# Clinical review

## Gastro-oesophageal reflux disease

Mark Fox, Ian Forgacs

King's College Hospital, Denmark Hill, London SE5 9RS
Mark Fox
*specialist registrar gastroenterology*
Ian Forgacs
*consultant gastroenterologist*

Correspondence to:
I Forgacs
ian.forgacs@kcl.ac.uk

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Gastro-oesophageal reflux disease (GORD) is present when the passage of gastric contents into the oesophagus causes symptoms or damages the mucosa. Potent suppression of gastric acid secretion with proton pump inhibitors is a highly effective and safe treatment for many patients with symptoms associated with reflux. It would be wrong to conclude, however, that proton pump inhibitors had solved the problem of GORD. The relation between reflux symptoms, endoscopic findings, and exposure of the oesophagus to acid is not straightforward. Some patients with a convincing history of heartburn fail to respond well to proton pump inhibitors. Although symptoms may be severe, at endoscopy the oesophagus is often found to be normal, and pH studies may not disclose the cause of symptoms that persist despite treatment for acid suppression.

Apart from typical symptoms of reflux many other problems have been linked to GORD, including dysphagia, hoarseness, non-cardiac chest pain, and chronic cough. It can, however, be difficult to identify those patients who will benefit from antireflux treatment. Most serious is the increased risk of oesophageal adenocarcinoma in patients with reflux symptoms, in particular those with Barrett's columnar lined oesophagus. Since the 1980s the incidence of oesophageal carcinoma has increased sixfold, more rapidly than any other common cancer.

This review explains how recent research has begun to unravel these problems by explaining what can be learnt from physiological and clinical observations. It seems that however well gastric acid secretion can be suppressed, we are far less successful at managing reflux itself.

### Summary points

- Gastro-oesophageal reflux disease (GORD) is common, causes a variety of symptoms, and is associated with important diseases, including asthma and oesophageal adenocarcinoma
- Genetic influences and lifestyle factors such as smoking, obesity, and dietary behaviour may be involved in the development of GORD
- The structure and function of the gastro-oesophageal junction is of key importance in reflux disease—as the condition becomes more severe, the risk of reflux during transient relaxations of the lower oesophageal sphincter rises and the volume of refluxate increases
- Routine endoscopy is not required for reflux symptoms in the absence of features that cause alarm
- Proton pump inhibitors provide safe and effective long term management for most patients with typical reflux symptoms, but are less effective for atypical symptoms
- Non-acid reflux is an important cause of persistent symptoms in patients who fail to respond to proton pump inhibitors

### Sources and selection criteria

We identified large randomised controlled trials on acid suppression in patients with GORD. This research has been systematically reviewed by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence, and leading journals. High quality, evidence based guidelines for the management of GORD are available, yet the literature focuses on patients with typical reflux symptoms and the healing of erosive oesophagitis. Few large, well designed studies have investigated patients with atypical symptoms (for example, chest pain, cough) and non-erosive disease in whom acid suppression fails more often than in patients with symptoms typical of GORD. Insufficient evidence for definitive systematic review exists, therefore we identified studies through Medline, whose terms reflected the symptomatic basis used for defining GORD, and we also examined our own database for appropriate publications that tackle these issues.

### Who gets reflux disease?

Inherited and acquired factors both contribute to the development of GORD (see bmj.com). The prevalence of reflux symptoms is high in the parents of affected people, and concordance of reflux disease is higher in identical twin pairs than it is in non-identical twin pairs.[w1 w2] It is estimated that genetic factors contribute 18-31% to the cause of GORD; nevertheless a recent systematic review re-emphasised the importance of lifestyle factors.[1] Smokers are more likely to have reflux symptoms. Obesity is also associated with GORD. Moreover obese people tend to eat larger meals and choose rich, energy dense foods, dietary factors that increase the risk of reflux. In contrast, although patients often think that coffee, chocolate, and alcohol can trigger symptoms, firm evidence linking specific

