Gastro-oesophageal reflux disease

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Summary

Gastro-oesophageal reflux disease refers to reflux of gastric contents into the oesophagus leading to oesophagitis, reflux symptoms sufficient to impair quality of life, or long-term complications. Transient relaxation of the lower oesophageal sphincter is believed to be the primary mechanism of the disease although the underlying cause remains uncertain. Obesity and smoking are weakly associated with the disease and genetic factors might be important. A negative association with *Helicobacter pylori* exists, but eradication of *H pylori* does not seem to cause reflux disease. Diagnosis is imprecise as there is no gold standard. Reflux symptoms are helpful in diagnosis but they lack sensitivity. Ambulatory oesophageal pH monitoring also seems to be insensitive despite high specificity. Empirical acid suppression with a proton-pump inhibitor (PPI) has reasonable sensitivity but poor specificity. Some evidence suggests that once patients develop the disease, severity is determined early and patients seem to continue with that phenotype long term. Unfortunately, most patients do not respond to life-style advice and require further therapy. H_2 receptor antagonists and PPIs are better than placebo in oesophagitis, with a number needed to treat of five and two, respectively. In non-erosive reflux disease, acid suppression is better than placebo but the response rate is lower. Most patients need long-term treatment because the disease usually relapses. The role of endoscopic therapy is uncertain. Anti-reflux surgery is probably as effective as PPI therapy although there is a low operative mortality and morbidity.

Introduction

Gastro-oesophageal reflux disease is a common problem and is expensive to manage in both primary and secondary care settings. The annual direct cost for managing the disease is estimated to be more than $9 billion dollars in the USA.[1] There have been major advances in the diagnosis, pathophysiology, and treatment of this disease, which we will review here.

Definitions

There is no gold standard test for objectively diagnosing gastro-oesophageal reflux disease, and definitions have therefore relied on a combination of disease characteristics. For example, an international working group[2] defined the disease as the reflux of gastric contents into the oesophagus leading to oesophagitis, reflux symptoms sufficient to impair quality of life, or risk of long-term complications. This definition builds on previous ones[3,4] and emphasises that gastro-oesophageal reflux becomes a disease when it either causes macroscopic damage to the oesophagus or affects quality of life. Empirical evidence suggests that quality of life is likely to be impaired if a patient has two or more episodes of symptomatic reflux per week.[5]

The disease can be subdivided into reflux oesophagitis and endoscopy-negative reflux disease (or non-erosive reflux disease). The presence and severity of oesophagitis at endoscopy was prone to significant interobserver error, but this problem has been improved by the Los Angeles classification, which defines the disease by the occurrence of mucosal breaks (figure 1).[6] Patients with non-erosive reflux disease have no mucosal breaks in the oesophagus, but have typical reflux symptoms.[7] The accuracy of symptoms for diagnosis is uncertain, but it is well recognised that absence of heartburn does not exclude gastro-oesophageal reflux disease. There is therefore likely to be some misclassification of patients with non-erosive reflux disease, but this definition is the best available.

Search strategy and selection criteria

We did a MEDLINE search of articles published between 1966 and August, 2005, using the terms "oesophagitis", "gastro-oesophageal reflux", "peptic oesophagitis". All terms were merged using the set operator "OR" and the search was limited to "human" and "English language" studies.

Epidemiology

There have been a series of systematic reviews that have improved understanding of the epidemiology of the disease.[8–11]

Prevalence and incidence

One systematic review[8] identified 31 articles that assessed the period prevalence of heartburn symptoms in the community, reporting on a total of 77 671 patients. In western populations, 25% of people report having heartburn at least once a month, 12% at least once per week, and 5% describe daily symptoms (figure 2). In east Asian populations, prevalence is much lower with 11% reporting heartburn at least once per month, 4% weekly, and 2% having daily symptoms.[12] There is a paucity of information about the prevalence of heartburn in other geographical regions, but symptoms of gastro-oesophageal reflux disease are uncommon in non-Western populations.[9]

Recent population-based endoscopic data have shown that asymptomatic oesophagitis is common, but the natural history remains unknown. In a random sample of the Swedish adult population, reflux symptoms were reported by 40% and oesophagitis was diagnosed in

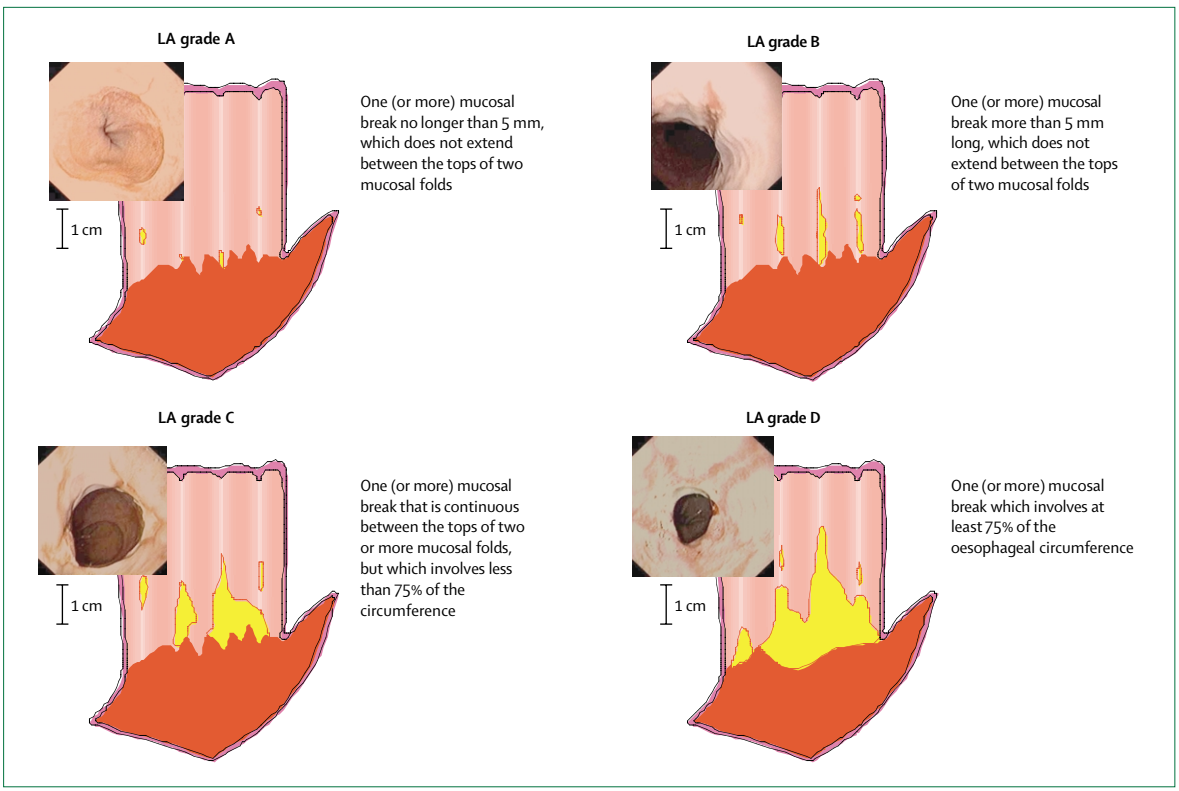

Figure 1: Los Angeles classification of oesophagitis

nearly 16%; however, 37% of those with oesophagitis had no symptoms of gastro-oesophageal reflux disease.[13] The disease is a relapsing and remitting disorder, but by contrast with data for period prevalence there are few longitudinal studies that describe the incidence of heartburn in the population. A systematic review identified only three articles[8] that reported on the incidence of heartburn in a total of 6366 people. The adjusted yearly incidence of weekly heartburn is probably around 1·5–3%.[8]

Risk factors

The cause of the disease is unknown and epidemiological studies have been undertaken to assess whether demographic, genetic, lifestyle, or environmental factors are associated with the disease.

