patiënten met gele slijmen, werd GORZ aangetoond bij 44 patiënten (75%). Tijdens de 24-uren galreflux metingen werd bij 32 patiënten (55%) pathologische galreflux vastgesteld; dit verschijnsel was geassocieerd met gele keelslijmen. Proximale oesofagale galreflux metingen toonden hoge waarden bij alle onderzochte patiënten. Met behulp van chemische analyse werden galzouten aangetroffen in 9 stalen van gele keelslijmen met een concentratie van gemiddeld 0.06 µM; in 7 transparante stalen van keelslijmen werden geen galzouten aangetroffen. Aansluitend op een behandeling met PPI's van gemiddeld 4 weken namen de klachten beduidend af bij de meeste patiënten terwijl 61% van hen klachtenvrij was. Bij patiënten met gele keelslijmen was er vaker een onderhoudsbehandeling met PPI's noodzakelijk dan bij patiënten met transparante keelslijmen. Met dit onderzoek toonden wij aan dat galreflux ook kan voorkomen in de proximale slokdarm en in de keelholte; dit laatste fenomeen is geassocieerd met geel gekleurde keelslijmen. Wij besluiten dat galreflux en supra-oesofagale galreflux mede verantwoordelijk kunnen zijn voor reflux-gerelateerde supra-oesofagale symptomen en klinische tekens bij NKO patiënten. Bij patiënten met geel gekleurde keelslijmen werd in de meeste gevallen niet alleen pathologische galreflux aangetoond maar ook een verhoogde zuurblootstelling in de distale en proximale slokdarm. De resultaten van dit onderzoek tonen aan dat onverklaarde refractaire overvloedige keelslijmen suggestief zijn voor gastro-oesofagale reflux en gastro-oesofago-pharyngeale reflux in het bijzonder. Geel gekleurde keelslijmen van onverklaarde oorsprong zijn suggestief voor supra-oesofagale galreflux.

Paroxysmale larynxspasmen (LS) kunnen eveneens veroorzaakt worden door GORZ maar onderzoek hierover is zeer beperkt. Bij 33 van 35 opeenvolgende patiënten (94%) met paroxysmale LS werd GORZ (oesofagitis en/of pathologische pH meting) aangetroffen. Patiënten met frequent recidiverende LS hadden, in vergelijking met patiënten met eerder occasionele LS, een hogere prevalentie van hiatale hernia, langduriger distale en proximale oesofagale zuurblootstelling, en hogere waarden van galreflux. Zes patiënten maakten gebruik van een symptoom merker tijdens de 24 uren pH meting: 21 van de 23 gedocumenteerde LS episodes (91%) traden simultaan op met zure reflux episodes in de slokdarm. Dit simultane optreden suggereert een oorzakelijk verband tussen reflux episodes enerzijds en LS episodes anderzijds. Bij alle patiënten verdwenen de LS episodes binnen de 6 weken aansluitend op een standaard gedoseerde PPI behandeling. Deze studie toont niet alleen de rol aan van gastro-oesofagale reflux in de pathogenese van LS en de efficiëntie van antireflux therapie maar suggereert verder dat LS, bij volwassenen (met een normale stembandmobiliteit), beschouwd kan worden als een typische, maar vaak miskende, supra-oesofagale manifestatie van gastro-oesofagale reflux.

Tot slot konden wij in enkele pre-liminaire studies aantonen dat de aanwezigheid van oesofagitis en een hogere oesofagale zuur- en galblootstelling geassocieerd zijn met de noodzaak van een PPI onderhoudstherapie bij patiënten met reflux-gerelateerde NKO symptomen. De respons van een disposable en gemakkelijk te plaatsen miniatuur zuurblootstelling-sensor kan patiënten identificeren welke een PPI onderhoudsbehandeling vereisen.

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REFERENCES

1. Anggiansah A, Taylor G, Bright N, Wang J, Owen WA, Rokkas T, Jones AR, Owen WJ. Primary peristalsis is the major acid clearance mechanism in reflux patients. Gut 1994; 35: 1536-1542.
2. Bain WM, Harrigton JW, Thomas LE et al. Head and neck manifestations of gastroesophageal reflux. Laryngoscope 1983; 93: 175-179.
3. Baldi F, Ferrarini F, Longanesi A, Ragazzini M, Barbara L. Acid gastroesophageal reflux and symptoms occurrence. Analysis of some factors influencing their association. Dig Dis Sci 1989; 34: 1890-1893.
4. Batch AJG. Globus pharyngeus (Part 1). J Laryngol Otol 1988: 102: 152-158.
5. Batch AJG, Thomson HA. Acid reflux presenting as a persistent cough (letter). Ear Nose Throat J 1989; 68, 881.
6. Bechi P, Paucciani F, Baldini F, Cosi F, Falciai R, Mazzanti R, Castagnli A, Pesseri A, Boscherini S. Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique. Dig Dis Sci 1993; 38: 1297-1306.
7. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111: 1313-1317.
8. Bernstein LM, Baker LA. A clinical test for esophagitis. Gastroenterology 1958; 34: 760.
9. Bortolotti M. Laryngospasm and reflex central apnoea caused by aspiration of refluxed gastric content in adults. Gut 1989, 30, 233-238.
10. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg 1999; 121: 255-262.
11. Bough DI, Sataloff RT, Castell DO, Hills JR, Gideon RM, Spiegel JR. Gastroesophageal reflux laryngitis resistant to omeprazole therapy. Journal of Voice 1995: 9: 205-211.
12. Burton DM, Pransky SM, Katz RM, Kearns DB, Seid AB. Pediatric airway manifestations of gastroesophageal reflux. Ann Otol Rhinol Laryngol 1992; 101: 742-749.
13. Caldwell MT, Byrne PJ, Brazil N, Crowley V, Attwood SE, Walsh TN, Hennessy TP. An ambulatory bile reflux monitoring system: an in vitro appraisal. Physiol Meas 1994; 15: 57-65.
14. Caldwell MT, Lawlor P, Byrne PJ, Walsh TN, Hennessy TP. Ambulatory oesophageal DGER monitoring in Barrett's esophagus. Br J Surg 1995; 82: 657-660.
15. Carlsson R, Dent J, Watts R, et al. Gastro-oesophageal reflux disease (GORD) in primary care: An international study of different treatment strategies with omeprazole. Eur J Gastroenterol Hepatol 1998: 10: 119.
16. Castell DO, Richter JE, Robinson M et al. Efficacy and safety of lansoprazole in the treatment of erosive esophagitis. Am J Gastroenterol 1996; 91: 1749-1758.
17. Chambers CW, Davis WE, Cook PR, Nishioka GJ, Rudman DT. Long-term outcome analysis of functional endoscopic surgery: correlation of symptoms with endoscopic examination findings and potential prognostic variables. Laryngoscope 1997; 107: 504-510.
18. Champion GL, Richter JE. Atypical presentations of gastroesophageal reflux disease: chest pain, pulmonary and ear, nose, throat manifestations. Gastroenterologist 1993; 1: 18-33.

