ARTICLE

The management of gastro-oesophageal reflux disease

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SUMMARY

If there are no features of serious disease, suspected gastro-oesophageal reflux disease can be initially managed with a trial of a proton pump inhibitor for 4–8 weeks. This should be taken 30–60 minutes before food for optimal effect.

Once symptoms are controlled, attempt to withdraw acid suppression therapy. If symptoms recur, use the minimum dose that controls symptoms. Patients who have severe erosive oesophagitis, scleroderma oesophagus or Barrett's oesophagus require long-term treatment with a proton pump inhibitor.

Lifestyle modification strategies can help gastro-oesophageal reflux disease. Weight loss has the strongest evidence for efficacy.

Further investigation and a specialist referral are required if there is no response to proton pump inhibitor therapy. Atypical symptoms or signs of serious disease also need investigation.

Introduction

Gastro-oesophageal reflux disease (GORD) is a condition in which reflux of the stomach contents into the oesophagus results in symptoms or, occasionally, complications. This is distinct from asymptomatic physiological reflux and from functional heartburn, where the symptoms resemble GORD but are unrelated to acid reflux.[1]

GORD is one of the most common gastrointestinal conditions in Australia. It is estimated to occur in 10–15% of the population, with a rising prevalence, most likely due to obesity.[1-3] In addition to obesity, risk factors include advanced age, male gender, Caucasian ethnicity, diets high in fats, sugars and salt, and smoking.

Pathophysiology

Defective function of the lower oesophageal sphincter leads to excessive acid exposure in the lower oesophagus, most commonly during transient lower oesophageal relaxations.[1] In the majority of cases, this leads to symptoms such as heartburn and regurgitation. However, in a small but important minority, complications of peptic oesophagitis may occur including oesophageal strictures, Barrett's oesophagus and rarely oesophageal adenocarcinoma, the rate of which is increased fivefold in patients with chronic GORD compared to the general population.[2]

Although hiatus hernia is statistically associated with gastro-oesophageal reflux, the presence of a hiatus hernia is neither required nor sufficient for a diagnosis of GORD. The presence of a hiatus hernia is relevant to surgical treatment, but does not affect the approach to medical therapy.

Initial assessment

A presumptive diagnosis of GORD can be made based on the typical symptoms of heartburn and regurgitation. The presence of either symptom has an overall sensitivity of 49% and specificity of 74%.[4]

Heartburn is described as a burning, retrosternal, rising sensation associated with meals, although this definition is often poorly understood by the general population.[4] Practitioners need to be aware of this and clarify the nature of the symptoms being discussed when the term is used. Regurgitation is described as the effortless appearance of gastric contents in the throat or mouth without associated nausea or retching.[4] Other non-specific symptoms include vomiting, anorexia, dysphagia, cough and other respiratory or oropharyngeal symptoms.[2,5-8]

While several validated symptom-based questionnaires exist, their use is largely limited to research studies.[4] The correlation between symptoms and the severity of oesophagitis is weak, but if typical features are present without 'red flags' (Box 1)[9] then there is no need for gastroscopy in the initial assessment and empirical treatment can commence.

A trial of a proton pump inhibitor (PPI) is frequently used. Although neither particularly sensitive nor specific, a trial is useful, cost-effective and helpful in predicting which patients will respond to therapy. Treatment should continue for 4–8 weeks. While a

negative trial does not exclude the diagnosis, it does reduce its likelihood and should prompt consideration of alternative diagnoses.[10]

Further investigations

Further investigations may be required in patients who do not respond to a trial of acid suppression, or have red flags or chronic symptoms.[9]

Endoscopy

The primary role of gastroscopy is to look for complications and to exclude other diagnoses. It is therefore only indicated in certain situations (Box 2) and should not be repeated if negative. Normal macroscopic findings are seen in almost two-thirds of patients with reflux symptoms and a normal endoscopy does not exclude GORD.[9] Gastroscopy can exclude Barrett's oesophagus and erosive GORD, which allows the patient to be informed that the focus of treatment will be on symptom control and that further endoscopy is not required.

Eosinophilic oesophagitis should be considered in patients, particularly men, in their 20s and 30s with a history of food allergy or atopy who present with dysphagia or refractory symptoms suggestive of GORD. Biopsy may be needed to exclude eosinophilic oesophagitis.[11] There is no evidence that routine screening for Barrett's oesophagus improves mortality or is cost-effective.[12] However, it may have a role in high-risk groups such as the overweight and Caucasian males over 50 years old with no previous endoscopic investigation.

