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Upper GI tract disorders

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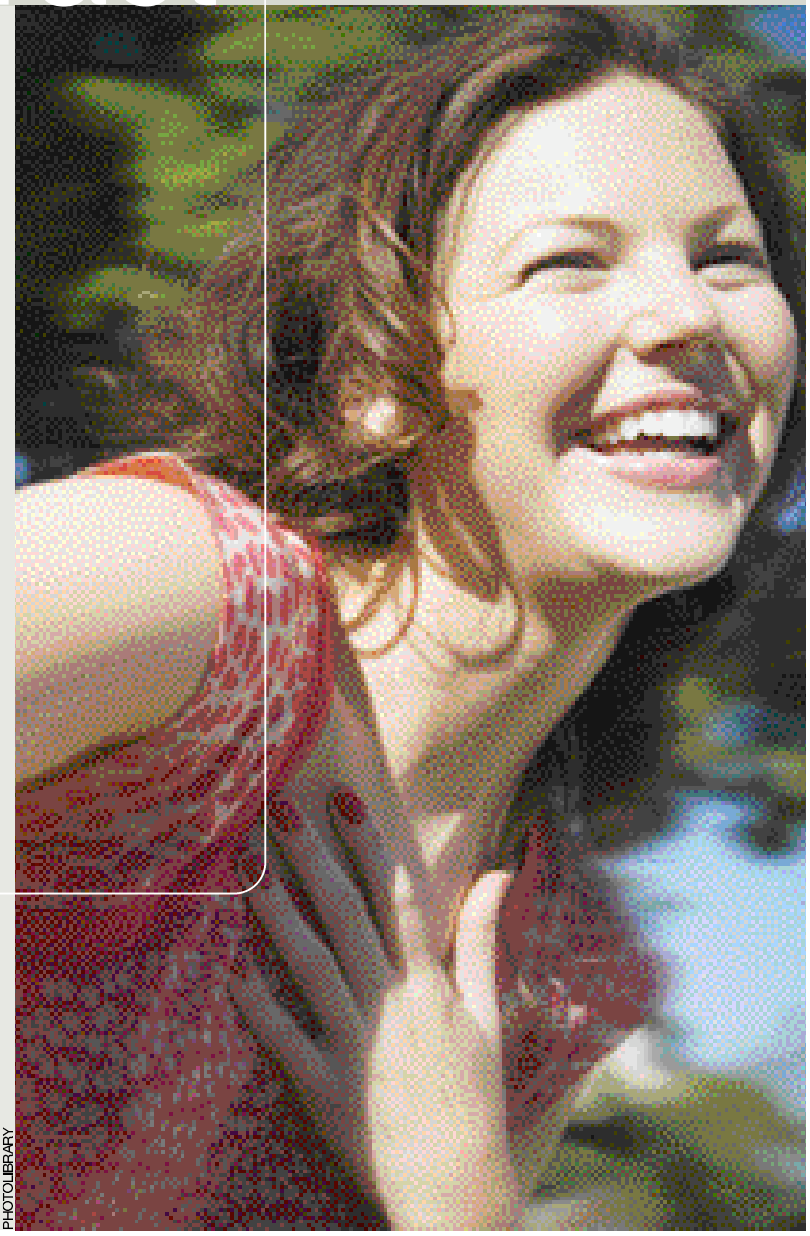

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Update on gastro-oesophageal reflux disease

GORD in infants and children: when to investigate and when to treat

Dealing with reflux in pregnancy

Helicobacter pylori infection: when to search for it and how to diagnose it

Towards a diagnosis of functional dyspepsia

Investigation and management of noncardiac chest pain

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Upper GI tract disorders
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SYDNEY OFFICE
Level 1, 57 Grosvenor Street,
Neutral Bay, NSW 2089

POSTAL ADDRESS
PO Box 1473,
Neutral Bay, NSW 2089

TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488

EMAIL
Editorial enquiries
katemurchison@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
prueanderson@medicinetoday.com.au
irenaaleksoska@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

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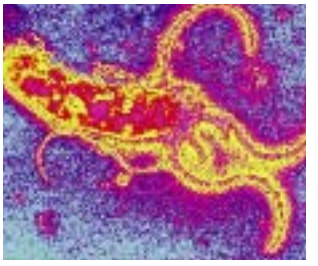

