

Recommended management of GORD in general practice

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Gastro-oesophageal reflux disease is a common complaint in its mildest form and often related to lifestyle. Our Drug review describes the properties, efficacy and side-effects of the available drug options, followed by an analysis of prescription data and sources of further information.

Gastro-oesophageal reflux disease (GORD) is a common disorder characterised by pathological exposure of the oesophageal mucosa to gastric juice. In its mildest form it is an extremely common complaint affecting up to 40 per cent of adults.¹

Symptoms

Symptoms of GORD cover a wide spectrum. Patients most commonly complain of heartburn or retrosternal pain related to meals, recumbency and stooping. Other well-recognised symptoms include epigastric pain, regurgitation, waterbrash and dysphagia. Nausea and back pain are more atypical presentations.

Pathophysiology

GORD is a result of exposure of the lower oesophageal mucosa to gastric contents. This is usually gastric acid

but may occasionally be alkaline, *ie* bile. Reflux of gastric contents into the oesophagus is prevented by both physiological and anatomical mechanisms. These comprise:

- the lower oesophageal sphincter – made up of the distal smooth muscle of the oesophagus
- the intra-abdominal segment of oesophagus – acting as a valve that closes in response to a rise in intra-abdominal pressure
- the diaphragm
- peristalsis of the oesophagus – returning gastric contents to the stomach.

Patients with hiatus hernia will not have the benefit of the valve action of the intra-abdominal oesophagus. However, it is important to note that symptoms of GORD and the presence of a hiatus hernia correlate poorly and are not synonymous.

Reflux of gastric contents into the oesophagus is a normal physiological event. Symptoms occur when this becomes more frequent and prolonged. Factors that increase the likelihood of reflux or exacerbate symptoms are shown in Table 1, and Table 2 lists drugs associated with reflux.

It should be noted that only 2 per cent of patients with reflux symptoms will have evidence of oesophagitis on endoscopy.² Although there is evidence of a direct correlation between the severity of GORD and the degree of oesophageal exposure to acid, there is no correlation between symptoms and endoscopic findings.

Twenty-four-hour studies of oesophageal pH show that patients with more severe reflux disease have more prolonged and frequent episodes during which oesophageal luminal pH is less than 4.0.³

The most frequently used scale to grade reflux oesophagitis endoscopically is the Savary-Miller classification:

- Grade 1: single or isolated lesions affecting one longitudinal fold
- Grade 2: multiple erosive lesions, noncircumferential, affecting more than one longitudinal fold
- Grade 3: circumferential lesions
- Grade 4: chronic lesions, *eg* strictures (see Figure 2).

Investigation

Clinical history

The majority of patients will present with typical reflux symptoms (heartburn, acid regurgitation). These symptoms are approximately 90 per cent specific⁴ and, when they predominate, a clinical diagnosis can be made with reasonable confidence.

Helicobacter pylori

The prevalence of *Helicobacter pylori* is no greater in patients with GORD than the rest of the population. For patients with reflux found to be positive for *H. pylori*, eradication of the organism does not achieve any benefit.

Barium swallow/meal

This is not a sensitive diagnostic test since oesophagitis must be severe to be detected radiologically, although a hiatus hernia may be readily demonstrated.

However, it will detect other pathology such as strictureing (see Figure 2), peptic ulceration and carcinoma. From this perspective it may have a part to play in reassuring some patients. In addition, barium swallow does show motility disorders which may be contributing to symptomatology. The radiation dose must, however, be considered, particularly in the young.