Demographic factors

The relation between age and prevalence of reflux symptoms is unclear. One study suggested that period prevalence of the disease increases with age,[14] but most cross-sectional studies have found no association.[15–17] Furthermore, a longitudinal study[18] reported that heartburn did not become more common in 1290 individuals followed up over 7 years. One study suggested an association between advancing age and fewer reflux symptoms, but more severe oesophagitis.[19] A systematic review[8] reported a similar period prevalence of heartburn in men and women. This finding contrasts with endoscopy database studies in which male sex was a significant risk factor for oesophagitis.[20] The effect of sex in oesophagitis is probably small, and the community studies might not have shown an association with heartburn because of the inaccuracy of symptoms in the diagnosis of the disease. Alternatively, prevalence could be similar between the sexes, but men can have more severe reflux disease and therefore may have more reflux oesophagitis than women.

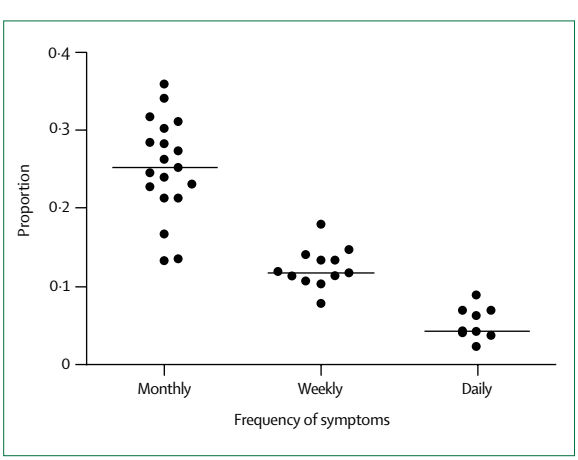

Figure 2: Summary of observational studies assessing the period prevalence of heartburn in Western populations (from data identified in reference 8)

Lifestyle and environmental factors

There is some evidence for lifestyle factors being associated with the underlying causes of gastro-oesophageal reflux disease because the main mechanism of the disease seems to be inappropriate relaxation of the lower oesophageal sphincter. Obesity can disrupt this sphincter, perhaps because of increased intra-abdominal pressure[21] and mechanical pressure on the diaphragm leading to hiatal hernia and increased transient relaxation of the sphincter.[22] Smoking,[23] alcohol,[24] coffee,[25] and chocolate[26] also have pharmacological effects that reduce the tone of the sphincter. Fatty foods delay gastric emptying, which could also predispose to the disease.[27] There is a systematic review of the effect of obesity on gastro-oesophageal reflux disease,[28] but the epidemiological association with the other lifestyle factors is unclear so we reviewed the published work in this area.[29–38]

A systematic review[28] of observational studies that assessed the association between obesity and reflux symptoms identified eight articles with extractable data. Overall, there was a positive association between a body-mass index of 25kg/m^2 or more and reflux symptoms (odds ratio 1·43, 95% CI 1·16–1·77). There were a further five studies that assessed oesophagitis and obesity, and again there was a positive association (1·76, 1·16–2·68). There therefore seems to be a weak association between obesity and gastro-oesophageal reflux disease, although the possibility that this link is due to residual confounding cannot be excluded. Even if the association is causal, the modest odds ratio suggests that it will play a minor part in the pathogenesis of the disease.

We identified seven studies[29–35] that have investigated smoking status in patients with either oesophagitis or reflux symptoms. Three showed a positive association, three did not show any significant association, and one reported a negative association. Most studies reported odds ratios of more than 2·0, which suggests that any association is likely to be weak. These seven studies[29–35] also investigated alcohol intake in patients with oesophagitis or reflux symptoms. Four reported no association and three showed a positive association. Again, the odds ratios in all studies were less than 2, which suggests that alcohol has an equivocal relation with gastro-oesophageal reflux disease and any effect is likely to be small.

There are two studies[34,36] that have assessed the association between coffee intake and reflux symptoms, and both were negative. Additionally, two studies have evaluated the role of fat intake on reflux symptoms; one reported a weak positive association between reflux symptoms and fat intake (1·33, 1·01–1·74)[37] and the other was negative.[38] One study did not find any association with chocolate[36] and reflux symptoms.

Helicobacter pylori infection is an environmental factor that has declined as gastro-oesophageal reflux disease, and oesophageal adenocarcinoma associated with the disease, has increased in the developed world.[39] Such observations have led to the hypothesis that *H pylori* might protect against the disease.[39] A systematic review[40] of observational studies has confirmed that there is a negative association between *H pylori* and gastro-oesophageal reflux disease, although this finding is most apparent in Asian countries. A systematic review of randomised trials[41] did not show any effect of *H pylori* eradication in causing reflux disease, although the number of trials available for analysis was small. This finding is lent support by data from two studies[42,43] that investigated population screening for and treatment of *H pylori* infection. There was no increase in reflux symptoms in almost 3000 patients with *H pylori* infection who were randomly assigned eradication therapy compared with placebo. As with all epidemiological studies, association does not mean causation, and any apparent protective ecological effect of *H pylori* could be due to confounding factors.[44]

Genetic factors

Genetic factors could have a role in the disease because there is evidence that reflux symptoms cluster within families,[45] although the strength of this aggregation is debated.[46] There have been two studies[47,48] that have assessed the prevalence of reflux symptoms in monozygotic versus dizygotic twins, and these have given the most insight into the role of genetics in the disease. Both studies reported significantly higher case-wise concordance rates for reflux symptoms in monozygotic compared with dizygotic twins. Data from the Swedish Twin Registry[47] suggested that 31% (95% CI 23–39%) of reflux disease is due to additive genetic factors, whereas a UK Twin Registry study[48] suggested that this figure was 43% (32–55%). An active search for genes in GORD is ongoing.