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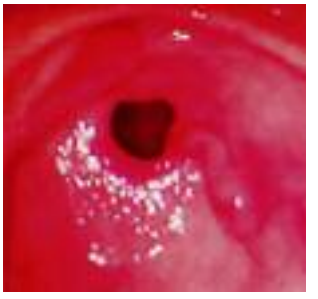

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Upper GI tract disorders

Gastrointestinal complaints are common and often lead to patients presenting in general practice. In this series of articles originally published in *Medicine Today*, and updated as necessary for this publication, a number of leading gastroenterologists provide clinical perspectives on the management of some of the most frequently encountered conditions. While functional disorders overall are the main reason for consultation, the evolving understanding and management of reflux in adults and children and during pregnancy is important. Chest pain, although usually requiring exclusion of ischaemic heart disease, not uncommonly results from oesophageal pathology. *Helicobacter pylori*, undoubtedly one of the major discoveries in the last century, still poses questions as to which infected patients should be treated.

In the first article, Dr Edmund Tse and Professor Richard Holloway point out that a careful history is important in diagnosing gastro-oesophageal reflux (GOR) disease given that more than half of these patients have a normal gastroscopy. A trial of treatment with a proton pump inhibitor (PPI) can aid in diagnosis, but if alarm symptoms are present or if symptoms persist, investigation is indicated. Treatment also needs to be given long term, either continuously or intermittently, being driven by symptoms, and the PPIs are the most effective agents in this regard.

Dr Ralf Heine, in his article on reflux in children and infants, explains that presentation in this group may be with extra-oesophageal symptoms including failure to thrive, aversive feeding behaviour and aspiration. GOR in infants also occasionally results from cow's milk protein intolerance, and this needs to be considered particularly if there is a failure of response to acid suppressant agents. In general, the prognosis of GOR in infants is excellent, with symptoms usually remitting by 18 months of age.

In the third article, Associate Professor Chris Rayner notes that up to two-thirds of women experience daily reflux symptoms during pregnancy, particularly in the third trimester. Investigation, however, is rarely indicated. Mild symptoms often respond to lifestyle modification such as elevation of the head of the bed and avoidance of late meals, smoking and alcohol. Antacids are safe in pregnancy, and the use of other agents, including PPIs, is discussed.

Dr Lay Gan and Professor Anne Duggan describe when infection with *H. pylori* should be considered and how to diagnose it. They point out that infection is generally acquired in early childhood and that most infected individuals do not develop any clinically significant disease during their lifetime. In those in whom treatment is indicated, success rates of around 90% are achieved with PPI-based triple therapy.

Dr Jamshid Kalantar and Professor Nick Talley consider functional dyspepsia, and point out that it is often difficult to distinguish this condition from organic dyspepsia without investigation. Endoscopy in particular needs to be carried out when patients present with dyspepsia and are over the age of 55 or have alarm symptoms. Otherwise, testing for *H. pylori* and treatment in those infected are recommended. If symptoms persist and in patients not infected with *H. pylori*, a trial of therapy with a PPI is recommended.

Finally, noncardiac chest pain is examined by Associate Professor Geoff Hebbard and Dr Claudia Krieger-Gruebel. In most cases the natural history is benign and the most common cause is GOR disease. If symptoms fail to resolve with a PPI, further causes should be sought.

In summary, this compilation provides an excellent overview of some of the most common gastroenterological conditions encountered in clinical practice, and I hope that it will provide readers with an updated clinical perspective. MT

ASSOCIATE PROFESSOR CHRISTOPHER S. POKORNY FRACP, FRCP, FACG
Consultant Medical Editor, *Medicine Today*;
Conjoint Associate Professor of Medicine, University of New South Wales; and
Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.

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Update on gastro-oesophageal reflux disease

EDMUND TSE
MB BS, FRACP

RICHARD H. HOLLOWAY
MD, FRACP

Dr Tse is a Research Fellow in the Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, and Professor Holloway is Professor of Medicine and Director of the 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

In 2006 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 reflux. The

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.**

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 6). 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

