# Update on gastro-oesophageal reflux disease

**EDMUND TSE**
MB BS

**RICHARD H. HOLLOWAY**
MD, FRACP

Dr Tse is Senior Registrar, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, and Associate Professor Holloway is Associate Professor of Medicine and Senior Consultant Gastroenterologist, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, SA.

**Gastro-oesophageal reflux disease is an increasingly common problem in the community, and most patients are managed in general practice. A symptom-based diagnosis can be supported by a trial of therapy. Most patients will require long term treatment.**

Gastro-oesophageal reflux disease is a common clinical problem. Surveys suggest that it is present in up to 10 to 20% of people in western populations. There is evidence that the prevalence of reflux disease is increasing. The reasons for this have not been defined precisely, but obesity (BMI >30 kg/m$^2$) is likely to be a significant factor. There is a dose response association between BMI and reflux symptoms, even within the normal range for BMI. The risk of reflux symptoms is also increased by alcohol consumption (more than seven standard drinks a week) and having a first-degree relative with heartburn. Reflux disease is a chronic disorder in most patients. Although mild symptoms may be intermittent, more severe symptoms tend to occur daily. Most patients will require long term management.

Management of reflux disease occurs mainly in the primary care setting, with specialist referral recommended only for difficult or complicated cases. Initially, diagnosis is based on symptoms alone; however, symptoms of reflux disease may overlap with those of other gastrointestinal problems, particularly dyspepsia and irritable bowel syndrome. Differentiation between dyspepsia and reflux disease is relevant as management strategies and responses to treatment differ. Until recently the distinction between the two has sometimes been unclear. Indeed some authorities have combined them in management strategies.

## The Montreal definition of reflux disease

Recently, a large expert international working group carefully reviewed the available literature and developed a new definition and classification of reflux disease.[1] Reflux disease was defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. This definition not only inscribes the relationship between reflux disease and the reflux of gastric contents, it also thereby excludes the previously troublesome entity of 'functional heartburn', a disorder characterised by heartburn-like discomfort but without any association with

**IN SUMMARY**

- **A careful history is the most useful method for the diagnosis of reflux disease.**
- **A symptom-based diagnosis can be supported by a trial of proton pump inhibitor (PPI) therapy.**
- **Endoscopic abnormalities are found in fewer than half of all patients with reflux symptoms.**
- **Investigations are warranted if the diagnosis is unclear, symptoms persist despite treatment, or alarm symptoms suggest complications.**
- **Initial therapy with a standard dose of a PPI is the most effective treatment.**
- **Most patients will require long term treatment; intermittent, symptom-driven, on-demand treatment with PPIs is a cost effective approach in many patients.**
- **In experienced hands, antireflux surgery is an effective alternative to PPI therapy in the long term management of reflux disease.**

reflux. The definition also allows for the inclusion of asymptomatic patients with complications of reflux disease such as Barrett's oesophagus, or with extra-oesophageal symptoms such as cough.

The Montreal definition of reflux disease further classifies the manifestations of reflux disease into four syndromes: two oesophageal and two extra-oesophageal syndromes (see the flowchart on page 16). This was based on the recognition that reflux disease may manifest clinically in different ways and that the diagnosis of reflux may be made by different means – e.g. symptom based or based on endoscopic findings or oesophageal pH monitoring.

## Diagnosis of reflux disease

### Symptoms

As mentioned above, the diagnosis of reflux disease in primary care relies on symptoms (Table 1). Most patients in the primary care setting will not have any visible mucosal damage on endoscopy, and other investigations such as oesophageal pH monitoring are not cost effective as first-line measures.

The characteristic symptoms of reflux disease are heartburn and regurgitation. In patients in whom these symptoms are troublesome, it is reasonable to initiate a trial of therapy without investigation. The definition of troublesome is ultimately up to the patient, but mild symptoms that occur for at least two days a week, or moderate and/or severe symptoms that occur more than once a week, are often considered troublesome by patients. Patients often poorly understand the term 'heartburn'; providing them with a description of heartburn, such as 'a burning feeling rising up from the stomach or lower chest towards the neck', will help to identify more patients with reflux disease.