19. Champion GL, Richter JE, Vaezi MF, Singh S, Alexander R. Duodeno-gastro-esophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology 1994; 107: 747-754.
20. Chernow B, Johnson LF, Janowitz WR, Castell D. Pulmonary aspiration as a consequence of gastroesophageal reflux: a diagnostic approach. Dig Dis Sic 1979; 24: 839-851.
21. Cherry J, Margulies SI. Contact ulcer of the larynx. Laryngoscope 1968; 78: 1937-1940.
22. Coffin LA. The relations of the upper air passages to disease of the gastrointestinal tract. Ann Otol Rhinol Laryngol 1903; 12; 521-526.
23. Contencin P, Narcy P. Nasopharyngeal pH monitoring in infants and children with chronic rhinopharyngitis. Int J Ped Otorhinolaryngol 1991; 22: 249-256.
24. Copper MP, Smit CF, Stanojcic LD, Devriese PP, Schouwenburg PF, Mathus-Vliegen LM. High incidence of laryngopharyngeal reflux in patients with head and neck cancer. Laryngoscope 2000, 110: 1007-1011.
25. Corso MJ, Pursani KG, Mohiuddin MA, Gideon RM, Castell JA, Katzka DA, Katz PO, Castell DO. Dig Dis Sci 1998; 43: 1513-1517.
26. Delahunty JE. Acid laryngitis. J Laryngol Otol 1972; 86: 335-342.
27. Delahunty JE, Cherry J. Experimentally produced vocal cord granulomas. Laryngoscope 1968; 78: 1941-1947.
28. DelGaudio JM, Waring JP. Empiric esomeprazole in the treatment of laryngopharyngeal reflux. Laryngoscope 2003; 113: 598-601.
29. Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC, Petrie DJ. Mechanisms of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 1980; 65: 256-267.
30. Dent J, Yeomans ND, Mackinnon M, Reed W, Narielvala FM, Hetzel DJ, Solcia E, Shearman DJC. Omeprazole versus ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. Gut 1994; 35: 590-598.
31. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophagal reflux disease. Arch Intern Med 1995; 155: 2165-2173.
32. Deveney CW, Benner K, Cohen J. Gastroesophageal reflux and laryngeal disease. Arch Surg 1993: 128:1021-1025.
33. DiBaise JK, Huerter JV, Quigley EMM. Sinusitis and gastroesophageal reflux disease. Ann Intern Med 1998: 129: 1078.
34. DiBaise JK, Lof J, Quigley EM. Can symptoms predict esophageal motor function or acid exposure in gastroesophageal reflux disease? A comparison of esophageal manometric and twenty-four-hour pH parameters in typical and extraesophageal gastroesophageal reflux disease. J Clin Gastroenterol 2001; 32: 128-132.
35. DiBaise JK, Olusola BF, Huerter JV, Quigley EMM. Role of GERD in chronic resistant sinusitis: a prospective open label, pilot trial. Am J Gastroenterol 2002; 97: 843-850.
36. Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. Am J Gastroenterol 1993; 88: 25-29.
37. Dodds WJ, Dent J, Hogan WJ et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982; 307: 1547-1552.
38. Donnely RJ, Berrisford RG, Jack CI, Tran J, Evans CC. Simultaneous tracheal and esophageal pH monitoring: investigating reflux-associated asthma. Ann Thoracic Surg 1993; 56: 1029-1034.

39. Dua K, Bardan E, Ren J, Sui Z, and Shaker R. Effect of chronic and acute cigarette smoking on the pharyngo-upper oesophageal sphincter contractile reflex and reflexive pharyngeal swallow. Gut 1998; 43: 537-541.
40. Dua K, Bardan E, Ren J, Sui Z, and Shaker R. Effect of chronic and acute cigarette smoking on the pharyngoglottal closure reflex. Gut 2002; 51: 771-775.
41. Ducolone A, Vandevenne A, Jouin H, Grob JC, Coumaros D, Meyer C, Burghard G, Methlin G, Hollender L. Gastroesophageal reflux in patients with asthma and chronic bronchitis. Am Rev Respir Dis 1987; 135: 327-332.
42. Eherer AJ, Habermann W, Hammer HF, Kieser K, Friedrich G, Krejs GJ. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled study. Scand J Gastroenterol 2003; 38: 462-467.
43. Ekstrom T, Tibbling L. Gastro-oesophageal reflux and triggering of bronchial asthma: a negative report. Eur J Respir Dis 1987; 71: 177-180.
44. El-Serag HB, Hepworth EJ, Lee P, Sonnenberg A. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol 2001a; 96: 2013-2018.
45. El-Serag HB, Lee P, Buchner A, Inadomi JM, Gavin M, McCarthy DM. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. Am J Gastroenterol 2001b; 96(4): 979-983.
46. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurological defects. Gastroenterology 2001c; 121: 1294-1299.
47. El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997; 113: 755-760.
48. Ergun GA, Kahrilas PJ. Clinical applications of esophageal manometry and pH monitoring. Am J Gastroenterol 1996; 91: 1077-1089.
49. Farkkila MA, Ertama L, Katila H et al. Globus pharyngis, commonly associated with esophageal motility disorders. Am J Gastroenterol 1994; 89(4), 503-508.
50. Fackler WK, Richter JE. Diagnostic tests for gastroesophageal reflux disease. In: Orlando RC. Gastroesophageal reflux disease. New York, Basel: Marcel Dekker, Inc. 2000: 118-119.
51. Fass R, Fennerty MB, Ofman JJ, Gralnek IM, Johnson C, Camargo E, Sampliner RE. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. Gastroenterology 1998; 115: 42-49.
52. Feldman M, Hartford WV, Fisher RS, Sampliner RE, Murray SB, Greski-Rose PA. Treatment of reflux esophagitis resistant to H_2-receptor antagonists with lansoprazole, a new H+/K+-ATPase inhibitor: a controlled, double-blind study. Am J Gastroenterol 1993; 88: 1212-1217.
53. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective randomized clinical and manometric study. Gastroenterology 2001; 121: 5-14.
54. Fitzgerald JM, Allen CJ, Craven MA, Newhouse MT. Chronic cough and gastroesophageal reflux. Can Med Assoc J 1989; 140: 520-524.
55. Fouad YM, Katz PO, Hattlebakk JG, Castell DO. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol 1999; 94: 1464-1467.
56. Fuchs KH, DeMeester TR, Albertucci M. Specificity and sensitivity of objective diagnosis of gastroesophageal reflux disease. Surgery 1987; 102: 575-580.

