

Medical treatment of gastro-oesophageal reflux disease

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Gastro-oesophageal reflux disease is common and is a chronic recurring condition. In view of our improved knowledge about the pathogenesis and complications of gastro-oesophageal reflux, the therapy should be individualized and a cost-effective approach should be attempted in its management.

The prevalence of gastro-oesophageal reflux disease (GORD) is high and presents many challenges to clinicians. Over the last decade, there have been significant advances in our understanding of its pathogenesis and major improvements in therapy. Because of the magnitude of the problem and chronic nature of the disease, it is essential to adopt a cost-effective and patient-oriented approach to the management of this condition.

GORD: A CHALLENGE OF THE NEW MILLENNIUM?

GORD is a major problem in Western countries since the prevalence is rising, perhaps because *Helicobacter pylori* infection is decreasing in the community and the two appear inversely related. From a physician's perspective, the challenges presented by GORD are many but principally are that the condition is common, it is often chronic, it is expensive to treat long term and there is very little knowledge about the pathogenesis of its possible complications, in particular Barrett's mucosa and oesophageal adenocarcinoma.

HOW COMMON IS HEARTBURN?

Most will be familiar with symptoms of GORD. Heartburn is the commonest symptom of reflux disease and is usually described as a retrosternal burning feeling rising from the stomach or lower chest up towards the neck, often associated with a bitter taste in the mouth. Heartburn and so-called acid regurgitation are among the commonest of all gastrointestinal symptoms, affecting around 30% of the population at one time or another, and about 10% of most Western communities on a regular basis.

In a population-based study in the USA, the prevalence of heartburn experienced at least

weekly was 17.8%, with 42.4% of the population reporting at least one episode of heartburn in the previous year (Locke et al, 1997). The prevalence increases with age, and there is a slight male predominance. Interestingly, in the Far East, heartburn is much less commonly reported and there is no immediately obvious explanation for this.

CAN GORD BE DEFINED?

According to the Genval Workshop Report (Denval et al, 1999) the term 'gastro-oesophageal reflux disease' should be used to include all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health-related wellbeing (quality of life) as a result of reflux symptoms, after adequate reassurance of the benign nature of their symptoms. Physical complications include any of the local oesophageal complications of oesophagitis, or asthma, aspiration pneumonia and laryngitis attributable to reflux.

The characteristic symptoms of heartburn and acid regurgitation are sufficiently specific to allow an accurate diagnosis of GORD in many patients. Unfortunately they are the predominant symptoms in only 50–60% of patients with GORD and often these are mixed with other dyspeptic symptoms, rendering the diagnosis more difficult when based upon symptomatology alone. Atypical symptoms of GORD include dysphagia, odynophagia, angina-like chest pain, shortness of breath, chronic cough or hoarseness.

ENDOSCOPY-NEGATIVE REFLUX DISEASE: A DIFFERENT ENTITY?

Several recent studies have shown that many patients with heartburn in a primary care setting have no visible abnormalities at endoscopy but

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respond to acid suppressive therapy. Erosive disease is present in only a small proportion of patients and is not generally predictive of the severity or frequency of heartburn at the time of examination.

In one study, Robinson et al (1998) showed that in patients who frequently took antacids and had not previously sought medical attention, 53% had a normal oesophageal mucosa, while 47% had erosive oesophagitis. The term 'endoscopy-negative reflux disease' is reserved for individuals who satisfy the definitions of GORD, but do not have either Barrett's epithelium or definite endoscopic oesophageal mucosal breaks (oesophageal mucosal erosion or ulceration).

Endoscopy-negative reflux disease may be somewhat distinctive in terms of presentation, pathophysiology and therapeutic responses. Diagnosis may be particularly challenging, since endoscopy, by definition, will be unhelpful and histological criteria for the diagnosis of 'microscopic oesophagitis' have not been generally agreed. It is usually accepted that the dominant mechanism of symptom production in reflux disease is by contact of the oesophageal mucosa with acid and/or pepsin. Oesophageal pH monitoring, on the contrary, may show slightly abnormal or even normal acid exposure in endoscopy-negative reflux disease.