*References w1-w41 and additional information are on bmj.com*

Characteristic responses of the oesophagus in patients with gastro-oesophageal reflux disease

| Characteristic | Endoscopy negative reflux disease | Erosive oesophagitis (inflammatory) | Columnar lined oesophagus (metaplastic) |
|---|---|---|---|
| Prevalence | 50% | 40% | 10% |
| Extent of exposure to acid | Mild to moderate | Mild to severe | Moderate to severe |
| Response of mucosa | Highly sensitive and reactive to acid reflux (repeated swallowing may protect mucosa from severe disease) | Increasing severity or grade of inflammation with increasing exposure to acid | Increasing length of metaplastic columnar lined oesophagus with increasing exposure to acid |
| Presentation | High burden of typical and atypical symptoms | Typical symptoms of reflux, heartburn prominent | Delayed presentation or comparatively mild symptoms due to relative insensitivity to acid |
| Response to acid suppression | Often incomplete (especially of atypical symptoms) | Good symptomatic response and healing of mucosa | Prompt symptomatic response but little or no regression of columnar lined oesophagus |
| Complications | Associated with other functional bowel disease; impaired quality of life | Risk of peptic stricture with severe disease | Ulceration and stricture with severe disease |
| Malignant potential | Low | Low | Relatively high |

foods with GORD is lacking.[1] Advice on lifestyle, such as stopping smoking, losing weight, and avoiding large, late meals can reduce the frequency and severity of reflux symptoms, although it is rare for these measures to remove the need for acid suppression.[w3]

## *Helicobacter pylori* and GORD

*Helicobacter pylori*, a spiral shaped bacterium located in the mucous layer of the stomach, may inhibit or exacerbate acid reflux depending on how the infection affects the stomach. Distal (antral) gastritis increases the production of gastric acid. In this condition the eradication of *H pylori* not only reduces the risk of peptic ulceration but also the risk of acid reflux. Conversely, generalised atrophic gastritis decreases the production of gastric acid; as a result *H pylori* eradication may increase the severity of reflux. However, in clinical practice this information is rarely available, and well designed studies have found little or no overall effect of *H pylori* eradication on GORD.[w4 w5] Of more concern is that chronic *H pylori* infection is associated with an increased risk of peptic ulceration and gastric cancer. For this reason current guidelines recommend *H pylori* eradication irrespective of potential effects on GORD.

## Why does reflux occur?

Everybody experiences gastro-oesophageal reflux at some time. In health, reflux of air (belching) occurs during transient relaxations of the lower oesophageal sphincter triggered by gastric distension (bloating).[w6] Small volumes of ingested food and gastric acid may pass into the oesophagus during such episodes; but GORD is present only when the reflux of gastric contents causes frequent, severe symptoms or mucosal damage.

Although the underlying causes of GORD remain uncertain, the structure and function of the gastro-oesophageal junction are of key importance in this condition. Compared with healthy people, those with mild to moderate GORD do not necessarily have more transient lower oesophageal sphincter relaxations.[2] Rather, structural changes at the gastro-oesophageal junction reduce the resistance to reflux during these events.[w7] As these changes become more pronounced, the risk of reflux during transient lower oesophageal sphincter relaxations rises and reflux volume increases and extends further up the oesophagus. These effects increase the frequency and severity of reflux symptoms.[3 w8] In patients with severe GORD a hiatus hernia is often present. This exacerbates the severity of reflux because large volumes of gastric contents pass unimpeded into the hiatal sac. When this occurs, increased abdominal pressure on straining and even deep breathing may be enough to force refluxate into the oesophagus.[w9]

## How does the oesophagus respond to reflux?

Patients with GORD typically present with heartburn and acid regurgitation, although many other symptoms and conditions have been linked to the condition (Box 1). Endoscopy may reveal erosive oesophagitis or Barrett's columnar lined oesophagus, although many patients have no evidence of injury to the mucosa. Indeed the link between exposure of the oesophagus to acid, reflux symptoms, and endoscopic findings is weak. The reasons for the paradox of severe symptoms in the presence of relatively mild reflux are becoming clearer.