57. Gabriel and Jones. The importance of chronic laryngitis. J Laryngol Otol 1960; 74: 349-357.
58. Galli J, Cammarota G, Calò L, Agostino S, D'Ugo D, Cianci R, Almadori G. The role of acid and alkaline reflux in laryngeal squamous cell carcinoma. Laryngoscope 2002; 112: 1861-1865.
59. Galmiche JP, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. Aliment Pharmacol Ther 1997: 11: 765.
60. Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms. Chest 1994; 106: 1793-1796.
61. Gaynor EB. Gastroesophageal reflux as an etiologic factor in laryngeal complications of intubation. Laryngoscope 1988; 972-979.
62. Gaynor EB. Otolaryngologic manifestations of gastroesophageal reflux. Am J Gastroenterol 1991; 86: 801-808.
63. Geterud A, Bove M, Ruth M. Hypoharyngeal acid exposure: an independent risk factor for laryngeal cancer? Laryngoscope 2003; 113: 2201-2205.
64. Gill C, Morrison MD. Esophagolaryngeal reflex in a porcine animal model. J Otolaryngol 1997; 27: 76-80.
65. Ginsberg GG, Barkun AN, Bosco JJ et al. Endoscopic anti-reflux procedures. Gastrointest Endosc 2002; 56: 625-628.
66. Hanson DG, Conley D, Jiang J, Kahrilas P. Role of esophageal pH recording in management of chronic laryngitis; an overview. Ann Otol Laryngol 2000; 109: 4-9.
67. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of anti-reflux therapy for the treatment of chronic laryngitis. Ann Otol Rhinol Laryngol 1995; 104: 550-555.
68. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest 1997; 111: 1389-1402.
69. Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW, Bradley LA. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. Am J Med 1996; 100: 395-405.
70. Harmon JW, Johnson LF, Maydonovic CL. Effects of acid and bile salts on the rabbit esophageal mucosa. Dig Dis Sci 1981; 26: 65-72.
71. Helm JF, Dodds WJ, Hogan WJ et al. Acid neutralizing capacity of human saliva. Gastroenterology 1982; 83: 69-74.
72. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med 1984; 310: 284-288.
73. Helm JF, Dodds WJ, Riedel DR et al. Determinants of esophageal acid clearance in normal subjects. Gastroenterology 1983; 85: 607-612.
74. Hetzel D, Dent J, Reed W et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988; 95: 903-912.
75. Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. J Voice 2002; 16: 564-579.
76. Hogan WJ, Shaker R. Extraesophageal complications of gastroesophageal reflux disease. In: Orlando RC. Gastroesophageal reflux disease. New York, Basel: Marcel Dekker, Inc. 2000: 259-278.
77. Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. Dig Dis Sci 1991; 32: 1275-1279.

78.
79.
80.
81.
82.
83.
84.
85.
86.
87.
88.
89.
90.
91.
92.
93.
94.
95.
96.

78. Holma B, Hegg PO. pH- and protein-dependent buffer capacity and viscosity of respiratory mucus. Their interrelationship and influence on health. Sci Total Environ 1989; 84: 71-82.
79. Howard PJ, Heading RC. Epidemiology of gastro-esophageal reflux disease. World J Surg 1992; 16: 288-293.
80. Ing AJ, Ngu MC, Breslin ABX. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994; 149: 160-167.
81. Irwin RS, Curley FJ, French CL. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and oucome of specific therapy. Am Rev Respir Dis 1990; 141: 640-647.
82. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenic aspects. Chest 1993; 104: 1511-1517.
83. Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastro-esophageal reflux disease in an adult population. Ann Med 1995; 27: 67-70.
84. Jack CIA, Calverly PMA, Donnelly RJ, Tran J, Russell G, Hind CR, Evans CC. Simultaneous tracheal and esophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 1995; 50: 201-204.
85. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with "reflux laryngitis." Gastroenterology 1991; 100: 305-310.
86. Jamieson GC, Duranceau AC. The development of surgery for gastro-oesophageal reflux disease. In: Jamieson GC, ed. Surgery of the oesophagus; Edinburgh: Churchill Livingston, 1988: 233.
87. Janssens J, Vantrappen G, Vos R, Ghillebert G. The acid burden over an extended period preceding a reflux episode is a major determinant in the development of heartburn. Gastroenterology 1992; 103: A90 (abstract).
88. Jaspersen D, Weber R, Hammar CH , Draf W. Effect of omeprazole on the course of associated esophagitis and laryngitis. J Gastroenterol 1996; 31: 765-767.
89. Jindal JR, Milbrath MM, Shaker R, Hogan WJ, Toohill RJ. Gastroesophageal reflux disease as a likely cause of "idiopathic" subglottic stenosis. Ann Otol Rhinol Laryngol 1994; 103: 186-191.
90. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974; 62: 325-332.
91. Johnson LR. Gastric secretion. In: Johnson LR, ed. Gastrointestinal physiology; fifth edition; St.-Louis, Mosby, 1997: 82.
92. Johnsson F, Joelsson B. Reproducibility of ambulatory oesophageal pH monitoring. Gut 1988; 29: 886-889.
93. Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1987; 22: 14-18.
94. Kahrilas PJ. Gastroesophageal reflux disease. JAMA 1996; 276: 983-988.
95. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association: technical review on the clinical use of esophageal manometry. Gastroenterology 1994; 107: 1865-1884.
96. Kahrilas PJ, Dodds WJ, Dent J, Haeberle B, Hogan WJ, Arndorfer RC. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 1987; 92: 466-471.

97. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986; 91: 897-904.
98. Kahrilas PJ, Ergun GA. Otolaryngologic manifestations of GERD. In: Richter JE, ed. Ambulatory esophageal pH monitoring: a practical approach and clinical applications. 2 nd ed. New York, NY: Igaku-Shoin, 1997: 133-148.
99. Kahrilas PJ, Quigley EMM. Clinical esophageal pH recording: A technical review for practice guideline development. Gastroenterology 1996; 110: 1982-1996.
100. Kambic V, Radsel Z. Acid posterior laryngitis. J Laryngol Otol 1984; 98: 1237-1240.
101. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. Am J Med 1994; 96: 321-326.
102. Kasapidis P, Xynos E, Mantides A, Chrysos E, Demonakou M, Nikolopoulos N, Vassilakis JS. Differences in manometry and 24-hour ambulatory pH-metry between patients with and without endoscopic or histologic esophagitis in gastroesophageal reflux disease. Am J Gastroenterol 1993; 88: 1893-1899.
103. Katz PO. Ambulatory esophageal and hypopharyngeal pH monitoring in patients with hoarseness. Am J Gastroenterol 1990; 85: 38-40.
104. Katzka DA. Motility abnormalities in gastroesophageal reflux disease. Gastroenterol Clin North Am 1999 Dec; 28(4): 905-915.
105. Kauer WK, Peters JH, DeMeester TR et al. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. Ann Surg 1995; 222: 135-136.
106. 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: 633-638.
107. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-esophageal reflux disease. Lancet 1990; 335: 205-208.
108. Klinkenberg-Knol EC, Nelis F, Dent J et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. Gastroenterology 2000; 118: 661.
109. Knight RE, Wells JR, Parrish RS. Esophageal dysmotility as an important co-factor in extraesophageal manifestations of gastroesophageal reflux. Laryngoscope 2000; 110: 1462-1466.
110. Knill-Jones RP, Card WI, Crean GP, James WB, Spiegelhalter DJ. The symptoms of gastro-oesophageal reflux and of oesophagitis. Scand J Gastroenterol 1984; 19: 72-76.
111. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. The effect of the $GABA_B$ agonist baclofen in patients with symptoms and duodeno-gastro-esophageal reflux refractory to proton pump inhibitors. Gut 2003; 52: 1397-1402.
112. Koek GH, Tack J, Sifrim D, Lerut T, Janssens J. The role of acid and duodenogastroesophageal reflux in symptomatic reflux disease. Am J Gastroenterol 2001; 96: 2033-2040.
113. Koek GH, Vos R, Flamen P, Sifrim D, Lammert F, Vanbilloen, Janssens J, Tack J. Esophageal clearance of acid and bile: a combined radionuclide, pH and Bilitec® study. Gut 2004; 53(1): 21-26.
114. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hours pH monitoring and experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101(Suppl): 1-78.

115. Koufman JA, Belafsky P, Bach K, Daniel E, Postma G. Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. Laryngoscope 2002: 112: 1606-1609.
116. Larrain A, Carrasco E, Galleguillos F, Sepulveda R, Pope CE. Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. Chest 1991: 99: 1330-1336.
117. Leite LP, Johnston BT, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci 1997; 42(9): 1859-1865.
118. Lewin JS, Gillenwater AM, Garrett JD et al. Characterization of laryngopharyngeal reflux in patients with premalignant or early carcinomas of the larynx. Cancer 2003; 97: 1010-1014.
119. Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985; 94: 516-519.
120. Locke GR, Talley NJ, Fett SL, Zinsmeyer AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population based study in Olmsted County, Minnesota. Gastroenterology 1997; 112: 1448-1456.
121. Loehrl TA, Smith TL, Darling RJ, Torrico L, Prieto TE, Shaker R, Toohill RJ, Jaradeh SS. Autonomic dysfunction, vasomotor rhinitis, and extraesophageal manifestations of gastroesophageal reflux. Otolaryngol Head Neck Surg 2002; 126: 382-387.
122. Lorenz R, Jorysz G, Clasen M. The globus syndrome: value of flexible endoscopy of the upper gastrointestinal tract. J Laryngol Otol 1993; 107: 535-537.
123. Loughlin CJ, Koufman JA. Paroxysmal laryngospasm secondary to gastroesophageal reflux. Laryngoscope 1996; 106: 1502-1505.
124. Maceri RM, Zim S. Laryngospasm: an atypical manifestation of severe gastroesophageal reflux disease (GERD). Laryngoscope 2001; 111: 1976-1979.
125. Mansfield LE, Hameister HH, Spaulding NS et al. The role of the vagus nerve in airway narrowing caused by intraesophageal hydrochlorid acid provocation and intraesophageal distension. Ann Allergy 1981; 47: 431-434.
126. Mansfield LE, Stein MR. Gastroesophageal reflux and asthma: a possible reflex mechanism. Ann Allergy 1978; 41: 224-226.
127. Marks RD, Richter JE, Rizzo J, Koeler RE, Spenney JG, Mills TP, Champion G. Omeprazole versus H_2-receptor antagonists in treating patients with peptic stricture and esophagitis. Gastroenterology 1994; 106: 907-915.
128. Maronian NC, Azadeh H, Waugh P, Hillel A. Association of laryngopharyngeal reflux disease and subglottic stenosis. Ann Otol Rhinol Laryngol 2001; 110: 606-612.
129. Marshall RE, Anggiansah A, Owen WA, Owen WJ. The relationship between acid and bile reflux and symptoms in gastroesophageal reflux disease. Gut 1997; 40: 182-187.
130. Mattioli S, Pilotti V, Spangaro M, Grigioni WF, Zannoli R, Felice V, Conci A, Gozzetti G. Reliability of 24-hour home esophageal pH monitoring in diagnosis of gastroesophageal reflux. Dig Dis Sci 1989; 34: 71-78.
131. McNally PR, Maydonovic CL, Prosek RA, Collette RP, Wong RKH. Evaluation of gastroesophageal reflux as a cause of idiopathic hoarseness. Dig Dis Sci 1989; 34: 1900-1904.
132. Metz DC, Childs ML, Ruiz C, Weinstein GS. Pilot study of the oral omeprazole test for reflux laryngitis. Otolaryngol Head Neck Surg 1997; 16: 41-46.