The diagnosis may rest on a positive symptom association and a successful therapeutic trial with an acid suppressant or antacid. Accordingly, increased oesophageal sensitivity to acid may play an important role in endoscopy-negative reflux disease. There is often some symptom overlap in these patients with other functional gastrointestinal disorders and symptomatic response to acid suppression therapy may not always be as effective in these patients compared to those with erosive oesophagitis. Endoscopy-negative reflux disease does not usually appear to progress to oesophagitis, when followed over a period as long as 10 years (Isolauri et al, 1997).

IS ENDOSCOPY NECESSARY IN THE DIAGNOSIS OF GORD?

Endoscopy is useful in establishing the severity of oesophagitis and in identifying complications, but it is not necessary in all patients with typical symptoms. However, when symptoms are variable or atypical, an objective assessment of mucosal damage confirms the diagnosis of GORD. There are several grading systems available in the literature with limited studies validating their use. The recognition of minor endoscopic mucosal changes (erythema, oedema and friability) included in the grade 1 changes in the Savary-Miller classifica-

tion shows marked intra-observer variability. However, the newer classification system (Los Angeles classification) (*Table 1*) has been found to be reliable, predictive of heartburn severity and response to therapy (Lundell et al, 1999).

The finding of hiatus hernia cannot be used as a criterion in the diagnosis of GORD although the two are often associated. Routine biopsy of the oesophageal mucosa is generally unhelpful in the diagnosis of reflux disease and therefore unnecessary.

Early endoscopy is indicated in the group of patients presenting with dyspepsia for the first time over the age of 45–50 years, atypical symptoms or alarm symptoms (such as dysphagia, weight loss or haematemesis) because of diagnostic uncertainty and the need to exclude oesophageal stricture, peptic ulcer or malignancy. Early endoscopy is also indicated in patients with chronic severe reflux symptoms (at least twice a week for at least 6 months) when attempts should be made to plan the long-term management.

TRIAL WITH ACID SUPPRESSANTS TO DIAGNOSE GORD

Symptom relief with acid suppressants can be used therapeutically to make a provisional diagnosis of reflux disease, both before the endoscopy, or later if endoscopy is negative. It has been found to be most sensitive when a high dose proton pump inhibitor (PPI) is used (Schindlbeck et al, 1995) and some would use it to avoid endoscopy in patients with typical symptoms of reflux of milder severity, in the absence of alarm symptoms.

PROLONGED AMBULATORY PH MONITORING IN GORD DIAGNOSIS

Twenty-four-hour pH monitoring is no longer considered to be the gold standard in the diagnosis of GORD as it lacks sensitivity, specificity and reproducibility (Ghillebert et al, 1995). Normal acid exposure values are recorded in up to a quarter of patients with reflux oesophagitis and in

TABLE 1.
The Los Angeles classification for the endoscopic assessment of reflux oesophagitis

Grade	Definition
A	One or more mucosal breaks, not more than 5 mm in length
B	One or more mucosal breaks, more than 5 mm in length, not continuous between the tops of two or more mucosal folds
C	Mucosal breaks continuous between the tops of two or more mucosal folds, but involving less than 75% of oesophageal circumference
D	Mucosal breaks involving at least 75% of the oesophageal circumference

about one-third of patients with endoscopy-negative reflux disease. The correlation of symptoms with reflux episodes does increase the sensitivity of pH monitoring in the diagnosis of reflux disease. It should be reserved for patients with atypical symptoms, inappropriate response to therapy and in the assessment before antireflux surgery.

NATURAL HISTORY OF GASTRO-OESOPHAGEAL REFLUX

Despite the high prevalence of the condition, very few data are available on its long-term natural history. Most longitudinal studies are of GORD patients with endoscopic evidence of oesophagitis, the majority of which are on medical treatment. The disorder is usually chronic, spontaneous improvements occur in a minority and although almost all patients with erosive oesophagitis can be healed with adequate acid suppressive therapy, in 80% symptoms recur within 30 weeks of discontinuation of therapy (Hetzel et al, 1988). The severity of oesophagitis does not usually worsen in follow up of up to 10 years (Ollyo et al, 1993).