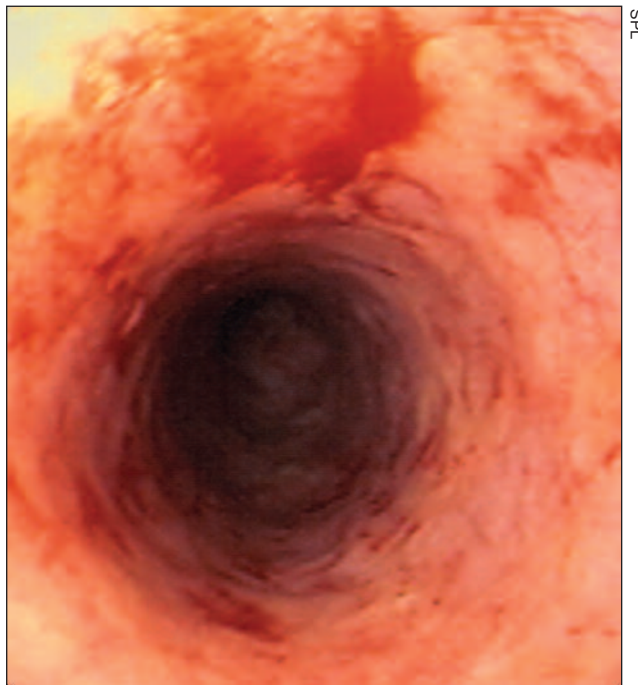


Figure 1. Inflamed and bleeding oesophagus due to acid reflux; lifestyle is an important factor in GORD and self-help measures should be encouraged where possible

Gastroscopy

This is the investigation of choice. Although it will not demonstrate reflux, it will show any resultant oesophageal damage. Other, more serious pathology such as carcinoma can be reliably excluded.

Twenty-four-hour pH monitoring

This provides evidence of reflux and is useful in some patients with an atypical history and a normal gastroscopy. It may be combined with other oesophageal function studies such as manometry. More recently Bravo pH probes have been developed and, although not as widely available, can be

- delayed gastric emptying, *eg* ingestion of fatty foods, leading to increased cholecystokinin release; gastric emptying may be abnormal in up to 40 per cent of GORD patients
- drugs (see Table 2)
- smoking (relaxes lower oesophageal sphincter) and alcohol (leads to increased acid production)
- pregnancy and increased weight (disturbs physiological antireflux mechanisms)
- exertion, bending, recumbency
- emotional factors
- stress – probably by delaying gastric emptying

Table 1. Risk factors for reflux or exacerbation of symptoms

- calcium-channel blockers
- nitrates
- theophyllines
- bisphosphonates
- corticosteroids
- NSAIDs

Table 2. Drugs associated with GORD¹⁴

used for patients intolerant of standard probes as they are catheter free. They also have the advantage of recording for up to 48 hours and may be more accurate; however, an endoscopy is needed to place them. In addition, impedance measurements may be useful in patients with alkaline reflux.

It should be noted that some patients will have a normal endoscopy and pH studies but yet have classical reflux symptoms. If further investigation of these patients with an 'acid-sensitive' oesophagus is required a Bernstein test could be considered, although this is very rarely used and correlation of symptoms with smaller falls in pH may provide similar information.

Complications

Barrett's oesophagus (see Figure 3)

Metaplastic columnar epithelium replaces normal stratified squamous epithelium in the lower oesophagus of those exposed to acid reflux. This is a premalignant condition, with patients diagnosed with Barrett's suffering a 30- to 50-fold increase in risk for adenocarcinoma. The overall risk is, however, small and it is still unclear as to whether all these patients should be enrolled into endoscopic screening programmes.

Oesophageal stricture (see Figure 2)

Benign peptic strictures causing progressive dysphagia in those with the most severe disease are estimated to occur in about 1 per cent of patients.¹

Oesophageal ulcer

This is a rare complication of severe reflux and usually presents with bleeding.

Management

The prime aim is symptom control. It is less clear as to whether active management prevents complications such as Barrett's oesophagus.

A significant element of GORD is lifestyle related, so the patient should be encouraged in self-help measures such as weight loss, cessation of smoking and raising the head of the bed on 10cm blocks; pillows should not be used as they may worsen GORD. This advice should be reinforced by the appropriate leaflet.