133. Miko TL. Peptic (contact ulcer) granuloma of the larynx. J Clin Pathol 1989; 42: 800-804.
134. Mittal RK, Chiareli C, Liu J, Shaker R. Characteristics of lower esophageal sphincter relaxation induced by pharyngeal stimulation with minute amounts of water. Gastroenterology 1996; 111: 378-384.
135. Mittal RK, Fisher M, McCallum RW, Rochester DF, Dent J, Sluss J. Human lower esophageal sphincter response to increased intra-abdominal pressure. Am J Physiol 1990; 258: G 624-630.
136. Mittal RK, McCallum RW. Characteristics and frequency of transient relaxations of the lower esophageal sphincter in patients with reflux esophagitis. Gastroenterology 1988a; 95: 593-599.
137. Mittal RK, Rochester DF, McCallum RW. Electrical and mechanical activity in the human lower esophageal sphincter during diaphragmatic contraction. J Clin Invest 1988b: 81; 1182-1189.
138. Mittal RK, Rochester DF, McCallum RW. Sphincteric action of the diaphragm during a relaxed LES in humans. Am J Physiol 1989; 256: 6139-6144.
139. Mittal RK, Stewart WR, Schirmer BD. Effect of a catheter in the pharynx on the frequency of transient lower esophageal sphincter relaxations. Gastroenterology 1992; 103: 1236-1240.
140. Morrison MD. Is chronic gastroesophageal reflux a causative factor in glottic carcinoma? Otolaryngol Head Neck Surg 1988; 99: 370-373.
141. Morrison M, Rammage L, Emmani AJ. The irritable larynx syndrome. J Voice 1999; 13; 447-455.
142. Moser G, Wenzel-Abatzi TA, Stelzeneder M et al. Globus sensation: pharyngoesophageal function, psychometric and psychiatric findings, and follow-up in 88 patients. Arch Intern Med 1998; 158: 1365-1373.
143. Nakayama F. Pathogenesis of gallstones. In: Nakayama F, ed. Cholelithiasis: causes and treatment. Tokyo-New York; Igaku-Shoin, 1997: 82.
144. Ness J, Sontag S, Schnell T. Prevalence of gastroesophageal reflux (GER) in consecutive patients with hoarseness. Gastroenterology 1992; 102: A134 (abstract).
145. Noordzij JP, Khidr AK, Desper E, Meek RB, Reibel JF, Levine PA. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. Laryngoscope 2002; 112: 2192-2195.
146. Noordzij JP, Khidr A, Evans BA, Desper E, Mittal RK, Reibel JF, Levine PA. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. Laryngoscope 2001; 111: 2147-2151.
147. Oelschlager BK, Thomas RE, Maronian N et al. Laryngoscopy and pharyngeal pH are complementary in the diagnosis of gastroesophageal-laryngeal reflux. J Gastrointest Surg 2002; 6: 189-194.
148. Öhman L, Olofsson J, Tibbling L, Ericssson G. Esophageal dysfunction in patients with contact ulcer of the larynx. Ann Otol Rhinol Laryngol 1983; 92: 228-230.
149. Ollyo JB, Lang F, Fontolliet C, Monnier P. Savary-Miller's new endoscopic grading of reflux-esophagitis: a simple, reproducible, logical, complete and useful classification. Gastroenterology 1990; 99: A100 (abstract).
150. Ollyo JB, Monnier P, Fontolliet C et al. The natural history, prevalence and incidence of reflux esophagitis. Gullet 1993; 3(suppl): 3-10.
151. Olson NR. Laryngopharyngeal manifestations of gastroesophageal reflux disease. Otolaryngol Clin North Am 1991; 24: 1201-1213.