Pathophysiology

The primary underlying mechanism could be impaired function of the lower oesophageal sphincter—a segment of smooth muscle in the distal oesophagus that tonically contracts so that the pressure in this area is at least 15 mm Hg above intragastric pressure.[49] This mechanism acts as a physiological barrier to prevent gastric contents from refluxing into the oesophagus. The sphincter relaxes in response to oesophageal peristalsis to allow the passage of food, liquid, or saliva into the stomach. There are brief periods when the sphincter relaxes when there is no swallowing or oesophageal peristalsis, and these events are termed transient lower oesophageal sphincter relaxations (TLOSRs). TLOSRs are physiological, and thus the oesophagus will be exposed to a small amount of acid in a healthy person after meals.[50] Oesophageal peristalsis and saliva, however, will rapidly return the pH of the oesophagus to normal. TLOSRs occur in response to gastric distension via a vagal reflex,[51] and in a healthy person most of these

events are not associated with any acid reflux. In patients with gastro-oesophageal reflux disease an increased proportion of TLOSRs are associated with reflux of gastric contents, and therefore the oesophagus is exposed to acid for extended periods. This process increases the risk of symptoms and oesophageal damage. In a few patients there is a permanent defect in the lower oesophageal sphincter leading to a constant decrease in resting tone. These patients usually have severe oesophagitis or complications, such as stricture or Barrett's oesophagus, because the oesophagus is exposed to acid for long periods, especially when the patient is supine.[52] A large hiatal hernia predisposes to TLOSRs[53] and increases the risk of developing oesophagitis.[54] A pocket of acid in the proximal stomach could escape meal-induced buffering, predisposing to distal acid reflux postprandially.[55] There is a close correlation between the duration of oesophageal exposure to gastric contents and the severity of mucosal disease.[56]

Other factors could also be important in determining the severity of the disease. Impaired oesophageal peristalsis after a reflux episode increases oesophageal acid exposure.[57] The amount of damage to the oesophageal mucosa can also be increased if pepsin is present in addition to acid.[49] Reflux of bile may also be important in a few cases, especially in those with Barrett's oesophagus.[56] The mutagenic potential of gastric acid juice can increase when it comes into contact with saliva, which is rich in nitrites. The nitrite content is converted into mutagenic chemicals, which could be important in the pathogenesis of neoplasia.[58]

Patients with non-erosive reflux disease have less oesophageal acid exposure than those with oesophagitis, and in some cases the amount of reflux is no different from that in healthy volunteers. In patients with non-erosive reflux disease, oesophageal visceral hypersensitivity, abnormal tissue resistance, or sustained oesophageal contractions have been proposed as potential causes of reflux symptoms.[59] These patients have also been shown to have an abnormal sensitivity to infusion of acid solution into the distal oesophagus.[60] In some, the oesophageal epithelial mucosa might not provide a sufficient barrier to acid damage. Acid reflux initially damages the junction between cells leading to increased cellular permeability to water and electrolytes.[61] These microscopic changes could explain the increased sensitivity to acid reflux in non-erosive reflux disease. Alternatively, one study suggested that sustained oesophageal contractions were better correlated with heartburn symptoms than with acid reflux.[62]

Diagnosis

The lack of a gold standard has hampered the assessment of the accuracy of various approaches to the diagnosis of gastro-oesophageal reflux disease. The absence of a reference standard can be overcome by use of techniques such as latent class analysis and Bayesian analysis, but as yet these methods have not been used in the assessment of the disease.[63] The accuracy and use of the different approaches to diagnose the disease are therefore uncertain. The tools available for diagnosis are endoscopy, symptom assessment, barium oesophagram, ambulatory pH monitoring, and the proton-pump inhibitor (PPI) test.

Upper gastrointestinal endoscopy

The identification of oesophagitis with upper-gastrointestinal endoscopy is highly specific (90–95%)[64] for gastro-oesophageal reflux disease, but has a sensitivity of only around 50%.[4] The extent of mucosal injury can be assessed at endoscopy and this has been categorised into grades A to D according to the Los Angeles classification (figure 1).[6] About 50% of patients with the disease will have a normal endoscopy in referral centres, but in primary care and the general population the rate of oesophagitis is lower.[13] Endoscopy can also evaluate any complications of the disease, such as stricture or Barrett's oesophagus, and is recommended if patients have alarm features with reflux symptoms, such as weight loss or progressive dysphagia.

There have been several advances to traditional endoscopy to investigate the disease. Ultra-thin endoscopes have been developed, which can be passed either orally or transnasally. These instruments are accurate and well tolerated by patients[65] without the need for sedation, but have not gained wide acceptance by practising clinicians. Magnification endoscopy has been evaluated to assess whether patients with non-erosive reflux disease have subtle changes in the oesophageal mucosa that could help in diagnosis. Small changes, such as white or red mucosa or oedema, however, are not reliably identified[6] and are of uncertain relevance in identification of gastro-oesophageal reflux disease.[66] One of the major advances in endoscopy in recent years is the development of a videotelemetry capsule that is small enough to be swallowed.[67] There were initial difficulties with this approach,[68] but accuracy seems to be improving[69] and it could be an alternative to traditional endoscopy in the future.

Oesophageal biopsies have been proposed as a method of identifying patients with non-erosive reflux disease. The presence of eosinophils and markers of increased epithelial cell turnover, such as basal-cell hyperplasia, have reasonable sensitivity but poor specificity,[70] whereas neutrophils in the oesophageal mucosa are specific but not very sensitive.[70] Electron microscopy of oesophageal biopsies suggested that dilated intercellular spaces could be an early marker of mucosal damage in gastro-oesophageal reflux disease, which occurs in patients with endoscopy-negative reflux irrespective of oesophageal acid exposure.[71] These observations are important but remain research tools, and oesophageal biopsies are not recommended for the routine assessment of gastro-oesophageal reflux disease.

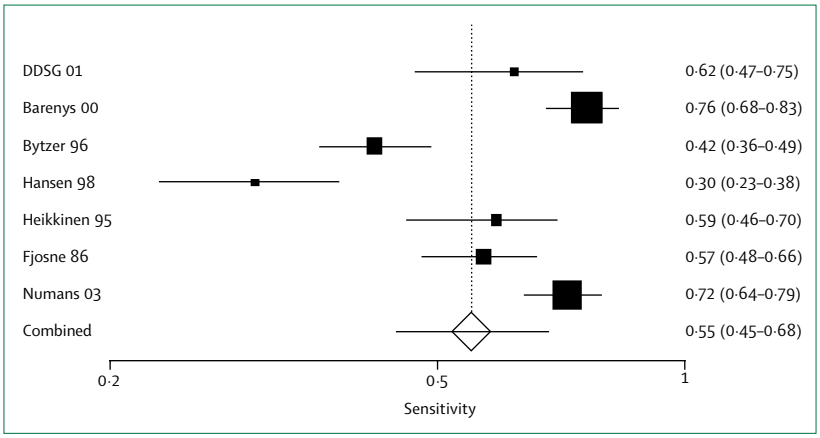

Figure 3: **Forest plot of the sensitivity of clinical history in the diagnosis of oesophagitis**