The mortality of longstanding GORD has been reported to be similar to the background population. However, this notion has been challenged by recent observations of a strong and probably causal relation between gastro-oesophageal reflux and oesophageal adenocarcinoma reported from a nationwide, population-based, case-control study in Sweden (Lagergren et al, 1999). Among persons with weekly heartburn or regurgitation for 5 years or more, as compared with persons without such symptoms, the odds ratio was 7.7 (95% confidence interval 5.3–11.4) for the subsequent development of oesophageal adenocarcinoma. The more frequent, more severe, and longer-lasting the symptoms of reflux, the greater the risk (odds ratio 43.5, 95% confidence interval 18.3–103.5).

Heartburn has a significant negative impact on the quality of life of the patient (Glise and Wiklund, 1997). Health-related wellbeing is impaired in proportion to the frequency of heartburn and the effect of heartburn on the quality of life tends to be similar irrespective of whether or not oesophagitis is present. Concern about reflux symptoms being the result of a life-threatening problem such as cancer is not uncommon among patients who have yet to be endoscoped, and can cause further impairment of health-related wellbeing in addition to the direct impact of symptoms. In one study, nearly three-quarters of patients had significantly reduced quality of life scores compared with the general population more than 10 years after diagnosis (McDougall et al, 1996).

The major complications of oesophagitis are ulceration (5%), stricture formation (8–20%)

and Barrett's epithelium (8–20%). Less than 2% of patients with oesophagitis develop significant gastrointestinal bleeding (Kharilas, 1998).

MANAGEMENT OF PATIENTS WITH GORD: ROLE OF LIFESTYLE MEASURES

Lifestyle modifications are generally believed to be the first step in the management of GORD. Dietary modification is advised with early evening meal, low fat, low calorie diet and avoidance of potential oesophageal irritants such as citrus juices, coffee, alcohol, cola and chocolates. Nocturnal reflux is abnormally increased in a subgroup of patients usually with severe oesophagitis and these patients may benefit from bedhead elevation. Cessation of smoking and loss of weight if overweight may be helpful. Unfortunately, although lifestyle modifications are symptomatically beneficial, there is little evidence of their efficacy in the healing of oesophagitis.

Various medications including sedatives, tranquilizers, anticholinergics, theophylline and calcium channel blockers promote gastro-oesophageal reflux by reducing lower oesophageal sphincter tone and thus should be avoided by all patients with GORD. There have been many reports implicating non-steroidal anti-inflammatory drugs in the pathogenesis of oesophagitis, oesophageal ulceration and stricture formation. It has been suggested that although they do not induce reflux in normal subjects, there is increased damage to the oesophageal mucosa in people with decreased lower oesophageal sphincter tone and increased basal gastric acid secretion (Scheiman et al, 1995).

DRUG THERAPY: STEP UP OR STEP DOWN?

For initial therapy of GORD patients with or without oesophagitis, there is a general ascending level of efficacy from antacids and alginates or histamine-2 (H_2) receptor antagonist or cisapride, to a combination of an H_2 receptor antagonist with cisapride, to a PPI (Vigneri et al, 1995). The progression of efficacy is essentially the same for initial and long-term therapy of GORD patients, irrespective of whether they have endoscopy-negative reflux disease or erosive oesophagitis.

PPI therapy is considered as initial treatment of choice by some, with subsequent trial of step down of the intensity of therapy as symptoms improve. Others would adopt the alternative step up approach where antacids and alginates and/or H_2 receptor antagonists are only replaced by more potent acid suppressants if symptoms continue unabated (*Figure 1*). Both approaches are effective in appropriate cases; however, the recent

trend tilts in favour of the step down approach as it leads to more prompt achievement of symptom control and healing of oesophagitis (Green et al, 1995). Maintenance therapy with a combination of cisapride and H₂ receptor antagonist is more effective than monotherapy with either and similarly maintenance therapy with either cisapride or H₂ receptor antagonist is less effective than with a PPI. The maintenance treatment should be stepped down to the lowest dose that controls symptoms. A practical approach to management of GORD is outlined in *Figures 2 and 3*.