152. Orlando RC. Review article: oesophageal mucosal resistance. Aliment Pharmacol Ther 1998; 12(3): 191-197.
153. Orlando RC, Bryson JC, Powell DW. Mechanism of H^+ injury in rabbit esophageal epithelium. Am J Physiol 1984; 246: G718-725.
154. Ormseth EJ, Wong RKH. Reflux laryngitis: pathophysiology, diagnosis and management. Am J Gastroenterol 1999: 94: 2812-2817.
155. Ossakow SJ, Elta G, Bogdasarian R, Colturi T, Nostrant TT. Esophageal reflux and dysmotility as the basis of persistent cervical symptoms. Ann Otol Rhinol Laryngol 1987; 96: 387-392.
156. Ott DJ, Ledbetter MS, Koufman JA, Chen MY. Globus pharyngeus: radiographic evaluation and 24-hour pH monitoring of the pharynx and esophagus in 22 patients. Radiology 1994; 191: 95-97.
157. 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: 3131-3138.
158. Pace F, Santalucia F, Bianchi Porro G. Natural history of gastroesophageal reflux disease without esophagitis. Gut 1991; 32: 845-848.
159. Parilla P, Ortiz A, Martinez de Haro LF, Aguayo JL, Ramirez P. Evaluation of the magnitude of gastroesophageal reflux in Barrett's esophagus. Gut 1990; 31: 964-967.
160. Patti MG, Debas HT, Pellegrini C. Esophageal manometry and 24-hour pH monitoring in the diagnosis of pulmonary aspiration secondary to gastroesophageal reflux. Am J Surg 1992; 163: 401-406.
161. Penagini R, Schoeman MN, Dent J, Tippett MD, Holloway RH. Motor events underlying gastroesophageal reflux in ambulant patients with reflux esophagitis. Neurogastroenterol Mot 1996; 8: 131-141.
162. Peters FT, Kleibeuker JH. Barrett's oesophagus and carcinoma. Recent insights into its development and possible prevention. Scand J Gastroenterol Suppl 1993; 200: 59-64.
163. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children. A prospective analysis. Arch Otolaryngol Head Neck Surg 2000; 126: 831-836.
164. Poe RH, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. Chest 2003; 123: 679-684.
165. Redo SF, Bames WA, de la Sierra CA. Perfusion of the canine esophagus with secretions of the upper gastrointestinal tract. Ann Surg 1959; 149: 556.
166. Ren J, Shaker R, Dua K, Trifan A, Podvran B, Sui Z. Glottal adduction response to pharyngeal water stimulation: evidence for pharyngoglottal closure reflex. Gastroenterology 1994; 106: A588 (abstract).
167. Ren J, Shaker R, Medda B, Bonnevier J, Kern M, Dunn B. Effect of acute esophagitis on the esophagoglottal closure reflex in a feline model. Gastroenterology 1995: 105: A677 (abstract).
168. Richter JE. Severe reflux esophagitis. Gastrointest Endosc Clin North Am 1994; 4: 677-697.
169. Richter JE. Typical and atypical presentations of gastroesophageal reflux disease. The role of esophageal testing in diagnosis and management. Gastroenterol Clin North Am 1996; 25: 75-102.
170. Richter JE. Extraesophageal presentations of gastroesophageal reflux disease. Seminars in gastrointestinal disease 1997a: 8: 75-89.

171. Richter JE. Ambulatory esophageal pH monitoring: practical approach and clinical applications. Second edition. Baltimore: Williams & Wilkins, 1997b.
172. Richter JE, Castell DO. GE reflux: pathogenesis, diagnosis and therapy. Ann Intern Med 1982; 97: 93-103.
173. Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124: 859-867.
174. Rydberg L, Ruth M, Lundell L. Does oesophageal motor function improve with time after successful antireflux surgery? Results of a prospective, randomized clinical study. Gut 1997; 41: 82-86.
175. Salo JA, Kivilaakso E. Contribution of trypsin and cholate to the pathogenesis of experimental alkaline reflux esophagitis. Scand J Gastroenterol 1984; 19: 875-881.
176. Sandmark S, Carlsson R, Falso O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis. Scand J Gastroenterol 1988; 23: 625-632.
177. Sarosiek J, McCallum RW. Mechanisms of oesophageal mucosal defence. Baillieres Best Pract Res Clin Gastroenterol 2000; 14: 701-717.
178. Sataloff RT, Castell DO, Katz PO, Sataloff DM. Reflux laryngitis and related disorders. San Diego, Calif: Singular Publishing Group, 1999.
179. Schindlbeck NE, Heinrich C, Konig A, Dendorfer A, Pace F, Muller-Lissner SA. Optimal thresholds, sensitivity, and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. Gastroenterology 1987; 93: 85-90.
180. Schindlbeck NE, Ippisch H, Klauser AG, Muller-Lissner SA. Which pH threshold is best in esophageal pH monitoring? Am J Gastroenterol 1991; 86: 1138-1141.
181. Schindlbeck NE, Klauser AG, Voderholzer WA, Muller-Lissner SA. Empiric therapy for gastroesophageal reflux disease. Arch Intern Med 1995; 155: 2165-2173.
182. Schnatz PF, Castell JA, Castell DO. Pulmonary symptoms associated with gastroesophageal reflux: use of ambulatory pH monitoring to diagnose and direct therapy. Am J Gastroenterol 1996; 91: 1715-1718.
183. Schoeman MN, Holloway RH. Integrity and characteristics of secondary oesophageal peristalsis in patients with gastro-esophageal reflux disease. Gut 1995a; 36: 499-504.
184. Schoeman MN, Tippett MD, Akkermans LM, Dent J, Holloway RH. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology 1995b; 108: 83-91.
185. Sears RJ, Champion G, Richter JE. Characteristics of distal partial gastrectomy patients with esophageal symptoms of duodeno-gastric reflux. Am J Gastroenterol 1995; 90: 211-215.
186. Shaker R, Bardan E, Gu C, Kern M, Torrico L, Toohill R. Intrapharyngeal distribution of gastric acid refluxate. Laryngoscope 2003; 113: 1182-1191.
187. Shaker R, Dodds WJ, Ren J, Hogan WJ, Arndorfer RC. Esophagoglottal closure reflex: a mechanism of airway protection. Gastroenterology 1992; 102: 857-861.
188. Shaker R, Milbrath M, Ren J. et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. Gastroenterology 1995; 109: 1575-1582.
189. Shaker R, Ren J, Zamir Z, Sarna A, Liu J, Sui Z. Effect of aging, position, and temperature on the threshold volume triggering pharyngeal swallows. Gastroenterology 1994; 107: 396-402.
190. Shaw GY, Searl JP, Young JL, Miner PB. Subjective, laryngoscopic, and acoustic measurements of laryngeal reflux before and after treatment with omeprazole. J Voice 1996; 10: 410-418.