These measures may be enough to render some patients symptom free. The majority, however, will still require pharmacological, endoscopic or surgical management.

Drugs used in GORD work by preventing acid entering the oesophagus, by neutralising acid or by reducing gastric acid production.

Antacids

These act by neutralising gastric acid and thus raising gastric pH. They are available over the counter, are suitable for mild symptoms and are best taken when the discomfort occurs or is expected. There is little clinical evidence of symptomatic relief over placebo.⁵

Alginates

These form a raft that floats on the surface of the gastric contents preventing their reflux into the oesophagus, and most are available as compound preparations that also includes antacids. There is some evidence of relief of symptoms.⁵

H₂-antagonists

This class of drugs competitively inhibits the actions of histamine at the H₂ receptors of the stomach, which are found in acid-secreting cells. Stimulation with histamine causes gastric acid secretion. Use of H₂-antagonists decreases basal and food-stimulated acid secretion by up to 90 per cent⁶ and they are established to be safe for long-term treatment. They have been used for some time in the treatment of reflux disease and are known to improve symptoms, although their duration of action is only six to eight hours.

Side-effects of H₂-antagonists (see Table 3) are minor. They include dizziness, rashes, diarrhoea and muscle pains. Compared to other drugs in the group cimetidine is also more likely to cause gynaecomastia and inhibition of cytochrome P450, which has implications for anticoagulant and anticonvulsant dosages. It may also cause confusion in older people and should not be used in these patients.

Proton-pump inhibitors

This class of drugs blocks H⁺/K⁺ATPase. This is known as the proton pump and is the final common pathway to acid secretion. Proton-pump inhibitors (PPIs) markedly reduce basal and stimulated gastric acid



Figure 2. Oesophageal strictures occur in around 1 per cent of patients and can be detected by barium swallow/meal

secretion and provide a high level of symptom control. Although the half-life of omeprazole is only one hour, its onset of action takes several hours and it affects acid secretion for two to three days.

Although PPIs are now the mainstay of treatment for reflux they are also the most expensive. In 2005 the NHS drugs bill for PPIs was £446 million, which is two-thirds of the total expenditure on GI drugs.⁷ However, PPIs are becoming more affordable as some are now available generically.

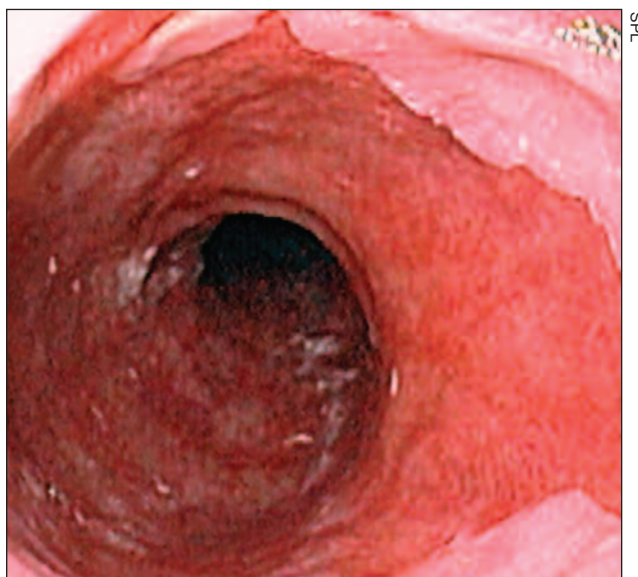


Figure 3. Barrett's oesophagus; patients with complications from reflux disease such as stricturing or Barrett's oesophagus should remain on a PPI

PPIs are well tolerated. Headache, abdominal pain and diarrhoea are the most commonly reported side-effects. Toxicology studies in rats have shown that life-long inhibition of gastric acid secretion with high-dose PPI leads to profound hypergastrinaemia, atrophic gastritis and progression to adeno and carcinoid tumour formation. However, though some human observational studies to date have reported increased incidence of tumour formation in patients using PPIs, it is likely that this is not a true effect but resulting from confounding factors.⁸⁻¹⁰