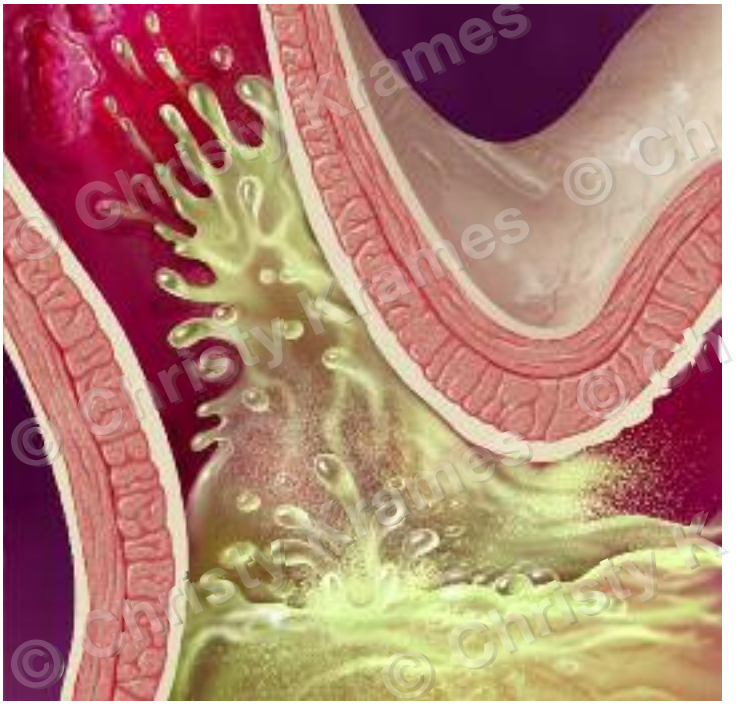
Symptoms

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 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.

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

CHART NOT AVAILABLE

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

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).

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

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 and b)
- 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).

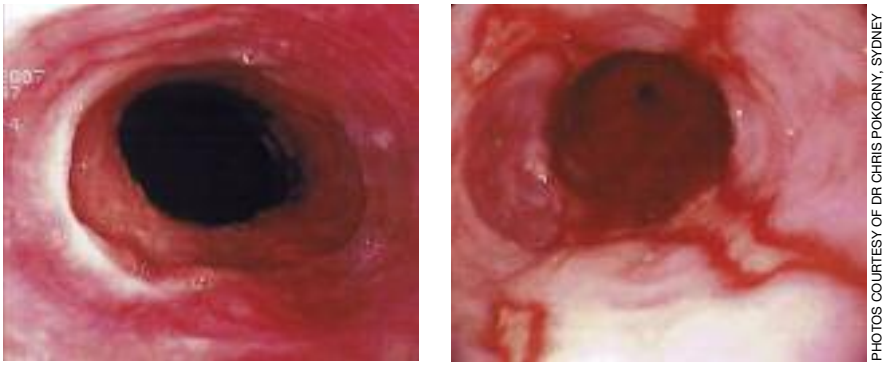
Endoscopic follow up of patients to assess healing of oesophagitis is generally unnecessary unless symptoms persist, as relief of symptoms with PPI therapy correlates well with healing of oesophagitis.

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.



PHOTOS COURTESY OF DR CHRIS POKORNY, SYDNEY

Figures 1a and b. Normal oesophagus (left) and severe ulcerative (right) oesophagitis on endoscopy.

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. However, minor intermittent dysphagia is relatively common and should not require investigation.

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 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

Table 3. Oral proton pump inhibitors indicated for GORD

Generic name	Recommended adult dosages*
Esomeprazole	• Erosive reflux oesophagitis: 40 mg/day for 4-8 weeks; maintenance: 20 mg/day • GORD (endoscopy normal): 20 mg/day for 4 weeks, then 20 mg/day as needed
Lansoprazole	• Reflux oesophagitis: 30 mg/day for 4 weeks • Long term maintenance: 15-30 mg/day
Omeprazole	• Symptomatic GORD: 10-20 mg/day, max 4 weeks • Erosive oesophagitis: 20-40 mg/day 4 to 8 weeks • Maintenance: 10-20 mg/day
Pantoprazole	• GORD symptoms: 20 mg/day for 4 weeks • Reflux oesophagitis: 20-80 mg/day for 4-8 weeks; maintenance: 20-40 mg/day
Rabeprazole	• GORD: 20 mg/day for 4-8 weeks; prophylaxis: 10-20 mg/day • 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 prescribing information for each product for full details on dosing and administration, including recommendations for adolescents and children when indicated.