## GORD: a spectrum of disease or a family of diseases?

Traditionally, GORD has been approached as a continuous spectrum of disease (fig 1). Endoscopy negative reflux disease was thought to represent mild disease, increasing grades of reflux oesophagitis indicating increasing severity of disease, whereas Barrett's columnar lined oesophagus was considered a very severe form of GORD. This had a profound effect on the management of GORD. Yet recent evidence has called this concept into question.[4] Firstly, progression from endoscopy negative reflux disease through erosive oesophagitis to Barrett's columnar lined oesophagus is rarely observed (and regression almost never occurs).[4] Secondly, oesophageal physiology and mucosal biology is not shared across the spectrum.[5 w10] Thirdly, the response to therapy, clinical course, and risk of complications (including malignancy) does not change in a continuous manner as expected in a spectrum of disease but is categorically different in the three groups (table).[4 5 w10]

The traditional concept focuses on injury to the oesophageal mucosa; the new model shifts attention to oesophageal symptoms. On this basis patients with endoscopy negative reflux disease would not be considered to have mild disease because such patients

**Box 1 Symptoms and conditions associated with gastro-oesophageal reflux disease**

**Typical symptoms**
Heartburn, acid regurgitation

**Atypical symptoms**
Dysphagia, globus sensation, non-cardiac chest pain, dyspepsia or abdominal pain

**Extra-oesophageal symptoms**
Hoarseness or sore throat, or both; sinusitis; otitis media; chronic cough; laryngitis or polyps on the vocal cords, or both; dental erosions; non-atopic asthma; recurrent aspiration or pulmonary fibrosis, or both

**Malignancy**
Oesophageal adenocarcinoma, head and neck cancer

often have severe and atypical symptoms. Moreover their response to acid suppression is often incomplete, because of hypersensitivity of the oesophagus to acid,[w10 w11] sensitivity to oesophageal distension by non-acid reflux,[6] or other events that are not directly associated with GORD, such as oesophageal spasm.[w12] These patients may also have symptoms of functional gastrointestinal disease such as irritable bowel syndrome.[w13]

In contrast, patients with erosive oesophagitis usually have typical reflux symptoms that respond to acid suppression and show healing of the erosions.[w14 w15] In patients with Barrett's columnar lined oesophagus the mucosa is often exposed to acid for prolonged periods; many do not have severe symptoms, however, because the metaplastic, columnar lining of the oesophagus is relatively insensitive to acid.[7] Recent studies have shown that the length of oesophagus affected in Barrett's columnar lined oesophagus increases with exposure of the oesophagus to acid as does the severity of erosive oesophagitis.[8 w16] Moreover, the cytokine profile in patients with the disease is different to the proinflammatory profile in patients with erosive oesophagitis.[5] These findings provide clear evidence that Barrett's columnar lined oesophagus does not represent the end of a spectrum in GORD but rather a different phenotypic response of the oesophageal mucosa to acid reflux. In summary, distinct oesophageal physiology and mucosal responses to acid reflux explain the differing presentation, clinical course, and malignant potential of patients with endoscopy negative reflux disease, erosive oesophagitis, or Barrett's columnar lined oesophagus.