MANAGEMENT OF COMPLICATIONS

Only a small number of patients with peptic stricture need repeated dilatation; most remain well and the frequency of dilatation may be reduced by PPIs administered long term.

Management of Barrett's oesophagus remains controversial. It is generally accepted that in Barrett's oesophagus oesophageal squamous mucosa is replaced by metaplastic intestinal columnar epithelium. It is pre-malignant and prolonged acid suppression therapy with conventional doses is of little value in reversing metaplasia. A combination of high-dose acid suppression with laser or photodynamic ablation of the metaplastic tissue with or without fundoplication has been suggested, but its long-term efficacy in preventing the development of adenocarcinoma still remains to be established. Most centres follow the policy of endoscopic surveillance, but controversy exists about the frequency of endoscopy, management of different grades of dysplasia and cost-effectiveness of such a surveillance programme (Heatley and Guillou, 1997). The risk of a patient developing adenocarcinoma in Barrett's oesophagus varies between about 1 in 50 to 1 in 400 patient years follow-up and the risk is greater in males who smoke and have a long segment of Barrett's mucosa.

HELICOBACTER PYLORI AND GORD: TO ERADICATE OR NOT?

It has been suggested that long-term PPI therapy may be associated with an increased risk of gastric mucosal atrophy in the presence of *H. pylori* infection and *H. pylori* eradication should be considered if long-term acid suppression is planned (Kuipers et al, 1996). However, the available evidence does not fully support this view. Conversely, *H. pylori* eradication may increase the risk of reflux disease if previously suppressed acid secretion recovers significantly as a result of healing of corpus gastritis (Labenz et al, 1997). Also, gastric pH monitoring studies have shown that the efficacy of acid suppression by PPIs is reduced after *H. pylori* eradication. In

the light of current knowledge, *H. pylori* eradication would not be generally recommended in the management of reflux disease.

WHEN TO REFER FOR ANTIREFLUX SURGERY?

Modern antireflux surgery techniques, particularly laparoscopic fundoplication, may offer an alternative to long-term acid suppressant therapy

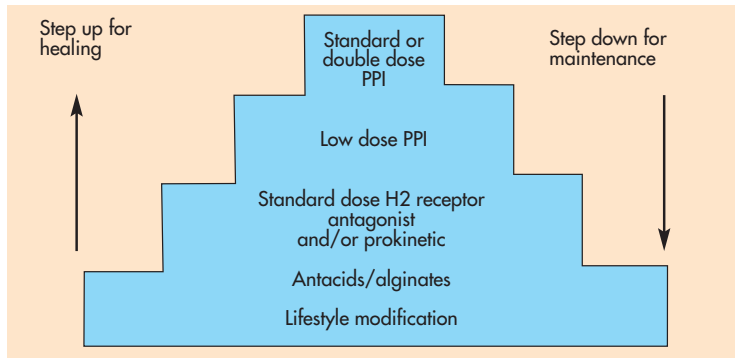


Figure 1. Step up/step down approach hierarchy.

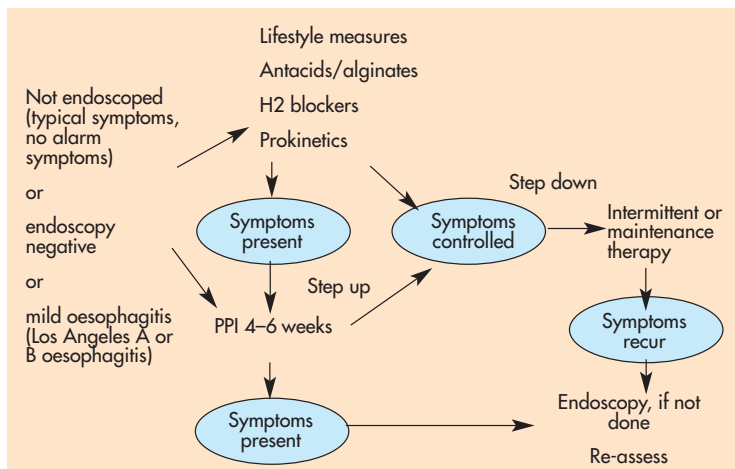


Figure 2. Gastro-oesophageal reflux disease management algorithm for mild or moderate disease. PPI= proton pump inhibitor.