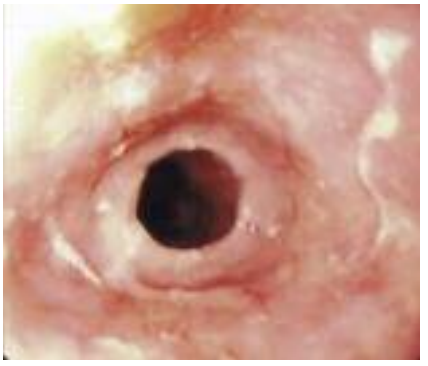


PHOTO COURTESY OF DR CHRIS POKORNY, SYDNEY

Figure 2. Oesophageal stricture.

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 (Figure 2).

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.

Over the past 12 months or so a number of safety concerns have arisen regarding long-term PPI use. These include an interference with the action of clopidogrel and an increase in the incidence of community-acquired pneumonia, *Clostridium difficile* colitis and fractures.[3,4] However, the evidence for these is either controversial or weak and any potential degree of impact small (odds ratio of <2). The low risks of PPI therapy need to be balanced against the undoubted benefits in the management of reflux disease. Nevertheless, unnecessary and inappropriate use of PPI therapy should be minimised.

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 3), 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 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.[5] 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

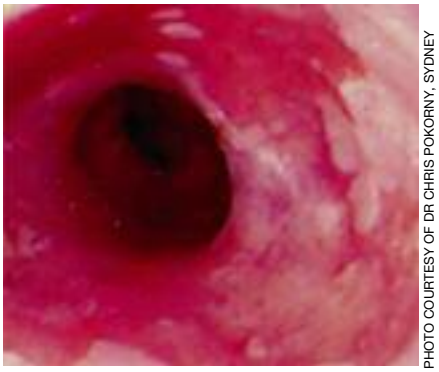


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Figure 3. Barrett's oesophagus.

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GORD in infants and children

when to investigate and when to treat

GPs commonly review infants and young children with suspected gastro-oesophageal reflux (GOR). Many of these patients are empirically treated with acid-suppressive medications. To avoid over-treatment, it is important to distinguish between uncomplicated GOR and gastro-oesophageal reflux disease (GORD), particularly in infants.

RALF G. HEINE
MD, FRACP

Dr Heine is a Paediatric Gastroenterologist and Allergist at the Department of Gastroenterology & Clinical Nutrition, Royal Children's Hospital, at the Department of Paediatrics, University of Melbourne, and at Murdoch Children's Research Institute, Melbourne, Vic.

Gastro-oesophageal reflux (GOR) is characterised by the involuntary and passive flow of gastric contents into the oesophagus. Although generally benign, it may occasionally be associated with significant morbidity. To avoid over-treatment, it is important to distinguish between uncomplicated GOR and gastro-oesophageal reflux disease (GORD), particularly in infants. Minor GOR in otherwise well infants is considered physiological. There are important differences between the clinical presentations of reflux disease in children and adults. Infants and young children with GORD often present with extra-oesophageal symptoms, including aversive feeding behaviours, failure to thrive or respiratory manifestations. The 'classic' symptoms of GORD, such as regurgitation, epigastric pain and heartburn, are more common in older children and adolescents. This article provides an overview of the clinical presentation, investigation and treatment of GORD in infants and children.

Causes

Transient lower oesophageal sphincter relaxation is the main mechanism leading to reflux episodes in adults, children and even preterm infants. Most individuals with GORD have normal lower oesophageal sphincter pressures. During reflux episodes,

IN SUMMARY

- **Infants and children commonly present to GPs with gastro-oesophageal reflux (GOR). It is important to distinguish between uncomplicated GOR and gastro-oesophageal reflux disease (GORD).**
- **Minor GOR in otherwise well infants is considered physiological. Children with GORD often present with extra-oesophageal symptoms, including aversive feeding behaviours, failure to thrive or respiratory manifestations, as well as the 'classic' symptoms such as regurgitation, epigastric pain and heartburn.**
- **GORD in infants may be caused by cow's milk protein intolerance. Other conditions such as eosinophilic oesophagitis should be considered in the differential diagnoses of GORD.**
- **The treatment of GORD should be based on the clinical manifestations and possible complications. It is important to establish whether the degree of GOR in each patient requires medical treatment or not.**
- **The prognosis of GORD in infancy is excellent, and symptoms usually remit by 12 to 18 months of age.**

gastric contents move passively along a pressure gradient from the stomach into the oesophagus. Gastric acid is cleared from the oesophagus by a two-step process. The acid bolus is first removed from the oesophagus by a peristaltic wave. In a second step, swallowed saliva neutralises the remaining mucosal acid coating.