Although the severity of symptoms is a poor predictor of the presence and severity of oesophagitis, certain symptoms should alert the practitioner to the possibility of severe or complicated disease and the need for referral and investigation. These alarm symptoms are dysphagia, odynophagia, haematemesis, choking attacks (particularly at night) and weight loss. However, mild intermittent dysphagia is common in patients with reflux disease, usually reflects impaired oesophageal motility and does not warrant investigation. Reflux disease may also be associated with nonspecific or atypical symptoms such as such as cardiac-type chest pain, cough, hoarseness, belching, bloating and non - specific abdominal discomfort and nausea.

**Gastro-oesophageal reflux disease**

The diagnosis of gastro-oesophageal reflux disease in the primary care setting relies on symptoms; most patients will not need endoscopy. A trial of proton pump inhibitor treatment is reasonable for patients who have troublesome typical symptoms. Symptoms such as dysphagia, odynophagia, haematemesis and choking attacks should alert the practitioner to the possibility of severe or complicated disease and the need for referral and investigation.



### Trial of therapy

A symptom-based diagnosis can be strengthened by a trial of therapy. This can be undertaken either as empirical initial therapy with standard doses of a proton pump inhibitor (PPI) for reflux disease, or as a formal therapeutic trial of a two-week course of double the standard dose of PPI. A trial of

**The Montreal definition of gastro-oesophageal reflux disease and its constituent syndromes[1]**

CHART NOT AVAILABLE

REPRODUCED WITH PERMISSION FROM BLACKWELL PUBLISHING LTD: VAKIL N, VAN ZANTEN SV, KAHRILAS P, DENT J, JONES R, THE GLOBAL CONSENSUS GROUP. THE MONTREAL DEFINITION AND CLASSIFICATION OF GASTROESOPHAGEAL REFLUX DISEASE: A GLOBAL EVIDENCE BASED CONSENSUS. AM J GASTROENTEROL 2006; 101: 1900-1920.

**Table 1. Symptoms of gastro-oesophageal reflux disease**

**Typical symptoms**
Heartburn
Regurgitation

**Atypical symptoms**
Cardiac-type chest pain
Dyspepsia
Belching
Bloating
Cough
Hoarseness
Sore throat

**Alarm symptoms**
Persistent or progressive dysphagia
Painful swallowing
Haematemesis
Weight loss
Nocturnal choking

PPI therapy has a diagnostic sensitivity that is comparable to that of oesophageal pH monitoring and substantially better than that of endoscopy. It also ensures that therapy is initiated early and provides prompt symptom relief in most patients.

**Table 2. When to investigate patients with suspected reflux symptoms**

- Diagnosis is unclear
- Symptoms persist
- Symptoms worsen on therapy
- Alarm symptoms suggest severe or complicated oesophagitis
- Symptoms suggest other possible diagnoses – e.g. other causes of oesophagitis, malignancy, gastro-duodenal ulcers or cardiac ischaemia

## Investigations

Investigations are necessary only in a minority of patients, primarily to clarify the diagnosis, assess disease severity, detect complications and define treatment strategies (Table 2).

### Endoscopy

When investigations are needed, endoscopy is the investigation of first choice. Although fewer than half of all patients with reflux symptoms will have diagnostic abnormalities on endoscopy, this investigation is useful to:

- exclude other possible diagnoses
- assess the severity of oesophagitis (Figures 1a to c)
- identify complications of reflux disease such as Barrett's oesophagus (note that current evidence does not support the use of endoscopy to screen for Barrett's oesophagus).

Endoscopic follow up of patients to

PHOTOS COURTESY OF DR CHRIS POKORNY, SYDNEY

Figures 1a to c. Mild (left), moderate (centre) and severe (right) ulcerative oesophagitis on endoscopy.

assess healing of oesophagitis is generally unnecessary unless symptoms persist, as relief of symptoms with PPI therapy correlates well with healing of oesophagitis.