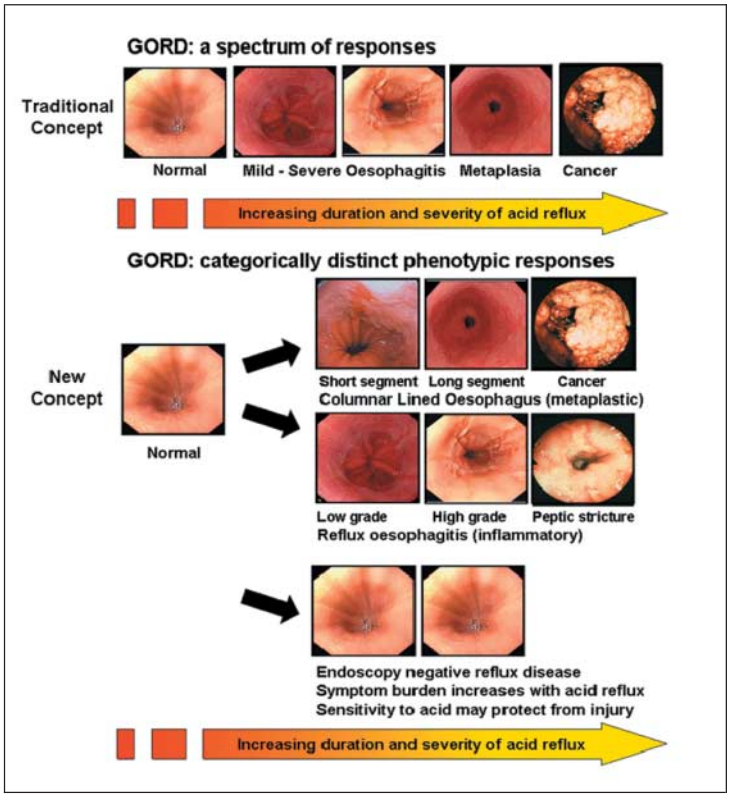



**Fig 1** Traditional concept of gastro-oesophageal reflux disease compared with new concept of disease as three distinct phenotypic responses of the oesophagus to acid reflux (Barrett's columnar lined oesophagus, reflux oesophagitis, and endoscopy negative reflux disease)

## Extraoesophageal reflux disease: another member of the GORD family

Epidemiological studies report an association between GORD and extraoesophageal symptoms and disease (box 1). Moreover, clinical experience suggests that antireflux therapy improves these problems in many patients.[w17-w19] The only large, well designed clinical trial in extraoesophageal reflux disease, however, highlighted the difficulty of establishing a link between acid reflux and symptoms of the pharynx and larynx.[w20] Affected patients may not have typical reflux symptoms or mucosal injury on endoscopy;[w21-w23] nevertheless, treatment of extraoesophageal reflux disease often requires high doses of acid suppression drugs for prolonged periods because the pharynx and larynx are exquisitely sensitive to acid and heal slowly.[w24 w25] Even weakly acidic reflux (pH 4-6) can trigger extraoesophageal symptoms.[9] Thus extraoesophageal reflux disease is different to typical GORD and seems to represent a distinct response to the reflux of gastric contents.

Extraoesophageal reflux and microaspiration may also play a part in non-atopic asthma. Reflux symptoms are reported by 45% of patients with asthma compared with 10% of the general population, and in a large case-controlled study, patients with erosive oesophagitis on endoscopy had a 50% higher likelihood of a diagnosis of asthma than matched controls.[10 11] Evidence from a systematic review also shows that medical and surgical treatment for reflux improved wheezing and coughing in 69% of patients, reduced the use of on-demand inhalers in 62%, and improved lung function in 26%.[10] Similar to other extraoesophageal symptoms, the clinical response was slower for respiratory symptoms than for symptoms typical of reflux and often required high doses of proton pump inhibitors for long periods (at least eight weeks).

## GORD and oesophageal adenocarcinoma: who is at risk?

Recent evidence of a strong and probably causal relation between gastro-oesophageal reflux and oesophageal adenocarcinoma has had a major effect on the awareness of doctors and patients of the potential risks of GORD.[12] Because the poor survival rates for this malignancy are improved only by early detection of the tumour, it is important to identify patients that might benefit from endoscopic screening or surveillance.

**Box 2 Factors determining immediacy of endoscopy**

**Symptoms requiring urgent referral of patients for endoscopy**
Gastrointestinal bleeding
Iron deficiency anaemia
Progressive unintentional weight loss
Progressive difficulty swallowing
Persistent vomiting
Epigastric mass on palpation
Suspicious barium meal result or other suspicious imaging result