Combination therapy with PPIs and H₂-antagonists may be useful in patients with resistant symptoms. Ranitidine has been shown to reduce nocturnal acid reflux more effectively than omeprazole.¹¹

More recently, concern has been raised regarding the concomitant use of PPIs and clopidogrel (Plavix). A recent cohort study showed that use of the two drugs after acute coronary syndrome was associated with an increased risk of adverse events;¹² however, further studies are needed.

In addition, there is some evidence of greater than expected incidence of enteric infection, including *Clostridium difficile*, in patients on acid suppression, especially PPIs (odds ratio of 2.05).¹³

Finally, there are case reports of PPIs causing acute interstitial nephritis. A recent systematic review showed this to be rare, idiosyncratic and difficult to predict.¹⁴

Prokinetic agents

Since up to 40 per cent of patients with GORD have delayed gastric emptying, it seems logical to suggest that prokinetic agents may have a part to play in management. Although most trial data are available on cisapride (now withdrawn), metoclopramide is commonly used today. This is a dopamine antagonist that, in addition to its central effects, has a significant local action on gastric motility, causing acceleration of gastric emptying as well as improving oesophageal clearance.

Metoclopramide is said to relieve symptoms of reflux about as effectively as H₂-antagonists.⁵ Side-effects include extrapyramidal effects, drowsiness, diar-

rhoea and depression. It may be more conveniently given twice daily using a slow-release formulation.

Domperidone is an alternative, with fewer side-effects but possibly less effective.

Bile reflux

Alkaline (bile) reflux may be a more common cause of reflux symptoms in patients with previous gastric or biliary surgery. Management of this group is difficult but a combination of a prokinetic agent and sucralfate (a mucosal-protective agent) is often beneficial.

What is the best management plan?

GORD is a common disorder for which patients often require medical treatment for prolonged periods of time. It therefore has a large impact on the resources of both primary and secondary care. As such, what is the optimum approach?

Making the diagnosis

It seems reasonable to treat a patient with classical symptoms of heartburn and waterbrash empirically. Those patients with alarm symptoms (dysphagia, weight loss, anaemia, haematemesis) should be singled out for early diagnostic endoscopy (see Table 4). In addition, patients over the age of 55 with unexplained, persistent, recent-onset symptoms should be considered for endoscopy.¹⁵

A case can be made for endoscoping all patients with significant and persistent reflux, not only for reassurance but also to detect those younger patients with Barrett's oesophagus who might benefit from screening. There is, however, a poor correlation between symptoms and the presence of Barrett's mucosa.

Lifestyle alterations

Patients should be given the following lifestyle advice:

- lose weight (if appropriate)
- stop smoking
- elevate the head of the bed
- avoid large and/or late meals
- avoid fatty meals or snacks
- avoid chocolate and alcohol
- avoid caffeine, spices, chillies, onions, garlic and fruit juices.

Pharmacological treatment

Healing The results from a number of randomised, blind studies indicate that both healing of oesophagitis and symptom relief is inferior with standard doses of H₂-antagonists compared to standard doses of PPIs and that the duration of treatment is important. After eight weeks of treatment with PPIs, healing rates for

Antireflux drugs	Side-effects
<i>Antacids</i>	GI disturbance
<i>Alginates</i>	GI disturbance
<i>H₂-antagonists</i>	GI disturbance, altered LFTs, headache, dizziness, rash, tiredness; rarely, pancreatitis, heart conduction defects, depression, hypersensitivity, blood disorders
<i>Proton-pump inhibitors</i>	GI disturbance, headache, dizziness, dry mouth, insomnia, drowsiness, malaise, blurred vision, rash, pruritus; rarely, taste disturbance, liver dysfunction, peripheral oedema, hypersensitivity, photosensitivity, fever, depression, interstitial nephritis, blood disorders, arthralgia, myalgia
<i>Metoclopramide</i>	extrapyramidal effects, hyperprolactinaemia, tardive dyskinesia, drowsiness, diarrhoea, depression, neuroleptic malignant syndrome, rashes, pruritus, oedema
<i>Domperidone</i>	hyperprolactinaemia, GI disturbance, extrapyramidal effects, allergic reactions