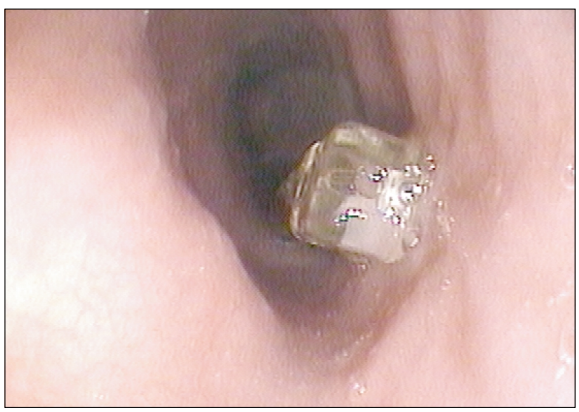

Figure 4: **Bravo capsule placed 6 cm above the Z line at endoscopy**

Symptom assessment

Heartburn and regurgitation are the cardinal symptoms of the disease.[7] Heartburn describes the sensation of discomfort or burning behind the sternum rising up to the neck, whereas regurgitation is the effortless return of stomach contents into the pharynx.[2] Patients often use the term heartburn to mean other upper gastrointestinal symptoms such as epigastric pain,[4] so it is important to clarify this in the history. Furthermore, in most languages there is not a direct translation for the word heartburn.[72] Symptoms often occur in clusters, and it can be difficult for the patient to define a predominant symptom.[73] Symptoms such as dysphagia, odynophagia, globus (lump in the throat), sore throat, laryngitis, water brash, and cough are other possible symptoms of the disease, but their diagnostic use is uncertain.

The accuracy of heartburn or regurgitation in the diagnosis of the disease is difficult to ascertain. Some studies have suggested that this approach is very useful,[74] whereas other interpretations of the same data are more cautious.[75] We did a systematic review[76] that identified seven studies[77–83] that assessed the accuracy of clinical opinion in the diagnosis of the disease in a total of 5134 patients. Endoscopy has excellent specificity, so it is possible to estimate the sensitivity of the clinical history in diagnosis of the disease. The sensitivity of reflux symptoms was generally disappointing when endoscopy was used as a gold standard, with a range of 30–76% and a pooled sensitivity of 55% (95% CI 45–68%) calculated with a random effects model (figure 3). Reflux symptoms are helpful in the diagnosis of the disease, but it is important to emphasise their lack of sensitivity; many patients with atypical upper gastrointestinal symptoms may have gastro-oesophageal reflux disease.

Ambulatory oesophageal pH monitoring

This test is usually done with a pH probe, which is passed transnasally to 5 cm above the manometrically determined lower oesophageal sphincter. The probe is able to obtain pH measurements every few seconds for 24 h and the data are collected by a battery-powered device carried by the patient. The patient also records when meals are eaten and symptoms are experienced. Acid-reflux episodes are defined as a pH fall below 4, and the total time under this threshold is the most reproducible measure of gastro-oesophageal reflux disease, with normal limits usually less than 5%.[84] The sensitivity of 24 h pH monitoring in patients with a normal endoscopy is around 60%, with a specificity of 85–90%,[84] although estimates are hampered by the lack of a gold standard. pH probes only measure acid and cannot detect non-acid reflux. Multichannel intraluminal impedance monitoring with pH sensors has been developed to detect acidic, weakly acidic, and non-acid reflux.[85] This technique has been validated fluoroscopically but its accuracy in the clinical setting needs further study.

Ambulatory 24 h oesophageal pH monitoring is not available in all hospitals, is uncomfortable, and is expensive. This test is usually reserved for patients for whom there is important diagnostic uncertainty or who are being considered for anti-reflux surgery. The development of a wireless device (Bravo pH probe, Medtronics, Minneapolis, USA) could overcome some of the disadvantages of the traditional approach to pH monitoring. The pill-sized device is attached endoscopically, 6 cm above the Z-line (the junction between oesophagus and stomach; figure 4). The pH is recorded on a pager-sized receiver held by the patient and transmitted by radiotelemetry. The capsule detaches and is passed spontaneously within 2 weeks. Currently, there are few data for the normal reference values for the wireless system,[86] but the ability to record over 48 h rather than 24 h should increase the sensitivity of the test.[87] The wireless system could be a major advance in the diagnosis of the disease because it is better tolerated than conventional pH monitoring,[87] although most patients do experience a mild foreign body sensation. The future for this approach will depend on developing reference values and ensuring that serious adverse events are rare. Since February, 2003, there have been 22 adverse events reported to the US Food and Drug Administration. Most

of these relate to device malfunction or failed detachment requiring endoscopic removal of the capsule. There were, however, two serious events: one report of oesophageal bleeding requiring transfusion and one oesophageal perforation.[88]

Barium oesophagram

The barium oesophagram is relatively cheap and less invasive than endoscopy. This test is reasonably accurate in detection of severe oesophagitis, but mild cases are missed.[89] Radiology lacks sensitivity and specificity for diagnosis of the disease, but is useful in detection of mild strictures and oesophageal motor abnormalities.

PPI test

Empirical acid suppression with a PPI makes intuitive sense. Gastro-oesophageal reflux disease is usually an acid-related disease, so if symptoms respond to acid suppression the patient is likely to have the disease. PPI therapy is very effective in healing oesophagitis so patients that continue to have symptoms are unlikely to have the disease. A systematic review[90] identified 15 studies that assessed the accuracy of normal or high-dose PPI for 1–4 weeks in the diagnosis of the disease. The pooled sensitivity was reasonable at 78% (95% CI 66–86%), but the specificity was poor at 54% (44–65%) when 24 h ambulatory pH was used as a gold standard. More data are needed for the definition of symptom response and the optimum dose and duration of PPI therapy, but at present empirical acid suppression has disappointing specificity in diagnosis of the disease. This could be because of the placebo response rate that is seen with trials of empirical therapy.

Complications and extra-oesophageal manifestations

There is a paucity of data on the long-term outcome of patients with different severities of reflux disease. Patients with severe symptoms over a long duration might intuitively be expected to be at higher risk of more severe reflux disease. Severity and duration of symptoms, however, seem to have a poor correlation with the presence or severity of oesophagitis.[91] A US veteran database study of more than 29 500 patients with uncomplicated erosive oesophagitis reported no patients developing complications after a mean of 4·2 years' follow-up.[92] Therefore, the possibility exists that once patients develop gastro-oesophageal reflux disease, the severity of disease is determined early and patients tend to continue with that phenotype for long periods.[91] Complications that develop include oesophageal strictures, oesophageal ulcers, Barrett's oesophagus, and oesophageal adenocarcinoma. Oesophageal strictures and ulcers have a prevalence of approximately 0·1% and 0·05%, respectively, and both are associated with white race, male sex, and increasing age.[93]