Patients with alarm symptoms should promptly undergo endoscopy, preferably before empirical therapy.

### Twenty-four-hour oesophageal pH and impedance monitoring

Twenty-four-hour oesophageal pH monitoring is a secondary investigation, used to test whether symptoms are related to acid reflux. It can be very helpful in patients in whom the diagnosis is unclear after a therapeutic trial and endoscopy.

Impedance monitoring, which can detect all reflux irrespective of its acidity, may provide useful information on the relationship of symptoms to reflux in patients with persistent symptoms despite PPI therapy.

### Barium swallow examination

Although barium swallow examination is not useful in the diagnosis of reflux, it may be helpful in patients with dysphagia to detect strictures, define the anatomy of large hiatus hernias and assess postoperative complications of fundoplication.

## Management strategies

The basic aims of management are to relieve symptoms, restore the patient's quality of life, heal oesophagitis (if present) and reduce the risk of complications. Treatment can be divided into the following two main stages:

- initial treatment, which aims to achieve rapid resolution of symptoms, thereby providing diagnostic confirmation and reassurance to the patient, and to

**Table 3. Oral proton pump inhibitors indicated for GORD**

| Generic name | Trade names | Recommended adult dosages* |
|---|---|---|
| Esomeprazole | Nexium | • Erosive reflux oesophagitis: 40 mg/day for 4-8 weeks; maintenance: 20 mg/day<br>• GORD (endoscopy normal): 20 mg/day for 4 weeks, then 20 mg/day as needed |
| Lansoprazole | Zoton | • Reflux oesophagitis: 30 mg/day for 4 weeks<br>• Long term maintenance: 15-30 mg/day |
| Omeprazole | Acimax, Losec, Meprazol, Omepral, Omeprazole Winthrop, Probitor | • Symptomatic GORD: 10-20 mg/day, max 4 weeks<br>• Erosive oesophagitis: 20-40 mg/day 4 to 8 weeks<br>• Maintenance: 10-20 mg/day |
| Pantoprazole | Somac | • GORD symptoms: 20 mg/day for 4 weeks<br>• Reflux oesophagitis: 20-80 mg/day for 4-8 weeks; maintenance: 20-40 mg/day |
| Rabeprazole | Pariet | • GORD: 20 mg/day for 4-8 weeks; prophylaxis: 10-20 mg/day<br>• Symptomatic: initially 10 mg/day, increasing to 20 mg/day for 4 weeks if necessary; maintain symptom control: 10 mg/day for up to 6 months (on demand regimen) |

* Refer to each product's prescribing information for full details on dosing and administration, including recommendations for adolescents and children when indicated.

heal oesophagitis if present
- long term management, which aims to maintain symptom remission in a cost effective manner acceptable to the patient and to minimise the risk of complications.

## Initial treatment

Patients with reflux are often concerned about the possibility that they may have a serious disease such as heart disease or cancer. Proper explanation of the symptoms is, therefore, important. Patients often ask about lifestyle measures to treat their reflux. The impact of these on reflux symptoms is usually weak, but they may be useful in patients with mild intermittent symptoms, particularly when these are related to specific factors. Avoidance of large meals, eating late at night, fatty and spicy foods, and alcohol, particularly wine, may help. Weight loss has been shown in epidemiological studies to be associated with a reduction in symptoms. Elevation of the head of the bed or use of a wedge pillow may be helpful for nocturnal symptoms, particularly regurgitation.

Many patients will have used antacids, antacid and alginate combinations, or over-the-counter $H_2$-receptor antagonists. This approach may be adequate for occasional intermittent symptoms; however, when the use of these medications becomes frequent or regular, patients should be reassessed for more effective therapy.