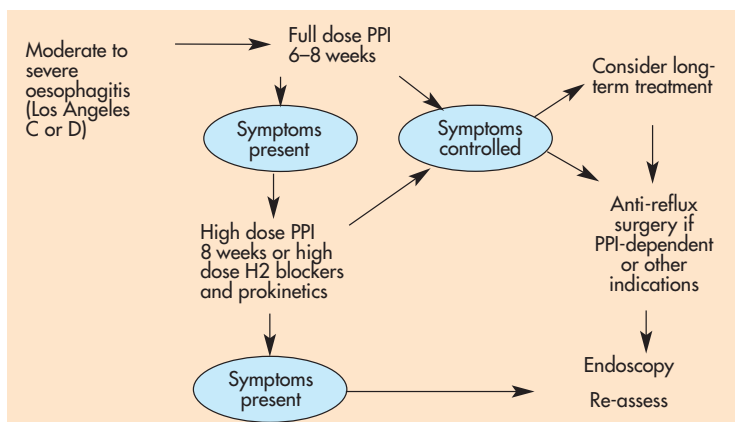


Figure 3. Gastro-oesophageal reflux disease management algorithm for severe disease. PPI= proton pump inhibitor.

in experienced hands. With the availability of potent acid suppressant medication, most patients, if compliant, can be treated very effectively. The indications for surgical referral would be patient preference, intractable regurgitation requiring intensive medical therapy with PPI dependence, presence of respiratory symptoms resulting from aspiration and volume reflux, and young patients with complicated GORD. Long-term studies comparing the outcomes and cost-effectiveness of the two modalities are currently being carried out and results are awaited with interest.

HEALTH ECONOMICS

GORD is common and is a chronic recurring condition. With the recent introduction of more effective and expensive pharmacological agents, such as PPIs, there is growing importance in the pharmacoeconomics of treatment. The magnitude of the problem is reflected in the fact that UK expenditure on PPIs is greater than any other drug, amounting to £334 million in 1997. An economic evaluation considers both costs and outcomes of the treatment and GORD economic evaluation studies have largely used the technique of cost-effectiveness analysis.

Studies vary with respect to the cost data collected, from drug costs only to all direct health care costs and indirect costs (i.e. productivity losses as a result of work absence). Given the therapeutic goals of treatment, a preferred outcome is one that offers a greater period of time free from symptoms, healing of oesophagitis and preventing complications over time (Sridhar et al, 2000).

CONCLUSIONS

The advent of PPIs as powerful acid suppressants has expanded the traditional approaches to the management of GORD. Endoscopy negative patients are more commonly presenting with reflux symptoms. Lifestyle measures are being less promoted but remain important in long-term symptomatic relief. Most patients will need long-term maintenance or intermittent therapy. The

choice between medical therapy and laparoscopic surgery often depends on patient preference. The relationship between gastro-oesophageal reflux, Barrett's oesophagus and oesophageal adenocarcinoma is an area of active research which will hopefully answer some of the outstanding problems in the management of this condition. **HM**

Conflict of interest: Dr Heatley has received a number of grants from pharmaceutical companies with products which have uses in this therapeutic area to aid in research.