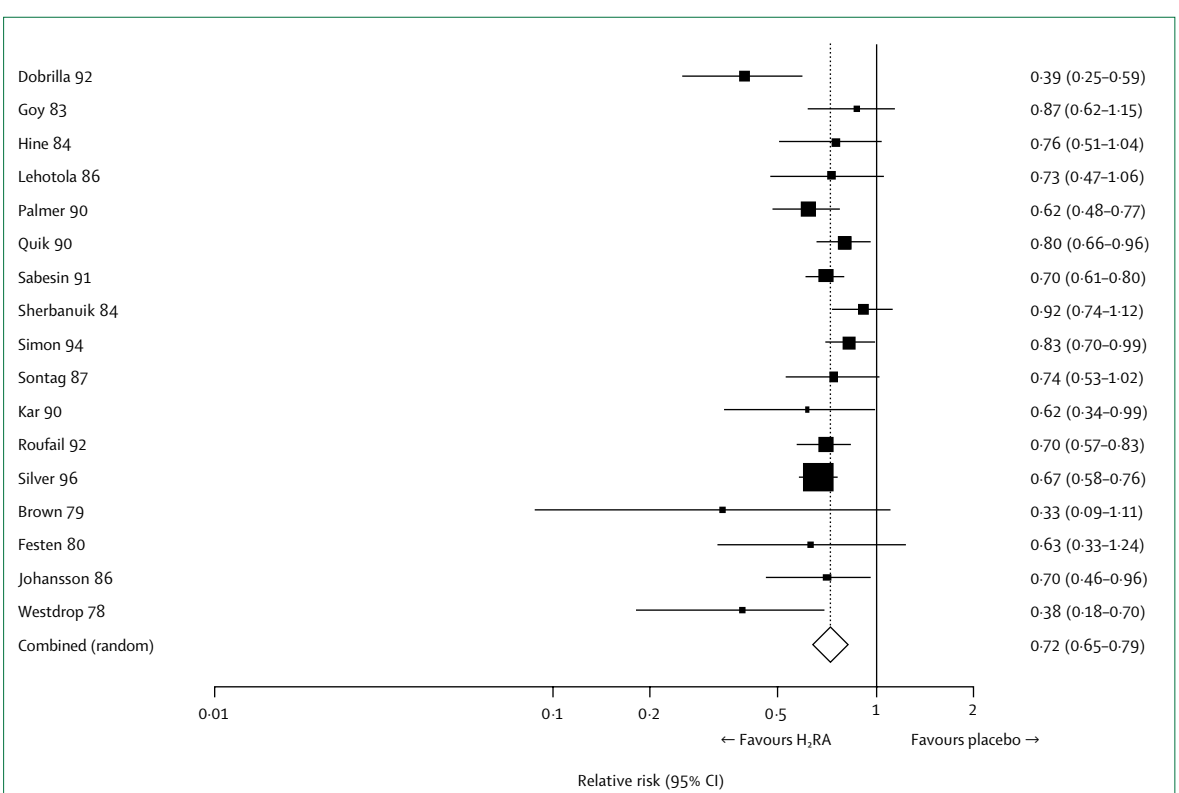

Figure 5: **Forest plot of randomised controlled trials comparing H_2 receptor antagonists with placebo in the treatment of oesophagitis over 4–8 weeks**

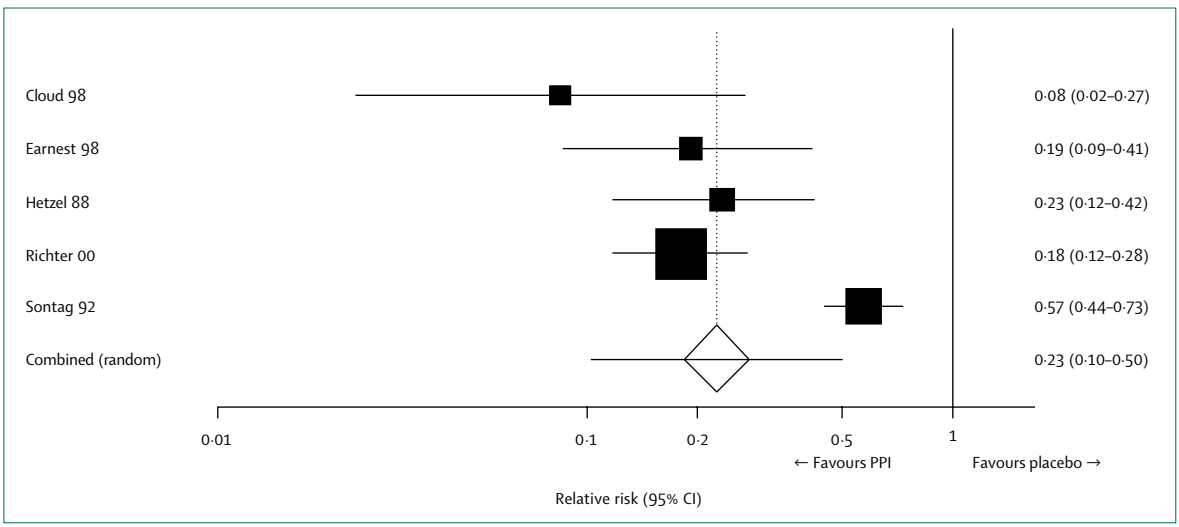

Figure 6: **Forest plot of randomised controlled trials comparing PPIs with placebo in the treatment of oesophagitis over 4–8 weeks**