PPIs are currently the treatment of choice for the initial treatment of reflux disease. A four-week course of treatment with standard doses is usually sufficient to adequately assess patient response, after which time decisions can be made about long term management (Table 3). The choice of PPI is not crucial. They are equally effective for most patients with reflux disease, either endoscopy-negative reflux disease or mild erosive reflux oesophagitis. However, esomeprazole 40 mg once daily has a demonstrated advantage in patients with severe reflux oesophagitis.[2] Patients who respond adequately to this treatment can then be transferred to maintenance therapy. Patients with persistent symptoms should be considered for referral to a specialist for investigation. However, as an interim measure, a trial of twice daily PPI therapy (i.e. double the standard dose) is reasonable.

Regurgitation, when significant, usually reflects relatively high-volume reflux. Although mild regurgitation may respond to acid inhibition, severe regurgitation is unlikely to do so as acid inhibition has only a small effect on the volume of reflux. Mechanical approaches such as elevation of the head of the bed or the use of a wedge pillow may help nocturnal regurgitation; patients with significant daytime regurgitation may require antireflux surgery.

After initial treatment, if symptoms have resolved it is worthwhile trying a period without treatment as some patients will remain in symptomatic remission for several months. However, this approach is inappropriate for patients who have been

shown to have severe oesophagitis on endoscopy.

### Long term management

Most patients with reflux disease will require long term treatment. As mentioned above, the aim of long term management is to maintain remission of symptoms and healing of oesophagitis with the most cost effective strategy. Symptom relapse after initial therapy should be treated by a repeat course of initial therapy. If symptoms then resolve, attempts should be made to step down to a lower level of therapy. This can be done by either:

- reducing the dose, or
- adopting 'on-demand' dosing whereby a single standard dose of PPI is taken only on days when symptoms are troublesome.

On-demand dosing is effective in a substantial proportion of primary care patients. Generally, patients will have satisfactory relief of symptoms when taking a PPI only once every two to three days. This step-down approach to therapy is not appropriate, however, in patients with severe oesophagitis (Los Angeles grades C and D). These patients will need at least daily standard doses of PPI to maintain remission and avoid complications such as strictures.

For patients whose symptoms relapse when the dose is reduced, treatment should be stepped up again to standard doses, which will need to be continued long term. A minority of patients, often those with severe oesophagitis, will require higher than standard doses of PPI to control their disease. Treatment of such patients should be carried out in consultation with a specialist. Failure to respond to standard doses may merely reflect an inadequate effect on gastric acid secretion, but it may also indicate severe oesophagitis or misdiagnosis. Suboptimal dosing is also common in patients with poorly controlled reflux disease. PPIs are best taken about 30 minutes before meals. Effects on acid secretion will be suboptimal if they are taken after meals or at bedtime.

Antireflux surgery is an alternative to long term acid suppression. Although it is particularly useful in patients who have failed medical therapy, it should also be considered in patients who have responded to medical therapy but who do not wish to take medication life long. This is especially relevant for young patients who may be facing decades of treatment. Patients' preferences for medical or surgical treatment are important factors in long term management, and the option of antireflux surgery should be discussed with all patients who require continuous high-level acid suppression.

Several novel endoscopic therapies have been devised for the treatment of reflux disease. Although some of the most recent techniques are showing promise in sham-controlled trials, none has been shown to be clearly better than, or even equivalent to, either best medical or surgical therapy. Currently, therefore, the routine use of these techniques is not justified.

## Barrett's oesophagus

Barrett's oesophagus, the transformation of the squamous mucosa in the distal oesophagus to a metaplastic columnar epithelium (Figure 2), is found in about 10 to 15% of patients with reflux disease who are endoscoped. Its importance lies in the potential for the development of adenocarcinoma, the lifetime risk of which is 2 to 5%.

Concern about the risks associated with the possible presence of Barrett's oesophagus in patients with reflux disease has been used to support the endoscopic screening of patients with reflux symptoms for Barrett's oesophagus. However, there is no convincing evidence that such screening is cost effective or even beneficial, and concern about the risks of Barrett's oesophagus in the average patient in the primary care setting should not influence management.