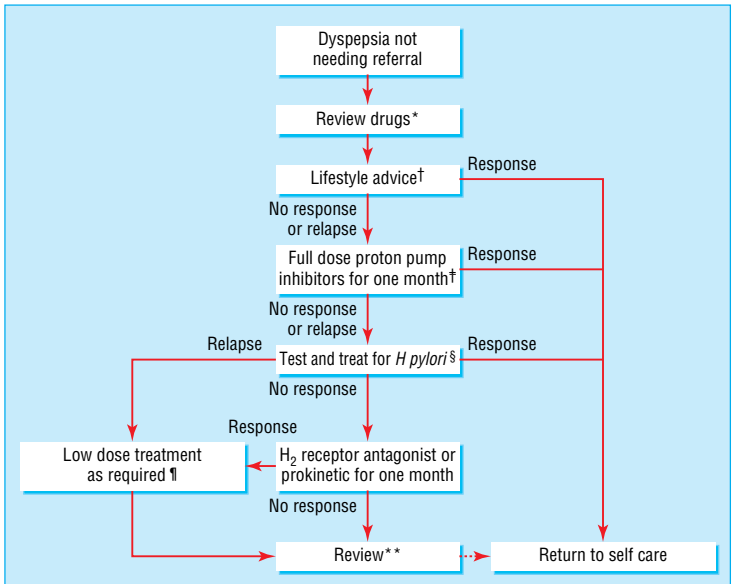
**Factors requiring consideration of referral of patients for endoscopy**
Previous gastric ulcer
Previous gastric surgery
Non-steroidal anti-inflammatory drug use
Pernicious anaemia
Family history of gastric cancer

The relative risk of developing oesophageal adenocarcinoma in patients with GORD is affected by personal factors and clinical history, increasing with male sex, smoking, obesity, age, and the frequency and severity of reflux symptoms.[12] Nevertheless, even for patients with all these risk factors, the absolute risk remains low (1 in 600 population per year); too low to justify screening on this basis.[w26] A high risk population can also be defined by endoscopy because the risk of cancer is not shared by all patients with reflux symptoms but is largely restricted to those with Barrett's columnar lined oesophagus (see bmj.com). Even for patients with "long segment" Barrett's columnar lined oesophagus, the absolute risk of developing oesophageal adenocarcinoma is small (1 in 200 population per year) in the absence of premalignant, dysplastic change on histology. Only 2-3% of affected patients die from oesophageal adenocarcinoma, and overall life expectancy is no different to age and sex matched members of the general population.[13] Although evidence of benefit from prospective studies is lacking, data from observational series and computer models suggest endoscopic surveillance can decrease mortality from cancer in patients with Barrett's columnar lined oesophagus. Current guidelines recommend endoscopic surveillance every 2-5 years for patients with Barrett's columnar lined oesophagus who are candidates for, and would accept, oesophagectomy should an early cancer be discovered.[14 15] The weakness of this strategy is that it fails to detect patients with the disease who lack symptoms that would cause alarm and therefore never undergo endoscopy.[7]

At present it is considered better "to err by performing unnecessary surveillance than by missing curable oesophageal neoplasms," albeit at considerable expense.[14] In the future, endoscopic surveillance may be rendered unnecessary by medical treatment. Laboratory evidence is growing that acid suppression reduces the malignant potential of Barrett's columnar lined oesophagus,[w29] and a recent retrospective study of patients with this condition suggests that the risk of developing dysplasia may be reduced by 75% by acid suppression.[16] Non-steroidal anti-inflammatory drugs may also protect against oesophageal cancer.[w30] The large, prospective AspECT (aspirin and esomeprazole chemoprevention in Barrett's metaplasia) trial is seeking to determine the effects of high dose and low dose proton pump inhibitors with and without low dose aspirin as chemoprevention.[w31]

## How to manage GORD: treat first, endoscope later

The UK National Institute for Health and Clinical Excellence has recently published guidelines on the management of dyspepsia (including reflux symptoms) that will have a major impact on clinical practice.[17] Routine endoscopic investigation is not necessary for patients of any age presenting with dyspepsia but no alarm symptoms (box 2). However referral for endoscopy is appropriate for patients aged 55 years and older with unexplained treatment resistant dyspepsia of more than four weeks' duration. In a recent prospective observational study the prevalence of gastric cancer was 4% (and serious benign disease 13%) in a cohort of patients referred urgently for alarm symptoms.[18] Referral for dysphagia or major weight loss at any age, together with those older than 55 years with alarm symptoms, would have detected 92% of the cancers found in the cohort. In contrast, the presence of typical reflux symptoms was less likely to indicate the presence of malignancy.[18]