191. Shi G, Bruley des Varannes S, Scarpignato C, Le Rhun M, Galmiche JP. Reflux-related symptoms in patients with normal esophageal exposure to acid. The acid hypersensitive esophagus. Gut 1995; 37: 457-464.
192. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastro-esophageal reflux disease. Am J Gastroenterol 2001a; 96: 647-655.
193. Sifrim D, Holloway R, Silny J, Xin Z, Tack J, Lerut A, Janssens J. Acid, non-acid and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology 2001b; 120: 1588-1598.
194. Singh S, Richter JE, Bradley, Haile JM. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain. Dig Dis Sci 1993; 38: 1402-1408.
195. Sloan S, Kahrilas PJ. Impairment of esophageal emptying with hiatal hernia. Gastroenterology 1991; 100: 596-605.
196. Sloan S, Rademaker A, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? Ann Intern Med 1992; 117: 977-982.
197. Small PK, Loudon MA, Waldron B, Smith D, Campbell FC. Importance of reflux symptoms in functional dyspepsia. Gut 1995; 92: 195-198.
198. Smit CF, Copper MP, Schoots IG, van Leeuwen JA, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. Ann Otol Rhinol Laryngol 2001; 110: 190-193.
199. Smit CF, van Leeuwen JA, Mathus-Vliegen LM, Devriese PP, Semin A, Tan J, Schouwenburg PF. Gastropharyngeal and gastroesophageal reflux in globus and hoarseness. Arch Otolaryngol Head Neck Surg 2000; 126: 827-830.
200. Smit CF, Tan J, Devriese PP, Mathus-Vliegen LM, Brandsen M, Schouwenburg PF. Ambulatory pH measurements at the upper esophageal sphincter. Laryngoscope 1998; 108: 299-302.
201. Smith JL, Opekun AR, Larkai E, Graham DY. Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. Gastroenterology 1989; 96: 683-689.
202. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes, key components of the diagnostic evaluation and outcome of specific therapy Chest 1995; 108: 991-997.
203. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. Surgery 1998; 124: 28-32.
204. Sontag S, O'Conell S, Khandelwall S, Miller T, Nemchausky B, Schnell TG, Serlovski R. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99: 613-620.
205. Sontag S, O'Connell S, Khandelwal S, Miller T, Nemchausky B, Schnell TG, Serlovsky R. Effect of position, eating and bronchodilators on gastroesophageal reflux in asthmatics. Dig Dis Sci 1990; 35: 849-856.
206. Spechler SJ. Barrett's esophagus: what's new and what to do? Am J Gastroenterol 1989; 84: 220-223.
207. Spechler SJ. Epidemiology and natural history of gastro-esophageal reflux disease. Digestion 1992; 51 (suppl.1): 24-29.
208. Stein HJ, Barlow AP, DeMeester TR, Hinder RA. Complications of gastroesophageal reflux disease. Ann Surgery 1992; 216: 35-43.

209. Stipa F, Stein HJ, Feussner H, Kraemer S, Siewert JR. Assessment of non-acidic esophageal reflux: comparison between long-term reflux aspiration test and fiberoptic bilirubin monitoring. Dis. Esophagus 1997; 10: 24-28.
210. Tack J, Bisschops R, Koek GH, Sifrim D, Lerut T, Janssens J. Dietary restrictions during ambulatory monitoring of duodeno-gastro-esophageal reflux. Dig Dis Sci 2003; 48: 1213-1220.
211. Tack J, Koek GH, Demedts I, Sifrim D, Janssens J. Gastroesophageal reflux disease poorly responsive to proton pump inhibitors: acid reflux, bile reflux or both? Am J Gastroenterol 2004; in press.
212. Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children? Laryngoscope 2002; 112: 1930-1934.
213. Tauber S, Gross M, Issing WJ. Association of laryngopharyngeal symptoms with gastroesophageal reflux disease. Laryngoscope 2002; 112: 879-886.
214. Timmer R, Breumelhof R, Nadorp JH, Smout AJ. Oesophageal motility and gastro-esophageal reflux before and after healing of reflux oesophagitis: a study using 24-hour ambulatory pH and pressure monitoring. Gut 1994; 35: 1519-1522.
215. Timon C, D'Dwyer, Cagney D et al. Globus pharyngeus: long-term follow-up and prognostic factors. Ann Otol Rhinol Laryngol 1991; 100: 351-354.
216. Tobey NA, Carson JL, Alkiek RA, Orlando RC. Dilated intercellular spaces: a morphological feature of acid reflux-damaged human esophageal epithelium. Gastroenterology 1996; 111: 1200.
217. Toohill RJ, Kuhn JC. Role of refluxed acid in pathogenesis of laryngeal disorders. Am J Med 1997; 103 (5A): 100S-106S.
218. Torrico S, Kern M, Aslam M, Narayan S, Kannappan A, Ren J, Sui Z, Hofmann C, Shaker R. Upper esophageal sphincter function during gastroesophageal reflux events revisited. Am J Physiol Gastrointest Liver Physiol 2000: 279: G262-G267.
219. Tuchman DN, Boyle JT, Pack AI et al. Comparisons of airway responses following tracheal or esophageal acidification in the cat. Gastroenterology 1984; 87: 872-881.
220. Turley SD, Dietschy JM. Re-evaluation of the 3 alpha-hydroxysteroid dehydrogenase assay for total bile acids in bile. J Lipid Res 1978; 19: 924-928.
221. Ulualp SO, Toohill RJ, Hoffman R, Shaker R. Possible relationship of gastroesophagopharyngeal reflux with pathogenesis of chronic sinusitis. Am J Rhinol 1999a; 13: 197-202.
222. Ulualp SO, Toohill RJ, Hoffman R, Shaker R. Pharyngeal pH monitoring in patients with posterior laryngitis. Otolaryngol Head Neck Surg 1999b; 120: 672-677.
223. Vaezi MF. Duodenogastroesophageal reflux. In: Castell DO, Richter JE, ed. The esophagus; Third edition; Philadelphia; Lippincott Williams & Wilkins, 1999: 424-426.
224. Vaezi MF, Hicks DM, Ours TM et al. Are there specific laryngeal signs for gastroesophageal reflux disease? Gastroenterology 2000; 118 (suppl 2): A490 (abstract).
225. Vaezi MF, Lacamera RG, Richter JE. Validation studies of Bilitec® 2000: an ambulatory duodenogastric reflux monitoring system. Am J Physiol 1994; 267: G1050-1057.
226. Vaezi MF, Richter JE. Synergism of acid and duodenogastroesophageal reflux in complicated Barrett's esophagus. Surgery 1995; 117: 699-704.
227. Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology 1996; 111: 1192-1199.