Table 3. Side-effects of drugs used in GORD management (BNF, Sept 2009)

grades 2-4 oesophagitis are 82-95 per cent but only 25-58 per cent with H₂-antagonists.¹⁶ Similar figures apply to heartburn relief.

Maintenance Again, PPIs are more effective than H₂-antagonists. At 12 months 80 per cent of patients on full-dose omeprazole were in remission compared with 49 per cent on ranitidine.¹⁷

Low-dose PPIs are also more effective than H₂-antagonists at maintaining long-term relief and almost as effective as full-dose PPIs. It has been shown that for prevention of recurrent oesophagitis 90 per cent of patients taking 30mg lansoprazole daily for 12

<ul style="list-style-type: none"> • GI bleeding • weight loss • dysphagia • persistent vomiting • iron-deficiency anaemia • epigastric mass • suspicious barium meal • age over 55 with unexplained, persistent, recent-onset symptoms

Table 4. Criteria for endoscopy¹⁴

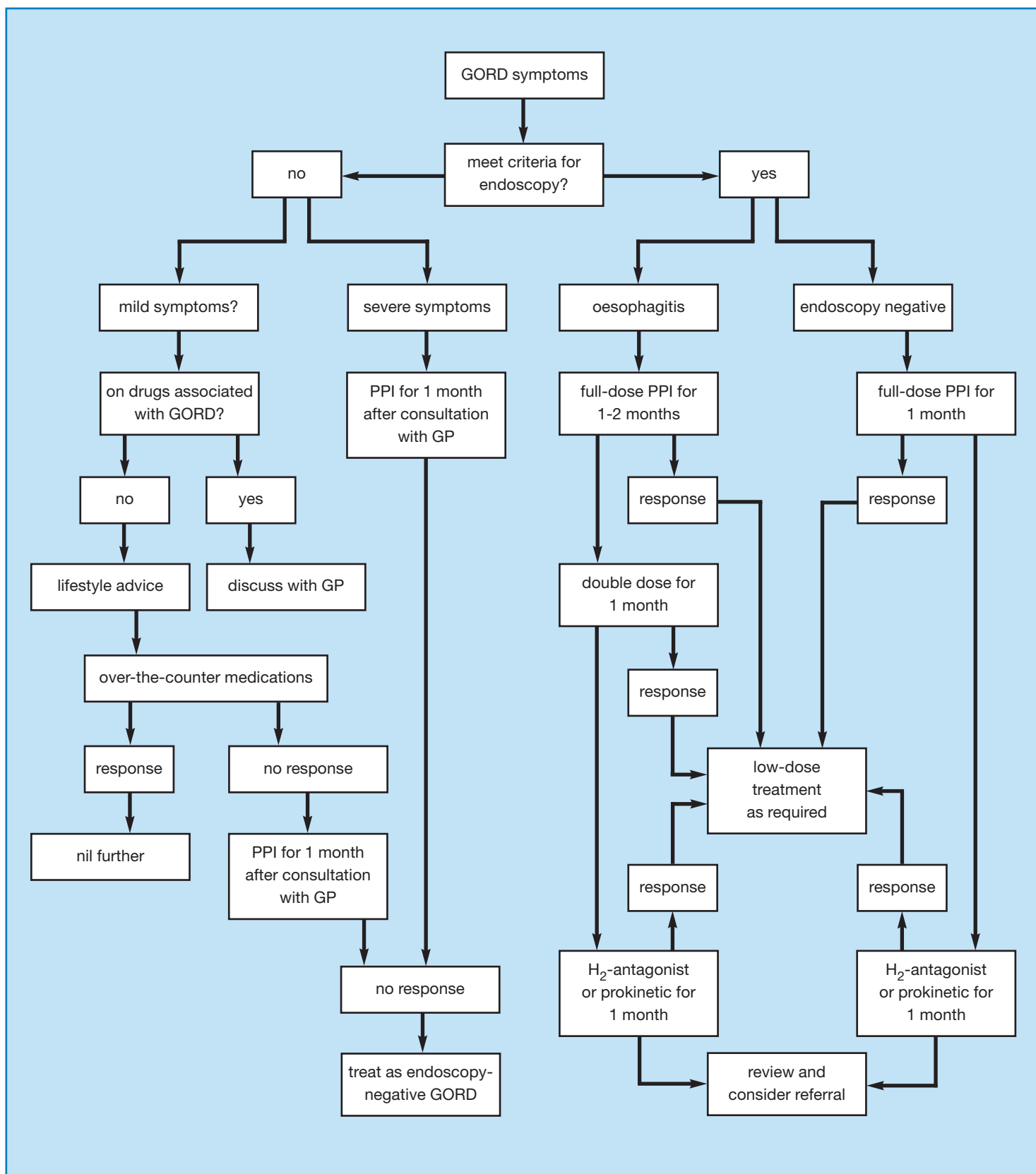


Figure 4. Recommended management of GORD patients

Key points

- GORD is a common disorder
- endoscopy is reserved for patients with alarm symptoms, or new, persistent symptoms over the age of 55
- step up treatment for mild symptoms
- step down treatment for all others

months remain healed compared with 79 per cent taking 15mg daily and 24 per cent on placebo.¹⁸

However, once healing has been achieved not all patients will require maintenance treatment. Over a year 72 per cent of patients have no relapse or only a single relapse needing intermittent treatment, and 47 per cent reach the end of the year without recourse to maintenance.¹⁹

Ultimately, the choice of intermittent or maintenance treatment with low-dose or full-dose PPI, *etc.*, will need to be determined by individual patient characteristics.