Barium swallow

There is no role for the barium swallow in the routine diagnosis of GORD. Findings of gastro-oesophageal reflux induced by position or abdominal pressure are neither sensitive nor specific for GORD.[5]

Oesophageal manometry and pH studies

These studies are only required in a minority of patients who are either refractory to treatment or are being assessed for surgery.[13,14] Usually a specialist consultation is needed.

Other investigations

Helicobacter pylori infection does not cause GORD and actually appears to be slightly protective against it, Barrett's oesophagus and oesophageal adenocarcinoma. *Helicobacter pylori* eradication is not effective in reducing the symptoms of GORD.[2]

Lifestyle modification

Of the non-pharmacological approaches to the management of GORD, weight loss has been shown to have a dose-dependent association with reduction of symptoms.[3] A reduction in the body mass index of 3.5 kg/m^2 can result in nearly a 40% reduction in the risk of having frequent symptoms.[1]

Other lifestyle modifications include elevation of the head of the bed and avoidance of meals 2–3 hours before bedtime if there are nocturnal symptoms.[10] While routine global elimination of specific food groups triggering reflux is not recommended, patients should avoid foods that specifically trigger their symptoms. Cessation of tobacco and alcohol are recommended but, while this may help some patients, it has not been shown to improve symptoms overall.[10] Drugs with anticholinergic or smooth muscle-relaxing properties may exacerbate reflux symptoms, as may drugs causing a chemical oesophagitis (e.g. oral bisphosphonates).

Acid suppression therapy

Many patients try over-the-counter medicines such as antacids or H_2-receptor antagonists before they

Box 1 Red flags* in gastro-oesophageal reflux

Recurrent vomiting

Dysphagia or odynophagia

Weight loss

Evidence of gastrointestinal blood loss
e.g. haematemesis, iron deficiency or anaemia

Duration of symptoms >5 years or <6 months

Epigastric mass

Age >50 years

* Red flags are warning symptoms and signs requiring further evaluation.[9]

Box 2 Indications for gastroscopy in gastro-oesophageal reflux disease[9]

Red flags (see Box 1)

Persistent symptoms despite an adequate trial of proton pump inhibitor therapy

Treatment of complications such as dilatation of oesophageal strictures

Evaluation of patients before and after anti-reflux surgical procedures

Screening for Barrett's oesophagus in high-risk patients (may be considered, e.g. in overweight men over 50 years, however evidence that screening improves outcomes is lacking)

visit a doctor. These treatments may be continued if they are effective, often with the addition of lifestyle modifications. If symptoms persist despite simple measures, and significantly interfere with quality of life, a trial of a PPI is appropriate (Fig.). This provides a degree of diagnostic confirmation and, in the case of suboptimal response, determines whether further investigation is required.