228. Vaezi MF, Richter JE. Twenty-four hour ambulatory esophageal pH monitoring in the diagnosis of acid reflux-related chronic cough. South Med J 1997a; 90: 305-311.
229. Vaezi MF, Richter JE. Duodenogastroesophageal reflux and methods to monitor nonacidic reflux. Am J Med 2001 Dec 3; 111 Suppl 8A: 160S-168S.
230. Vaezi MF, Schroeder PL, Richter JE. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. Am J Gastroenterol 1997b; 92: 825-829.
231. Van Herwaarden MA, Samson M, Smout AJ. Excess gastroesophageal reflux in patients with hiatal hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology 2000; 119: 1439-1446.
232. Vela M, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and non-acid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001; 120: 1599-1606.
233. Venables T, Newland R, Patel AC, et al. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997: 32: 965.
234. Vinjirayer E, Gonzales B, Brensinger C, Bracy N, Obelmejias R, Katzka DA, Metz DC. Ineffective motility is not a marker for gastroesophageal reflux disease. Am J Gastroenterol 2003; 98: 771-776.
235. Vitale GC, Cheadle WG, Sadek S, Michel ME, Cuschieri A. Computerized 24-hour ambulatory esophageal pH monitoring and esophagogastroduodenoscopy in the reflux patient. Ann Surg 1984; 20: 724-728.
236. Wani MK, Woodson GE. Laryngeal contact granuloma. Laryngoscope 1999; 109, 1589-1593.
237. Ward PH, Bercy G. Observations on the pathogenesis of chronic non-specific pharyngitis and laryngitis. Laryngoscope 1982; 92: 1377-1382.
238. Ward PH, Hanson DG. Reflux as an etiological factor of carcinoma of the laryngopharynx. Laryngoscope 1988; 98: 1195-1199.
239. Ward PH, Zwitman D, Hanson D, Berci G. Contact ulcers and granulomas of the larynx: new insights into their etiology as a basis for more rational treatment. Otolaryngol Head Neck Surg 1980; 88: 262-269.
240. Waring PJ, Lacayo L, Hunter J, Katz E, Suwak B. Chronic cough and hoarseness in patients with severe gastroesophageal reflux disease. Diagnosis and response to therapy. Dig Dis Sci 1995; 40: 1093-1097.
241. Wenzl TG, Schenke S, Peschgens T, Silny J, Heimann G, Skopnik H. Association of apnea and nonacid gastroesophageal reflux in infants: investigations with intraluminal impedance technique. Pediatr Pulmonol 2001; 31(2): 144-149.
242. White DR, Heavner B, Hardy SM, Prazma J. Gastroesophageal reflux and eustachian tube dysfunction in an animal model. Laryngoscope 2002; 112: 955-961.
243. Wiener GJ, Copper JB, Wu WC, Koufman JA, Richter JE, Castell DO. Is hoarseness an atypical manifestation of gastroesophageal reflux (GER)? An ambulatory 24-hour pH study. Gastroenterology 1986; 90: A1691 (abstract).
244. Wiener GJ, Koufman JA, Wu WC et al. The pharyngoesophageal dual ambulatory pH probe for the evaluation of atypical manifestations of gastroesophageal reflux disease. Gastroenterology 1987; 92: A1694 (abstract).
245. Wiener GJ, Koufman JA, Wu WC, Copper JB, Richter JE, Castell DO. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-h ambulatory pH monitoring. Am J Gastroenterol 1989; 84: 1503-1508.

246. Wiener GJ, Morgan TM, Copper JB et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci 1988; 33: 1127-1133.
247. Williams D, Thompson DG, Heggie L, O'Hanrahan T, Bancewicz J. Esophageal clearance function following treatment of esophagitis. Gastroenterology 1994; 106: 108-116.
248. Williams D, Thompson DG, Marples M, Heggie L, O'Hanrahan T, Bancewicz J. Identification of an abnormal esophageal clearance response to intraluminal distension in patients with esophagitis. Gastroenterology 1992; 103: 943-953.
249. Wilmer A, Tack J, Frans E, Dits H, Vanderschueren, Bobbaerts H. Duodenogastroesophageal reflux and esophageal mucosal injury in mechanically ventilated patients. Gastroenterology 1999; 116: 1293-1299.
250. Wilson JA. Swallowing is a precarious business. Gut 1998; 43: 453.
251. Wilson JA, Heading RC, Maran AGD, Pryde A, Piris J, Allen PL. Globus sensation is not due to gastro-oesophageal reflux. Clin Otolaryngol 1987; 12: 271-275.
252. Wo JM, Grist WJ, Gussack G, Delgaudio JM, Waring JP. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. Am J Gastroenterol 1997a; 92: 2160-2165.
253. Wo, J.M., Hunter, J.G., and Waring, J.P. Dual-channel ambulatory esophageal pH monitoring: a useful diagnostic tool? Dig Dis Sci 1997b; 42: 2222-2226.
254. Woo P, Noordzij P, Ross JA. Association of esophageal reflux and globus symptom: comparison of laryngoscopy and 24-hour pH manometry. Otolaryngol Head Neck Surg 1996; 115: 502-507.
255. Wynne JW, Ramphal R, Hood CI. Tracheal mucosa damage after aspiration. Am Rev Respir Dis 1981; 124: 728-732.
256. Ylitalo R, Ramel S. Extraesophageal reflux in patients with contact granuloma: a prospective controlled study. Ann Otol Rhinol Laryngol 2002; 111: 441-446.
257. Zeitoun P, Carteret E. Natural history of reflux esophagitis in adults. In: Mignon M, Galmiche JP, eds. Control of acid secretion. Paris, London: J Libbey, 1988: 225-238.

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