* Review for possible causes of dyspepsia – for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids, and non-steroidal anti-inflammatory drugs
† Offer lifestyle advice, including advice on healthy eating, weight reduction, and smoking cessation, promoting continued use of antacid or alginates
‡ Evidence is currently inadequate to guide whether full dose treatment for one month or *Helicobacter pylori* test and treatment should be offered first. Either treatment may be tried first with the other being offered if symptoms persist or return
§ Detection: use carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory based serology
Eradication: use a proton pump inhibitor, amoxicillin, clarthromycin 500 mg ($PAC_{500}$) regimen or a proton pump inhibitor, metronidazole, clarthromycin 250 mg ($PAC_{250}$) regimen. Do not retest even if dyspepsia remains unless there is a strong clinical need
¶ Offer low dose treatment with a limited number of repeat prescriptions. Discuss the use of treatment on an "as required" basis to help patients manage their own symptoms
** In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist for a second opinion. Emphasise the benign nature of dyspepsia. Review long term patient care at least annually to discuss treatment and symptoms

**Fig 2** Management flow chart for patients with uninvestigated dyspepsia (includes reflux symptoms). Adapted from National Institute for Health and Clinical Excellence guideline 17 (www.nice.org.uk)

Patients with reflux symptoms but no alarm symptoms should receive initial treatment with full dose proton pump inhibitors for one month (fig 2). Eradication therapy for *H pylori* can also be provided if infection is evident on serology or urea breath test. If symptoms return after treatment, and long term acid suppression is required, a step-down strategy to the lowest dose of proton pump inhibitor that provides effective relief of symptoms is more cost effective than the step-up approach.[17] If endoscopy is carried out and oesophagitis is present, a healing dose of proton pump inhibitor should be prescribed for two months (see bmj.com). In such patients symptoms usually relapse when treatment is withdrawn, and maintenance proton pump inhibitor therapy is usually required.[w4] Systematic reviews for the Cochrane Collaboration have confirmed that proton pump inhibitors are more effective than $H_2$ receptor antagonists (for example, ranitidine) at healing oesophagitis[w32] and maintaining remission from mucosal injury and symptoms.[w33] Long term management with proton pump inhibitors for over 10 years has been shown to be safe and effective, although the dose requirement may increase over time.[19]

Acid suppression with proton pump inhibitors provides effective relief of symptoms for most patients with GORD. Nevertheless the persistence of reflux symptoms in an important minority of patients receiving such therapy is a major problem in clinical practice. Changing the proton pump inhibitor preparation or increasing the dose (twice daily dosing) may be required for control of symptoms in patients with severe acid reflux.[19] This may also be effective in patients with endoscopy negative reflux disease who are hypersensitive to acid reflux and in patients with extraoesophageal reflux disease. Adding an $H_2$ receptor antagonist before bedtime may be useful if symptoms are prominent at night.[w34]

## What to do when proton pump inhibitors fail

If reflux symptoms fail to respond to full dose acid suppression then investigations must be carried out to confirm the diagnosis of GORD.[17] Endoscopy is appropriate, but ironically many patients who fail to respond to treatment have no evidence of mucosal injury (endoscopy negative reflux disease). Barium studies may show a hiatus hernia but are poor at detecting upper gastrointestinal inflammation or ulceration. Ambulatory monitoring of pH over 24 hours remains the standard for the diagnosis of GORD, confirming disease related exposure of the oesophagus to acid and the association of symptoms with acid reflux events. Prolonged monitoring of pH over 48 hours with the catheter free Bravo system (not universally available) may improve patient tolerance and increase diagnostic yield.[w35] Unfortunately the value of pH studies alone is limited in patients who fail to respond to proton pump inhibitors because persistent symptoms are rarely caused by persistent acid reflux. In contrast, combining pH and multichannel intraluminal impedance measurements detects both acid and non-acid reflux. Multichannel intraluminal impedance is a new technique that uses changes in electrical conductivity to follow the movement of fluid