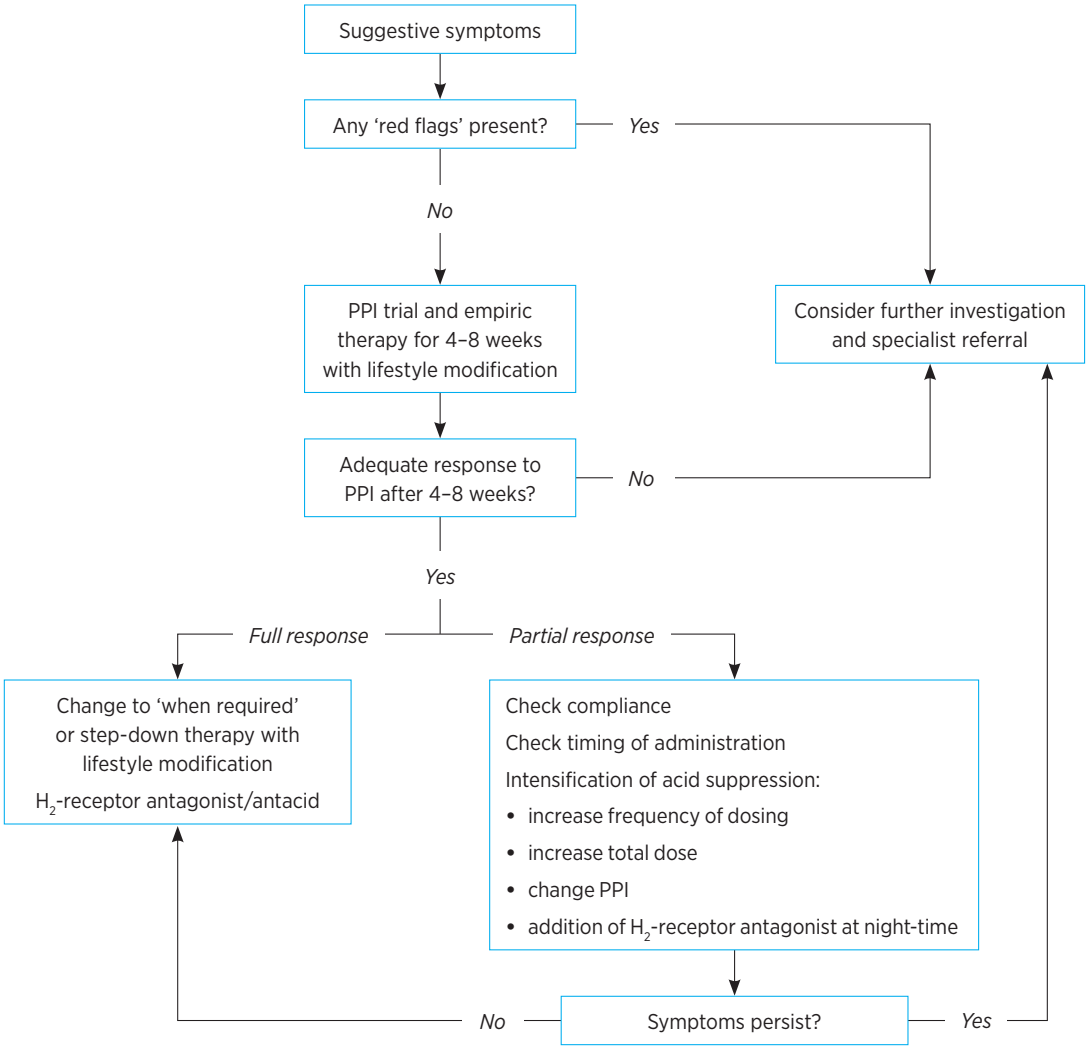
Pharmacology

PPIs are more potent at acid suppression than H_2-receptor antagonists. They block the final common pathway of acid secretion by irreversibly binding to and inactivating the proton pump (H^+/K^+-ATPase exchange). This results in a greater proportion of healed erosive oesophagitis compared with the use of H_2-receptor antagonists (84% ± 11% vs 52% ± 17%).[15]

PPIs have a short plasma half-life (mostly 1–2 hours) and are only effective when proton pumps are active (in the postprandial period). The timing of administration is therefore important, with the greatest efficacy being seen when PPI concentrations are maximal at the time of a meal. As the inactivation of the proton pump is irreversible, the biological half-life of the drug is considerably longer than its plasma half-life. Consequently, if an increase in acid suppression is required, a second dose taken later in the day (e.g. before the evening meal) is more effective than doubling the morning dose.

Start treatment with once-daily dosing 30–60 minutes before a meal. This is usually breakfast as the greatest amount of H^+/K^+-ATPase is present after a prolonged fast. Drug metabolism differs between individuals, and although some patients may respond better to

Fig. **Approach to management of gastro-oesophageal reflux disease**



PPI proton pump inhibitor

one drug than another, overall symptom relief appears to be equivalent. The most important differences between individuals are largely related to adherence and the timing of a dose, as well as the amount of PPI per unit dose.

Maintenance therapy

Patients with typical symptoms of GORD who respond to 4–8 weeks of PPI therapy can reduce their dose to 'when required' while continuing lifestyle measures, antacids and, when required, H_2-receptor antagonists as a less potent alternative to the PPI. There may be a period of acid hypersecretion following the withdrawal of PPI, but any symptoms will reduce over a period of about a month, after which recurring symptoms are most likely to be due to underlying reflux disease.[16] Using a PPI when required will be adequate for some patients, however 75–90% will relapse over six months.[5] This reflects the chronic nature of the condition rather than a failure of treatment. Surveillance gastroscopy is not required in patients with GORD.

An alternative approach is a more formal step-down of the PPI. The dose is reduced to determine the minimum needed to control symptoms. This may involve a gradual reduction in the dose or frequency with the aim of switching to 'when required' therapy. This approach allows patients to put lifestyle modifications into place and to find the lowest dose they need for adequate control of their symptoms.

Patients with evidence of significant erosive oesophagitis (Los Angeles Grades C, D), scleroderma oesophagus or Barrett's oesophagus should remain on maintenance PPI therapy even if they are asymptomatic.[17]

Adverse effects

The potential adverse effects of PPIs include headache and diarrhoea (less than 2%). Other important but rare adverse events include interstitial nephritis, hypomagnesaemia, reduced vitamin B_{12} absorption, increased *Clostridium difficile* infection and possibly community-acquired pneumonia.[7,10] An association between PPIs and osteoporotic fractures is likely to be due to shared risk factors including increased age and medical comorbidity.[18,19] A randomised trial found no evidence of an increased risk of cardiovascular events in patients taking PPIs and thienopyridines such as clopidogrel.[10,20] There was also no evidence that separating the doses of the two drugs changed cardiac risk.[21] If there are major concerns about the interaction, a PPI with less cytochrome P450 (CYP) metabolism such as rabeprazole may be used.