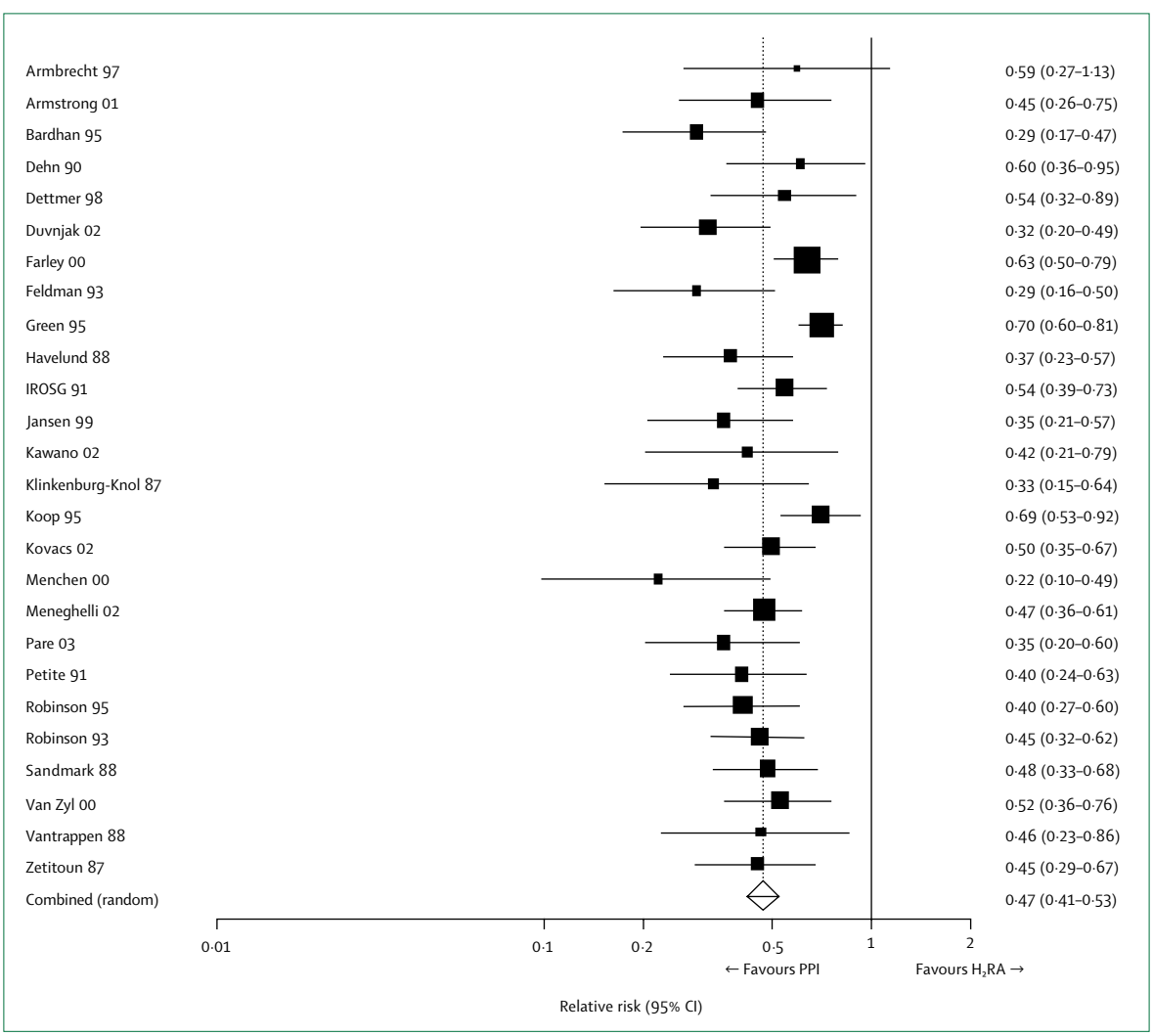

Figure 7: **Forest plot of randomised controlled trials comparing PPIs with H_2 receptor antagonists in the treatment of oesophagitis over 4–8 weeks**

Barrett's oesophagus describes a metaplastic change from squamous to columnar mucosa with intestinal metaplasia. Barrett's oesophagus is uncommonly detected in patients younger than 50 years, but is present in 1–2% of patients referred for endoscopy over this age threshold.[20] Barrett's oesophagus is associated with severe gastro-oesophageal reflux disease and it is thought to occur as a response to the mucosa adapting to long-term reflux of gastric contents,[94] although the direct epidemiological data to support this notion are weak.[95] Obesity has been associated with an increased risk of Barrett's oesophagus in patients who report weekly reflux symptoms.[96] Barrett's oesophagus is associated with an increased risk of oesophageal adenocarcinoma, with between 0·5%[97] and 1%[98] developing cancer each year. A review of the published work[99] identified three studies[100–102] that have assessed the association between reflux symptoms and oesophageal adenocarcinoma directly. All showed an increased risk of oesophageal adenocarcinoma with increasing duration, frequency, and severity of reflux, although the size of the association was variable. The risk of oesophageal adenocarcinoma with reflux disease is low at a population level and probably does not warrant screening of patients with reflux symptoms, but more data are needed.[103]

There have been various pulmonary, ear nose and throat, and oral diseases and symptoms that have been linked to reflux symptoms; these have been termed extra-oesophageal manifestations of gastro-oesophageal reflux disease. Non-cardiac chest pain is also often classified as an extra-oesophageal manifestation of the disease, although semantically this is incorrect because the chest pain is probably due to acid in the oesophagus. There is some epidemiological evidence of an association between reflux symptoms and many pulmonary or ear nose and throat disorders, but there does not seem to be an increased risk of these diseases with increasing severity of the disease.[104] Detailed discussion of extra-oesophageal manifestation is beyond the scope of this article.

Treatment

Lifestyle advice and antacid therapy is advocated as first-line treatment for the disease. Lifestyle factors are only weakly associated with reflux symptoms, so it is unlikely that these will have a major effect on the disease. Nevertheless, advice such as stop smoking, reduce alcohol intake, and weight loss in obese patients is likely to have wider benefits, even if the effect on reflux symptoms is small. There is some evidence from a randomised trial[105] that antacid therapy has a small effect on reflux symptoms, but the effect on oesophagitis is less clear. Most patients will not respond adequately to these first-line measures and need further treatment. The alternatives that are available include pharmacological, endoscopic, and surgical treatment.

Pharmacological therapy

Initial therapy

Acid suppression is the mainstay of treatment in both the acute and long-term treatment of the disease. A Cochrane systematic review[106] has been completed on the efficacy of pharmacological treatments for oesophagitis over 4–8 weeks. This review identified 18 trials[107–124] involving 2134 patients that compared H_2 receptor antagonists (H_2RA) with placebo. H_2RAs were effective in the treatment of oesophagitis compared with placebo (relative risk of oesophagitis persisting with H_2RA 0·72, 95% CI 0·65–0·79; figure 5) with a number needed to treat (NNT) of five (95% CI 3–22). There were five trials[125–129] that compared a PPI with placebo in 635 patients. PPIs were more effective than placebo in the treatment of oesophagitis (0·23, 0·01–0·5; figure 6) with an NNT of two (1·4–2·5). The review also identified 26 trials[130–155] involving 4064 patients that compared PPIs with H_2RA. PPI therapy was better than H_2RA therapy in the treatment of oesophagitis at 4–8 weeks (0·47, 0·41–0·53; figure 7) with an NNT of three (2·8–3·6). There were few eligible trials assessing prokinetic treatment, which had only slight efficacy for oesophagitis. The review highlighted that the effect of acid suppression on quality of life was poorly studied in placebo-controlled randomised trials. One trial published since the systematic review, however, suggested that PPI therapy improved quality of life, reduced sleep disturbance, and increased work productivity compared with placebo.[156]

Another Cochrane systematic review reported that PPI therapy was better than placebo and H_2RA therapy in endoscopy-negative reflux disease and undiagnosed reflux symptoms in primary care, although the effect was not as large as with oesophagitis.[157] There is some evidence that a lower proportion of patients with non-erosive reflux disease than those with oesophagitis achieve symptom control with acid suppression.[158]

Maintenance therapy

Gastro-oesophageal reflux disease usually relapses once drug therapy is discontinued, with about 80% having oesophagitis relapse after 6–12 months.[159] Most patients with the disease, therefore, need long-term drug therapy. A systematic review[159] of pharmacological therapies to prevent relapse of oesophagitis accorded with the good results for PPI therapy. The review identified ten eligible randomised trials involving 1583 patients with oesophagitis that compared the efficacy of PPIs with H_2RA therapy over 24–52 weeks. The overall relapse of oesophagitis was 22% in the PPI group compared with 58% in the H_2RA group with an NNT of 2·5 (2·0–3·4). Similar results were achieved with symptom relapse as an endpoint rather than oesophagitis recurrence. This review[159] also identified six trials that compared half-dose PPIs with H_2RA treatment in 1156 patients. Overall, 40% of the PPI group had a relapse of oesophagitis after 24–52 weeks compared with 66% of the H_2RA group (NNT 3·3, 2·5–5·0). Low-dose PPI therapy is therefore

better than H_2RA therapy, but is not as effective as a standard dose of PPI. These trials refer to patients with oesophagitis and there is insufficient long-term data for PPI therapy in endoscopy-negative reflux disease.[159]