Clinical presentation

Physiological GOR in infants presents with effortless regurgitation of breast milk or formula. These infants are otherwise well and thriving. Regurgitation of feeds at least once per day occurs in about half of infants under 3 months of age, and clinical improvement occurs from about 7 months of age. Mild to moderate GOR symptoms usually resolve without intervention by 12 to 18 months of age.

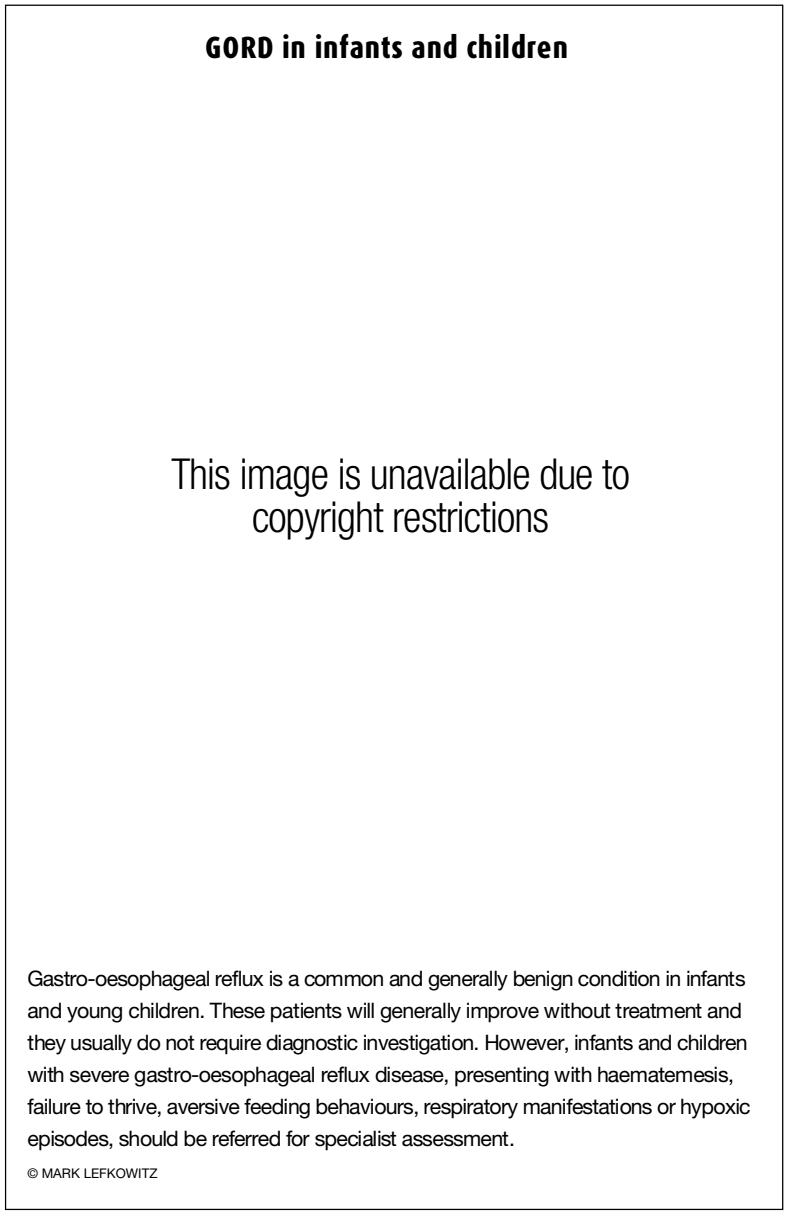
The clinical manifestations of GORD can be divided into acid-peptic mucosal damage, nutritional problems and respiratory complications (Table 1). In infants and young children, extra-oesophageal manifestations are common, whereas acid-peptic complications predominate in older children and adolescents.

Oesophagitis is caused by prolonged acid exposure, often in association with delayed oesophageal acid clearance. Oesophagitis may cause low-grade upper gastrointestinal bleeding and iron deficiency anaemia. However, acute haematemesis is uncommon. Children and adults with oesophagitis commonly complain of upper abdominal pain, heartburn (pyrosis) or painful swallowing (odynophagia). In patients with nonerosive reflux disease, symptoms are similar (but there is no histological evidence of epithelial erosion). Peptic strictures in the distal oesophagus may develop as a result of persistent mucosal inflammation and ulceration. Clinically, patients with peptic strictures may present with difficulty swallowing or oesophageal food bolus obstruction. Barrett's metaplasia may develop in the distal oesophagus after decades of untreated reflux oesophagitis and is a precursor to adenocarcinoma of the gastro-oesophageal junction.