Persistent symptoms

Approximately 20–30% of patients do not respond completely to PPI therapy and have persistent symptoms.[22] The initial step is to review the diagnosis, particularly if there was no response to acid suppression, as delayed gastric emptying, functional dyspepsia and functional heartburn (oesophageal hypersensitivity)[23] are common conditions that may be confused with GORD. Other explanations for a suboptimal response include non-adherence or inappropriate dosing.[22] Adherence to PPIs is often poor and is reported at 46–55% in those with persistent symptoms. There is also poor understanding of the pharmacokinetics of PPIs with nearly 70% of GPs and 20% of gastroenterologists incorrectly instructing patients about when to take doses.[23]

Options for intensification of acid suppression include increasing to twice-daily doses[10] or trying a different PPI in case there are individual pharmacokinetic and pharmacogenetic differences such as in CYP2C19 metabolism.[15,24] Further intensification of treatment may include addition of a night-time H_2-receptor antagonist (although tachyphylaxis may develop within 2–6 weeks)[15] or a mucosal protectant. However, there is only limited evidence for the use of prokinetic drugs or sucralfate, a protective mucosal surface agent, in the treatment of GORD.[10]

Medical management

In patients with medically refractory GORD, ongoing non-acid or weakly acid reflux is the most common cause.[15] Although baclofen can reduce the number of reflux events by inhibiting transient relaxations of the lower oesophageal sphincter, long-term data are lacking[15] and adverse effects such as drowsiness occur in up to 63% of patients.[16] Other drugs are currently under investigation,[15,25] but there do not appear to be any 'game changers' in the pipeline.

Surgical management

Indications for anti-reflux surgery include GORD with refractory symptoms despite maximal medical management or intolerance of treatment, and symptomatic complications unresponsive to medical therapy.[26] Laparoscopic fundoplication is the most common surgical procedure and is highly effective in well-selected patients.

Fundoplication involves construction of a cuff of gastric (fundus) tissue around the lower oesophageal sphincter junction.[25] This improves function via a variety of mechanical factors and also modifies the reflexes involved in the pathophysiology. Appropriate patient selection is essential, as symptoms must be due to GORD for the procedure to be effective. The strongest predictors of success include abnormal 24-hour pH scores, classic

SELF-TEST QUESTIONS

True or false?

1. Gastroscopy should be repeated after a course of proton pump inhibitor to confirm that gastro-oesophageal reflux disease has healed.

2. If a patient with gastro-oesophageal reflux disease does not improve with a course of proton pump inhibitor, the likely cause is persistent infection with *Helicobacter pylori*.

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symptoms of GORD and a positive PPI trial.[26] Factors that predict failure include a lack of response to PPI therapy and atypical features. Surgery does not lead to significant regression of Barrett's oesophagus or reduce the risk of oesophageal adenocarcinoma.

There is evidence that gastric bypass surgery, in particular the Roux-en-Y procedure or laparoscopic gastric banding, decreases GORD symptoms. This is at least in part because of the resulting substantial weight loss.[3] In contrast, sleeve gastrectomy often increases or precipitates the symptoms of reflux.

Endoscopic management

There are several endoscopic procedures for GORD but they are limited by the durability of symptomatic relief and the lack of correction of pathological reflux.[26] Other novel therapies currently include implantable electrical stimulators and placement of an expandable ring of magnetic beads around the lower oesophageal sphincter. However, experience with these is limited and they are yet to find their place in therapy.

Conclusion

GORD is one of the most common gastrointestinal conditions and may result in significant morbidity. In patients with typical symptoms, treatment can be based on symptoms alone with a trial of PPI therapy. Reduce treatment after a response is established. Further investigation is required if there are 'red flags', a lack of response to the trial or complications of GORD.

Geoffrey Hebbard has received research support, travel assistance or eaten food provided by most of the Australian manufacturers and/or distributors of acid suppressing medication (from cimetidine onwards). He has recently been paid to appear in a video presentation by NPS MedicineWise, and is involved in the (unpaid) writing of guidelines for the use of acid suppression in Therapeutic Guidelines.

Charlotte Keung has eaten food provided by the manufacturers and distributors of PPIs.

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