Intermittent or on-demand therapy

A systematic review[160] assessed the efficacy of intermittent courses of therapy (eg, 2–4 weeks) or on-demand acid suppression in the disease (where the patient takes a drug for symptom control for as many days as they wish). These data could not be pooled because the end-point in the trials varied. The systematic review[160] identified five trials that assessed on-demand H_2RA therapy, and all showed better efficacy than with placebo. There were also five trials of on-demand PPI therapy, which showed patients took the drug 33–50% of the time with 70–93% willing to continue treatment. Again, all studies showed that PPIs were significantly better than placebo. One subsequent study suggested that satisfaction was slightly higher in patients with the disease who were taking continuous PPI treatment than in those taking on-demand therapy, but the difference was small.[161] There were no studies comparing PPIs with H_2RA, and all placebo-controlled studies assessed non-erosive reflux disease. One trial compared continuous with on-demand PPI therapy in patients with LA grades A–D oesophagitis, and showed that oesophagitis relapse rates were higher in the on-demand group, although levels of satisfaction were similar between the two groups.[162]

Extra-oesophageal disease

There have been two systematic reviews[163,164] of extra-oesophageal disease and both suggest that patients with non-cardiac chest pain respond to PPI better than to placebo. We identified eight randomised controlled trials[163] that assessed 321 patients with a pooled relative risk for continued chest pain after PPI therapy compared with placebo of 0·54 (95% CI 0·41–0·71) and an NNT of three (95% CI 2–4). Systematic reviews, however, do not lend support to the use of acid suppression in other extra-oesophageal disorders, such as chronic cough[165] or asthma,[166] although more data are needed.

Endoscopic therapy

Acid suppression can be effective in most patients with gastro-oesophageal reflux disease, but long-term therapy is expensive and the treatment does not address the main abnormality in reflux disease: the abnormal relaxation of the lower oesophageal sphincter. This has led to great interest in new endoscopic therapies for the treatment of the disease, and these can be divided into three approaches: endoscopic suturing devices for the lower oesophageal sphincter; the endoscopic application of radio-frequency to the lower oesophagus; and the injection of bulking agents into the muscle layer of the distal oesophagus.[167]

The aim of endoscopic suturing devices is to insert three stitches circumferentially or longitudinally in the gastric cardia to plicate and strengthen the lower oesophageal sphincter. The procedures are technically demanding and can involve a long procedure time. Uncontrolled studies have suggested that antisecretory medication was decreased in more than 60% of patients, but there was no change in lower oesophageal sphincter pressure and oesophagitis had healed without treatment in only 25% of cases.[168] Good results were reported in a non-randomised study that compared laparoscopic fundoplication with endoscopic suturing, but more data are needed.[169]

Temperature-controlled radio-frequency energy delivered to the cardia could reduce the frequency of lower oesophageal sphincter relaxations. The mechanism by which this occurs is unclear. The procedure involves positioning a probe at the gastro-oesophageal junction and the application of radiofrequency to eight circumferential points in the cardia, which takes 40–60 min. A study of 118 patients with grade I or II oesophagitis[170] suggested that 87% no longer needed PPI therapy and healing of oesophagitis occurred in 68%. There was also improvement in 24 h oesophageal pH, but this still remained within the abnormal range in most patients after 6–12 months.

The third approach is to inject an insoluble copolymer (eg, polyethylene and polyvinyl alcohol) into the muscle layer of the oesophagus. This results in a polymer precipitating in the muscle layer. A study of 85 patients

Ref	Patients	n	Intervention	Control	Follow-up	Outcome
173	Heartburn, abnormal pH, no hiatus hernia >2cm, no LA grade C/D oesophagitis	64	RE+acid suppression if required	Sham procedure+acid suppression if required	6 months	No difference in oesophageal acid exposure or PPI therapy required. Active treatment associated with less heartburn symptoms
174	PPI-dependent heartburn patients	64	Entryx+PPI if required	Sham+PPI if required	6 months	69% off PPI in active therapy compared with 40% of controls (p<0·05). Significant reduction in symptoms in the active treatment group at 3 months
175	Heartburn, abnormal pH, no hiatus hernia >3 cm	47	Gastric plication	Sham procedure	12 months	No difference in relapse rates, PPI requirements, symptoms, or oesophageal acid exposure between the two groups
176	Heartburn, abnormal pH, no hiatus hernia >3 cm, no LA grade C/D oesophagitis	45	Gastric plication (n=15)	Sham procedure (n=17) or observation only (n=13)	3 months	Reduction in PPI requirements and heartburn in the active treatment group. No difference in oesophageal acid exposure between the two groups
177	Heartburn, abnormal pH, no hiatus hernia >3 cm	34	Gastric plication+PPI if required	Sham procedure+PPI if required	3 months	Significant improvement in oesophageal acid exposure with active treatment, although only normalised in two patients. No significant difference in overall PPI use or symptoms

RE=radiofrequency energy; PPI=proton pump inhibitor.

Table 1: **Summary of randomised controlled studies assessing the efficacy of endoscopic treatments**

	First-line therapy†	When to use endoscopy	Step up/down therapy	Role of *H pylori*	Other therapies
NICE[185]* (England and Wales)	PPI therapy	Endoscopy discouraged apart from alarm features and concern for malignancy in those older than 55 years.	Low-dose PPI therapy and PPI on demand	*H pylori* test and treatment recommended as part of management strategy of upper GI symptoms. No evidence *H pylori* has a role in GORD	1. Surgery may be beneficial but not for routine use. 2. Prokinetics not recommended. 3. Endoscopic therapy not addressed.
ACG[3] (USA)	PPI therapy, H_2RA therapy in milder cases of GORD	Endoscopy for those with symptoms suggestive of complications and those at risk of Barrett's oesophagus	The dose of PPI needed for symptom control. This will be full dose PPI or even increased dose PPI in many cases	Not discussed	1. Surgery is an option for maintenance therapy by an experienced surgeon. 2. Prokinetics not recommended but monotherapy may be useful in select patients with acid suppression. 3. Endoscopic therapy controls symptoms in selected patients with well documented GORD.
Genval[4] (International)	PPI therapy or H_2RA therapy (PPI strongly preferred)	Endoscopy for all patients experiencing reflux symptoms at least twice a week for 6 months	The dose of PPI needed for symptom control. Step down to H_2RA after low-dose PPI.	*H pylori* eradication not indicated in GORD	1. Indications for surgery not discussed but if performed should be by an experienced surgeon. 2. Prokinetics not usually indicated. 3. Endoscopic therapies not addressed.
Asia-Pacific[186]	PPI therapy	Symptoms persist despite PPI therapy, frequent relapses of symptoms with on-demand PPI therapy or alarm features present	On demand PPI therapy	*H pylori* does not have a role in the pathogenesis in GORD. Advisable that *H pylori* status checked and eradication given before long-term PPI therapy to reduce the risk of atrophic gastritis	1. Choice of surgery and medical therapy dependent on patient preference and available expertise. 2. Prokinetics not recommended. 3. Endoscopic therapy only in the context of a clinical trial.
Candy[187]* (Canadian)	PPI or H_2RA therapy (PPI preferred)	Patients that have been on acid suppressive medication for 5–10 years. Alarm features	PPI or H_2RA therapy to control symptoms	*H pylori* testing not required in GORD, however it is reasonable on a case by case basis.	1. Surgery is an option for patients on long-term acid suppression or have symptoms despite medical therapy. 2. Prokinetics not recommended. 3. Endoscopic therapies cannot be recommended for routine practice.
Australian[188]	PPI therapy	Alarm features, symptoms persist despite therapy, diagnosis unclear as symptoms are not characteristic	On-demand PPI therapy	Decision to test and treat for *H pylori* needs to be individualized. No evidence *H pylori* has a role in GORD. Long-term PPI therapy in presence of *H pylori* may increase the risk of gastric atrophy.	1. Surgery if fail to respond to medical therapy, side effects of therapy or patient desire not to take medication. 2. Prokinetics not recommended. 3. Endoscopic therapy only in the context of a clinical trial.