If patients with reflux disease are endoscoped, however, and found to have

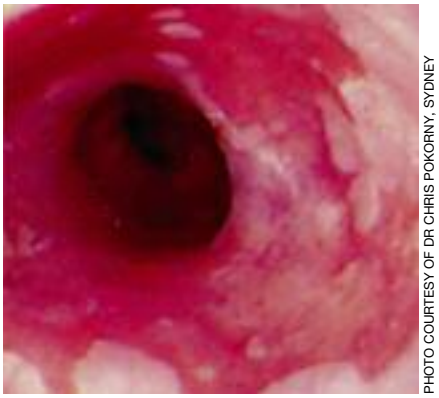

PHOTO COURTESY OF DR CHRIS POKORNY, SYDNEY

Figure 2. Barrett's oesophagus.

Barrett's oesophagus, current guidelines support endoscopic surveillance of the Barrett's mucosa to detect dysplasia, a precursor to the development of adenocarcinoma. Current guidelines recommend surveillance at three-year intervals in patients without dysplasia.

## Extra-oesophageal manifestations of reflux disease

Gastro-oesophageal reflux has been linked to several extra-oesophageal symptoms and diseases; however, the evidence supporting these links is often weak or circumstantial. Reasonable evidence exists to support reflux being a contributing factor for cough, laryngitis, asthma and dental erosions. It is rarely the sole cause, and for each of these conditions there are several other more common causes. Undoubtedly, reflux is the principal cause in some patients, but identifying these patients is difficult.

Recent studies assessing patients' responses to antireflux therapy have shown that reflux is unlikely to be related to asthma and laryngitis in the absence of typical reflux symptoms such a heartburn or regurgitation. Investigation of reflux as a possible cause of these extra-oesophageal syndromes should include a trial of high level, double dose (twice daily) acid suppression for at least one month. Endoscopy is usually unhelpful because most patients will not have erosive oesophagitis.

Oesophageal pH and/or impedance monitoring may identify abnormal patterns of reflux. However, as yet there are no reliable means of linking cough, asthma or laryngitis to such reflux.

## Helicobacter pylori

There is no evidence that *H. pylori* is involved in the pathogenesis of reflux disease. While epidemiological studies have shown a negative association between the presence of *H. pylori* and gastro-oesophageal reflux disease, studies of the effect of *H. pylori* eradication have failed to show a consistent worsening of reflux symptoms.[3] There is also weak but contradictory evidence that long term use of PPIs in patients with *H. pylori* gastritis will accelerate the development of atrophic gastritis and thereby the risk of cancer. Currently, therefore, there is no clear indication to test or treat *H. pylori* infection with respect to the management of reflux disease. MT

## Further reading

1. Vakil N, van Zanten S, Kahrilas P, Dent J, Jones R, the Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101: 1900-1920.
2. Gralnek I, Dulai G, Fennerty M, Spiegel B. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol 2006; 4: 1452-1458.
3. Delaney B, McColl K. *Helicobacter pylori* and gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2005; 22(Suppl 1): 32-40.

## References

1. Dent J, Jones R, Kahrilas P, Talley N. Management of gastro-oesophageal reflux disease in general practice. BMJ 2001; 322: 344-347.
2. Katelaris P, Holloway R, Talley N, Gotley D, Williams S, Dent J; Digestive Health Foundation of the Gastroenterological Society of Australia. Gastro-oesophageal reflux disease in adults: guidelines for clinicians. J Gastroenterol Hepatol 2002; 17: 825-833.
3. Moayyedi P, Talley N. Gastro-oesophageal reflux disease. Lancet 2006; 367: 2086-2100.

**DECLARATION OF INTEREST: Associate Professor Holloway is a consultant for, has received research support and honoraria from, and has been a speaker for, AstraZeneca and Janssen-Cilag. He has also been a speaker for Altana. Dr Tse: none.**