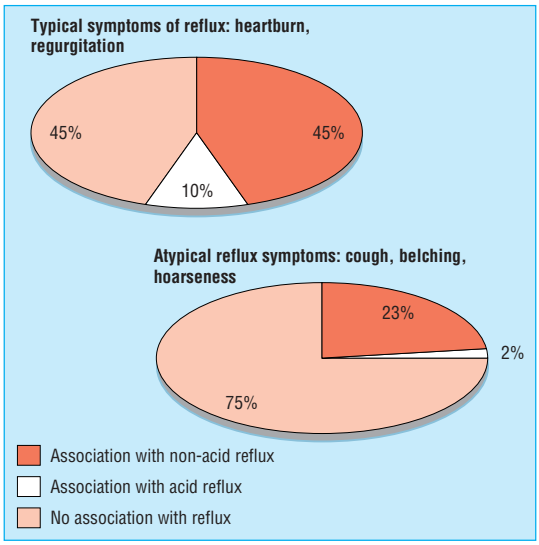



**Fig 3** Association of typical and atypical symptoms with acid and non-acid reflux detected by combined pH and multichannel intraluminal impedance studies in 58 patients receiving proton pump inhibitors. Adapted from Mainie, Tutuian, and Castell. Symptoms on PPI therapy associated with nonacid, acid or no reflux. American College of Gastroenterology presentation, Medical University of South Carolina, October 2004

and gas in the oesophagus (as yet, available only at research centres in the United Kingdom). Recent studies using this investigation have shown that proton pump inhibitors reduce acid reflux but have no effect on the overall number of reflux events. Clinical investigations have supported the promise of multichannel intraluminal impedance by confirming that non-acid volume reflux is a common cause of persistent reflux symptoms in patients receiving treatment for acid suppression (fig 3).[6 w8] Similarly, combining pH, multichannel intraluminal impedance, and manometry (to detect cough) has also shown great promise in extraoesophageal reflux disease. This technique documents when acid or non-acid reflux triggers cough and identifies patients who would be missed or wrongly diagnosed by standard pH studies (see bmj.com).[9 w36]

Although non-acid reflux can now be detected, medical management remains unsatisfactory. Increasing the dose of proton pump inhibitors does not tackle the cause of persistent non-acid reflux by reducing the volume of gastric secretion or strengthening the reflux barrier. Adding an $H_2$ receptor antagonist may reduce gastric acid secretion by direct inhibition of the parietal cell. Alginate preparations (for example, Gaviscon; Reckitt and Colman) form a viscous barrier over gastric contents. Prokinetics (for example, domperidone) may increase lower oesophageal sphincter tone and accelerate gastric emptying. None of these approaches, however, provides truly effective treatment for this condition.

## Surgical management of GORD

The realisation that patients fail to respond fully to medical therapy because of persistent non-acid reflux has revived interest in the surgical management of GORD. Antireflux surgery augments the reflux barrier by a full or partial "wrap" of the gastric fundus (fundoplication) around the lower oesophagus. Randomised studies have shown that the long term effects of open fundoplication are comparable to medical

treatment for GORD,[20 w38] and recent reports confirm that laparoscopic antireflux surgery has similar outcomes to the open procedure.[w39] Antireflux surgery is, however, associated with mortality (< 1%), and morbidity includes persistent dysphagia and the "gas-bloat" syndrome.[20 w39] Moreover, many patients still require antisecretory drugs; around half of those managed by surgery report the use of proton pump inhibitors at 5-10 years' follow-up. As a result, long term medical therapy with proton pump inhibitors is more cost effective than surgical management in most clinical scenarios and remains the standard management for GORD.[w40]

Nevertheless, antireflux surgery may be appropriate for young, otherwise healthy patients in whom medical management of GORD is ineffective or not tolerated. It is essential to confirm that gastro-oesophageal reflux rather than oesophageal dysmotility (for example, achalasia) or non-ulcer dyspepsia is responsible for persistent symptoms. In the past it was not possible to attribute symptoms to non-acid reflux. In the future it is likely that combined pH, multichannel intraluminal impedance, and manometry will provide this capability and identify patients who are likely to benefit from antireflux surgery.[9 w36]

Recently, endoscopic techniques have been developed with the aim of providing an alternative to antireflux surgery.[w41] These endoluminal therapies augment the reflux barrier by submucosal implants, radiofrequency energy delivery, or plication of the lower oesophageal sphincter. Short term benefits are reported by up to two thirds of patients.[w41] Long term results have been disappointing, however, and these techniques are not ready for routine use.