PPI=proton-pump inhibitor; GI=gastrointestinal; GORD=gastrointestinal-oesophageal reflux disease; NICE=National Institute of Clinical Excellence; ACG=American College of Gastroenterology. *Dyspepsia guidelines that included the management of gastro-oesophageal reflux disease. †After lifestyle modification and antacid therapy have failed.

Table 2: **Summary of management guidelines**

with the disease over 6–12 months[171] reported that 74% were not taking PPI therapy, with improvement (but not normalisation) of 24 h oesophageal pH and manometry. The mechanism of action is unclear, but could be due in part to a mechanical bulking effect. The US Food and Drug Administration have recently withdrawn the only licensed bulking agent (Entryx) from the US market because there have been difficulties with the bulking agent being injected incorrectly.

The problem with these uncontrolled studies is some of the effects might be due to a placebo response or regression to the mean. We did a systematic review[172] of randomised trials that assessed endoscopic therapy techniques. We identified five randomised trials[173–177] that compared therapy with a sham procedure in a total of 254 patients. The numbers were too small to draw any definitive conclusions, although these therapies seem to have a smaller effect on symptoms and PPI use than reported by uncontrolled studies, and three of four studies show no effect on 24 h oesophageal pH (table 1).

Surgery

Surgical fundoplication can correct the cause of the disease and prevent the need for long-term medication. A systematic review[178] identified six randomised controlled trials and three cohort studies that compared surgery with drug treatment. Most studies used H_2RA or antacids, or both, in the drug treatment group, and in these trials surgery was significantly better at maintaining oesophagitis healing and controlling symptoms. There is a paucity of trials comparing surgery with PPI therapy, but one report[179] suggested that both were equally effective at controlling symptoms provided patients in the medical treatment group were allowed to increase the dose of drug to twice daily if necessary. Interest in surgery has increased since the advent of minimally invasive techniques. A systematic review[180] identified six randomised controlled trials involving 449 patients that compared open and laparoscopic fundoplication. The review reported no significant difference in recurrence rate between laparoscopic and open fundoplication (odds ratio of relapse 0·80, 95% CI 0·24–2·68), but showed that laparoscopic fundoplication was associated with lower operative morbidity (NNT to prevent a complication: eight, 95% CI 3–16) and a shorter post-operative hospital stay than was the open procedure. The benefit of antireflux surgery in controlling symptoms must be balanced against the 0·5–1% risk of operative mortality.[181] The risk of mortality is reduced by laparoscopic surgery and the experience of the surgeon.[182] Long-term follow-up suggested that many patients continue to need acid suppressive medication.[183] There is also no convincing evidence that fundoplication reduces the risk of oesophageal adenocarcinoma in the long term.[184]

Management

There have been several guidelines[3,4,185–188] published on the management of the disease (table 2). There is a consensus that PPIs are the most effective therapy and should be continued long term at the lowest dose that controls symptoms. All agree that endoscopy has a role in the investigation of the disease, but the threshold at which endoscopy is recommended varies. The guidelines recommend surgery for selected cases. We have constructed a management strategy based on common themes from these guidelines.

After the clinical diagnosis has been made (usually on the basis of symptoms), reassurance and explanation with advice about lifestyle factors seems sensible, although any benefit is probably small. In the presence of alarm features, such as progressive dysphagia or weight loss, prompt endoscopy is recommended, although the sensitivity of these red flags is low for malignancy.[189] Current evidence lends support to initial therapy starting with best medical treatment, namely a PPI once daily for 4–8 weeks; we tell our patients to take this medication 30 min before a meal (usually breakfast) as theoretically this will best block meal-induced activation of the acid pumps. If symptoms resolve, it is worth trying to stop therapy, but relapse is the rule. An exception is documented severe oesophagitis; these patients need maintenance full-dose PPI therapy to control symptoms.

If symptoms continue despite adequate PPI use, endoscopy should be considered if this has not been done, although drug therapy in this setting can mask oesophagitis presence or grade. Causes of a lack of response to PPI therapy include inadequate compliance or dosing, nocturnal acid breakthrough (arbitrarily defined as a gastric pH <4 for >60 min despite twice daily PPI), non-acid reflux, and wrong diagnosis.[190] Very rare causes to consider are acid hypersecretory states (eg, Zollinger-Ellison syndrome) or drug resistance.

The goal of long-term treatment is to step down management to the lowest level of medical therapy that controls symptoms, or consider surgery. Patients who return with a relapse should be restarted on therapy at the level that previously controlled their symptoms, and then can be stepped down (eg, from a full-dose PPI to a half dose or an H_2RA).[191,192] In those with non-erosive reflux disease, on-demand therapy is a cost-effective alternative to maintenance treatment.[193]

Fundoplication surgery requires an experienced surgeon operating on a fit patient who has responded well to PPI therapy for best results. The advisability of surgery needs to be considered on a case by case basis. Indications for surgery include high-volume reflux (ie, severe regurgitation) despite PPI therapy, PPI intolerance, and patients who do not wish to take medication long term.

Contributors

NJT and PM participated in the planning, literature search, data extraction, data analysis, and writing of the report.

Conflict of interest statement

N J Talley has been a member of advisory boards of AstraZeneca, Axcan, EBMed, Giaconda, Solvay, Theravance, Yamanouchi, Boehringer-Ingelheim, and Chugai; has received research support from Merck, Forest, Novartis, Tap Pharmaceutical, and Boehringer-Ingelheim; and is supported by NIH RO1DK 65713-1 A1. P Moayyedi has been a member of advisory boards and the speakers bureau of AstraZeneca and Janssen-Ortho and Altana, and his chair is partly funded by an unrestricted grant given to McMaster University by AstraZeneca.

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