There has been debate as to whether patients should 'step up' or 'step down' treatment. It seems entirely reasonable to treat those patients with mild symptoms who do not warrant endoscopy on a step-up approach, starting with lifestyle alteration and antacids and working up through H₂-antagonists and PPIs if necessary (see Figure 4). This is in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines.^{15,20}

The debate intensifies, however, when considering those with more severe disease. The traditional approach is to step up treatment as with mild disease. Although this is initially slightly less expensive (one day of ranitidine 150mg twice daily = 5p, omeprazole capsules 20mg once daily = 6p), it is no longer the most effective in light of the superiority of PPIs. By using PPIs as first-line therapy, symptoms are controlled more quickly and more effectively and patients more easily reassured (see Figure 4). This rationale also complies with NICE guidelines.

There is little to choose between different PPIs, although a dispersible version (Zoton FasTab) is useful in older people and the newer esomeprazole (Nexium) is possibly more effective, though more expensive.²¹

Some patients will not gain symptom control with standard doses of PPIs. In this situation there are limited data to suggest that doubling the dose of PPI²² and preferably dividing the dose to a twice-daily regimen²³ may be more effective. This increased dose can subsequently be stepped down in 70 per cent of patients.

Although GORD is often a chronic relapsing disorder, many patients can be maintained on a reduced dose after their initial course. This may be a reduced

dose of a PPI or a weaker class of drug. It is worth noting that the maintenance dose of some newer PPIs may be almost as effective as the full dose of earlier drugs.²⁴ NICE recommends that if symptoms recur a PPI should be offered at the lowest possible dose to control symptoms.¹⁵

Those patients with complications from reflux disease such as stricturing or Barrett's oesophagus should remain on a PPI.