## Conclusion

GORD is a common condition that causes a wide range of troublesome symptoms and is associated with important diseases, including oesophageal adenocarcinoma. In the past the investigation of reflux symptoms was focused on endoscopic examination, and treatment was directed towards healing injured mucosa. More recently a shift to controlling symptoms is beginning to have a major effect on the management of GORD. Current guidelines advise a "treat first, endoscope later" approach, with further investigation reserved for patients who fail to respond to acid suppression with proton pump inhibitors. This change of focus should benefit many patients, especially those with severe symptoms but endoscopy negative reflux disease. The aim for patients with erosive oesophagitis will be complete remission of symptoms and mucosal healing. For those with Barrett's columnar lined oesophagus, attention will be directed to preventing progression to dysplasia and cancer. Future research will define the pathological basis of the different responses to acid reflux with an aim to provide clinicians with treatments specific to the needs of individual patients.

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**Additional educational resources**

National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/page.aspx?o=218377)—comprehensive, evidence based guidelines for the management of dyspesia in adults in primary care

The Cochrane Library (www.thecochranelibrary.com)—a variety of Cochrane reviews are available providing detailed, evidence based information on various aspects of GORD therapy

GERD Information Resource Center (www.gerd.com/)—excellent educational resources on GORD for the general public, healthcare providers, and researchers. Sponsored by AstraZeneca, manufacturer of esomeprazole

eMedicine (www.emedicine.com/radio/topic300.htm)—thorough review of GORD from a leading American based e-learning website

**Information for patients**

NHS Direct (www.nhsdirect.nhs.uk/en.aspx?articleID=571)—simple, patient oriented advice about GORD from the UK National Health Service

Patient UK (www.patient.co.uk/showdoc/23068673/)—patient oriented advice about GORD from a UK based site partially funded by advertisements (audio clips available for the partially sighted)

MedicineNet (www.medicinenet.com/gastroesophageal_reflux_disease_gerd/article.htm)—well illustrated, patient oriented advice about GORD from a free to view, American based site funded by advertisements

The Pediatric/Adolescent Gastro-esophageal Reflux Association (www.reflux.org/)—patient oriented advice about GORD in children and adolescents from an American based charity

1 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54:710-7.
2 Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. *Am J Gastroenterol* 2001;96:2569-74.
3 Sifrim D. Relevance of volume and proximal extent of reflux in gastro-oesophageal reflux disease. *Gut* 2005;54:175-8.
4 Fass R, Ofman JJ. Gastroesophageal reflux disease—should we adopt a new conceptual framework? *Am J Gastroenterol* 2002;97:1901-9.
5 Fitzgerald RC, Onwuegbusi BA, Bajaj-Elliott M, Saeed IT, Burnham WR, Farthing MJ. Diversity in the oesophageal phenotypic response to gastro-oesophageal reflux: immunological determinants. *Gut* 2002;50:451-9.
6 Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001;120:1599-606.
7 Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RK, Vasudeva RS, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology* 2003;125:1670-7.
8 Fass R, Hell RW, Garewal HS, Martinez P, Pulliam G, Wendel C, et al. Correlation of oesophageal acid exposure with Barrett's oesophagus length. *Gut* 2001;48:310-3.
9 Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005;54:449-54.
10 Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux?: a critical review of the literature. *Chest* 1998;114:275-83.
11 El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology* 1997;113:755-60.
12 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340:825-31.
13 Anderson LA, Murray LJ, Murphy SJ, Fitzpatrick DA, Johnston BT, Watson RG, et al. Mortality in Barrett's oesophagus: results from a population based study. *Gut* 2003;52:1081-4.
14 Spechler SJ. Managing Barrett's oesophagus. *BMJ* 2003;326:892-4.
15 Watson A, Heading RC, Shepherd NA, eds. Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. In: *Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus.* London: British Society of Gastroenterology, 2005:1.
16 El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2004;99:1877-83.
17 North of England Dyspepsia Guideline Development Group. *Dyspepsia: management of dyspepsia in adults in primary care.* London: National Institute for Health and Clinical Excellence, 2004.
18 Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005;54:40-5.
19 Klinkenberg-Knol EC, Nelis F, Dent J, Snel P, Mitchell B, Prichard P, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;118:661-9.
20 Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001;285:2331-8.

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