- Bate CM, Richardson PDI (1992) A one-year model for the cost-effectiveness of treating reflux oesophagitis. *Br J Med Econ* **2**: 5-11
- Dent J, Brun J, Fendrick AM et al (1999) An evidence-based appraisal of reflux disease management — the Genval Workshop Report. *Gut* **44** (suppl 2): S1-S16
- Ghillebert G, Demeyere AM, Janssens J et al (1995) How well can quantitative 24-hour intraoesophageal pH monitoring distinguish various degrees of reflux disease? *Dig Dis Sci* **40**: 1317-24
- Glise H, Wiklund I (1997) Measurement of the impact of heartburn and dyspepsia on quality of life. *Aliment Pharmacol Ther* **11**(suppl 2): 73-7
- Green JRB, Bate CM, Copeman MB, Taylor MD (1995) A comparison of cost-effectiveness of omeprazole and ranitidine in reflux oesophagitis. *Br J Med Econ* **8**: 157-69
- Heatley RV, Guillou PG (1997) Barrett's oesophagus — a ray of hope. *Eur J Gastroenterol Hepatol* **9**: 873-5
- Hetzel DJ, Dent J, Reed WD et al (1988) Healing and relapse of severe peptic oesophagitis after treatment with omeprazole. *Gastroenterology* **95**: 903
- Isolauri J, Luostarinen M, Isolauri E et al (1997) Natural course of gastroesophageal reflux disease: 17-22-year follow up of 60 patients. *Am J Gastroenterol* **92**: 37-41
- Kharilas P (1998) Gastroesophageal reflux disease and its complications. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal and Liver Disease*. WB Saunders and Co, Philadelphia
- Kuipers EJ, Lundell L, Klinkenberg-Knol EC et al (1996) Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux oesophagitis treated with omeprazole or fundoplication. *N Engl J Med* **334**: 1018-22
- Labenz J, Blum A, Bayerdorffer E, Meining A, Stolte M, Borsch G (1997) Curing *H. pylori* infection in patients with duodenal ulcer may provoke reflux oesophagitis. *Gastroenterology* **112**: 1442-7
- Lagergren J, Bergstrom R, Lindgren A, Nyren O (1999) Symptomatic gastroesophageal reflux as a risk factor for oesophageal adenocarcinoma. *N Engl J Med* **340**: 825-31
- Locke RG, Talley N, Fett S, Zinmeister A, Melton LJ (1997) Prevalence and clinical spectrum of gastroesophageal reflux: a population based study in Olmsted County Minnesota. *Gastroenterology* **112**: 1448-56
- Lundell LR, Dent J, Bennett JR et al (1999) Endoscopic assessment of oesophagitis: clinical and functional and further validation of the Los Angeles Classification. *Gut* **45**: 172-80
- McDougall NI, Johnston BT, Kee F, Collins JS, McFarland RJ, Love AH (1996) Natural history of reflux oesophagitis; a 10-year follow up of its effect on patient symptomatology and quality of life. *Gut* **38**(4): 481-6
- Ollyo JB, Monnier P, Fontollet C et al (1993) The natural history, prevalence and incidence of reflux oesophagitis. *Gullet* **3** (Suppl): 3-10
- Robinson M, Earnest D, Rodriguez-Stanley S et al (1998) Heartburn requiring frequent antacid use may indicate significant illness. *Arch Intern Med* **158**: 2373-6
- Scheiman JM, Patel PM, Henson EK, Nostrant TT (1995) Effect of naproxen on gastroesophageal reflux and oesophageal function: a randomized double-blind placebo-controlled study. *Am J Gastroenterol* **90**(5): 754-7
- Schindlbeck NE, Klausner AG, Voderholzer W et al (1995) Empiric therapy of gastroesophageal reflux disease. *Arch Intern Med* **155**: 1808-12
- Sridhar S, Goeree R, O'Brien BJ, Hunt R (2000) Cost-effectiveness of treatment alternatives for gastro-oesophageal reflux disease: a review and appraisal of the literature. In: Bodger K, Daly MJ, Heatley RV, eds. *Clinical Economics in Gastroenterology*. Blackwell Science, Oxford: 26-46
- Vigneri S, Termini R, Leandro G et al (1995) A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* **333**: 1106-10

KEY POINTS

- Gastro-oesophageal reflux disease is a common medical condition and can cause considerable morbidity.
- Heartburn and acid regurgitation are fairly specific symptoms for this condition and enable an accurate diagnosis to be made in many.
- Most patients do not have erosive oesophagitis on endoscopy.
- A therapeutic approach can be step up or step down. Both treatments are effective in appropriate cases, although the latter is gaining in popularity.
- Medical treatment is very effective and few patients need surgery.
- The relationship between gastro-oesophageal reflux, Barrett's oesophagus and oesophageal adenocarcinoma is complicated and currently under close scrutiny.