Surgical options

Since the introduction of laparoscopic fundoplication techniques for GORD in the early 1990s, surgery has become a more popular option. Fundoplication offers the possibility of curing oesophagitis and relieving symptoms without the need for long-term medication. Open fundoplication was reported to fail in 15 per cent, with dysphagia, reflux symptoms, delayed gastric emptying and gas bloat as common side-effects.

Laparoscopic fundoplication may be better, although it is reported that after three years 66 per cent will have some degree of heartburn and 33 per cent will be on prescription medication.²⁵ Another study found that 91 per cent of patients were satisfied with the outcome of their surgery (at two to eight years).²⁶

For these reasons careful selection of patients likely to benefit from surgery is necessary. It has a place in treating those who are refractory to or intolerant of medical therapy, those with large-volume reflux and possibly younger patients who wish to avoid life-long medication.

Endoscopic therapy

A number of endoscopic therapies for reflux disease are in various stages of development. All of these methods require prolonged endoscopy with deep sedation. They include endoscopic suturing and plication, injection of bulking agents and radio frequency ablation.

Long-term data are not yet adequate for such therapies to enter routine practice (www.nice.org.uk).

Conclusion

GORD is common and symptoms may be unrelated to endoscopic findings. Lifestyle changes and drug treatment are usually highly successful in relieving symptoms. Longer-term management should be individualised to the lowest effective dose of effective drug necessary to provide symptom relief taken either intermittently or for the longer term.

Newer endoscopic or laparoscopic surgical antireflux procedures should be reserved for patients who are unwilling or unable to continue long-term acid suppression or in whom such drugs are no longer helpful.

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Prescription review

GPs in England wrote almost 33 million prescriptions for PPIs in 2008, at a total cost of £208 million. This accounts for 91 per cent of all prescribing of anti-secretory drugs and mucosal protectants and 96 per cent of spending.

The volume of PPI prescribing has been increasing in recent years. In 2008, volume increased by 12 per cent over the previous year but costs fell by 11 per cent. Omeprazole overtook lansoprazole as the most widely prescribed PPI in 2006 and now accounts for 48 per cent of PPI prescribing by volume and 32 per cent by cost. The use of esomeprazole has changed little but that of pantoprazole (Protium) and rabeprazole

	No. scrips (000s)	Cost (£000s)
<i>PPIs</i>		
esomeprazole	1 484	42 003
lansoprazole	13 880	62 954
omeprazole	15 634	66 787
pantoprazole	722	15 126
rabeprazole	933	21 459
<i>Alginate preparations</i>	4 459	22 221

Table 5. Number and cost of prescriptions for PPIs and alginates in England, 2008

zole (Pariet) is declining. Alginate prescribing has remained stable over the past three years.

Resources

Organisation

The British Society of Gastroenterology. Tel: 020 7935 3150; e-mail: t.smith@bsg.org.uk; website: www.bsg.org.uk.

Guidelines

Dyspepsia – proven gastro-oesophageal reflux disease – management. NHS Clinical Knowledge Summaries.

Dyspepsia: managing dyspepsia in adults in primary care. CG17. NICE, August 2004. www.nice.org.uk/guidance/CG17.

Patient information

CORE (the gut and liver research charity) publishes

various patient information leaflets and also provides information on current research and relevant news. Tel: 020 7486 0341; e-mail: info@corecharity.org.uk; website: www.corecharity.org.uk.

The Gut Motility Disorders Support Network aims to offer telephone support and information to sufferers of GORD, and offers advice on suitable centres for treatment. Tel: 01398 351173; e-mail: help@gmdnet.org.uk.

Patient UK provides information leaflets on acid reflux and oesophagitis, dyspepsia, pregnancy and dyspepsia, PPIs, H₂-antagonists and antacids at www.patient.co.uk.