In infancy, GORD may cause significant feeding difficulties. Failure to thrive may ensue because of decreased feeding and loss of nutrients due to frequent regurgitation. Although irritable behaviour and persistent crying are commonly seen in these infants, the distress may not be directly related to GORD but caused by underlying conditions, such as cow's milk protein allergy. This type of allergy may also occur in breastfed infants because maternal dietary cow's milk protein may be secreted as intact antigen into human milk.

GORD in young children may present with respiratory complications, including aspiration, laryngitis, apparent life-threatening events or apnoeic episodes. The respiratory complications of GORD require a high degree of clinical awareness. It is important to understand that in patients with neurological impairment, aspiration episodes

GORD in infants and children



Gastro-oesophageal reflux is a common and generally benign condition in infants and young children. These patients will generally improve without treatment and they usually do not require diagnostic investigation. However, infants and children with severe gastro-oesophageal reflux disease, presenting with haematemesis, failure to thrive, aversive feeding behaviours, respiratory manifestations or hypoxic episodes, should be referred for specialist assessment.

Table 1. GORD in childhood: clinical manifestations

Acid-peptic mucosal damage
Haematemesis
Frequent regurgitation
Poor feeding/feeding refusal
Painful swallowing (odynophagia)
Heartburn (pyrosis)
Upper abdominal pain
Difficulty swallowing
Oesophageal food bolus obstruction
Nutritional problems
Failure to thrive
Micronutrient deficiencies (e.g. iron)
Respiratory complications
Pulmonary aspiration
Laryngitis
Apparent life-threatening events
Apnoeic episodes

may be relatively asymptomatic. GORD-associated chronic lung disease should be considered in all patients with impaired protective airway reflexes or dysphagia.

History

A detailed clinical history is important in the diagnosis of GORD. In infancy, most GORD episodes manifest as regurgitant reflux, and significant nonregurgitant ('silent') GORD is uncommon. The severity of regurgitant reflux, including frequency, estimated volume and associated symptoms, should be documented. Infants with reflux oesophagitis may present with aversive feeding behaviours or refusal. Older children can often describe their symptoms as retrosternal pain or heat sensation when swallowing, and may complain of intermittent regurgitation of gastric contents. Peptic strictures may present with oesophageal food bolus obstruction. A detailed dietary history, including review of growth parameters, should be obtained in all patients.

Physical examination

The physical examination of paediatric patients with GORD is not usually rewarding as most are relatively healthy. Pneumonia, persistent wheeze, stridor or a hoarse voice may point to respiratory complications of GORD. Weight and height should be measured in all paediatric patients.

Investigation

In general, GORD is a clinical diagnosis that does not require confirmation by investigations, unless specific complications are suspected. Three main investigations, described below, are used in infants and children with severe or atypical GOR symptoms. These are upper gastrointestinal barium study, oesophageal 24-hour pH monitoring and gastroscopy. The use of these investigations depends on the severity of GOR symptoms and response to basic therapeutic interventions. Chest x-ray, nuclear medicine scans or broncheoalveolar lavage may be indicated in patients with suspected respiratory manifestations.

Barium studies

Barium studies are mainly used to exclude anatomical abnormalities, such as hiatus hernia, peptic strictures, webs, extrinsic compression of the oesophagus or intestinal malrotation (which may present with persistent vomiting in infants and young children). Barium contrast liquid is administered by mouth or nasogastric tube. Radiological demonstration of reflux episodes under fluoroscopy does not reliably indicate the clinical severity of GORD or risk of complications.

Oesophageal 24-hour pH monitoring

Single or multilevel oesophageal 24-hour pH monitoring allows the quantification of GOR. The oesophageal environment above the lower oesophageal sphincter is normally alkaline. During reflux of gastric acid, the oesophageal pH drops rapidly to below 4, and pepsinogen is activated. Oesophageal pH monitoring measures the number and duration of reflux episodes. Apart from being a diagnostic tool for GORD, pH monitoring is also helpful in monitoring the efficacy of medical antireflux treatment or fundoplication. Oesophageal pH monitoring is of limited value in assessing respiratory complications of GORD.

Bioelectrical impedance monitoring is a novel, pH-independent technique that detects all fluid and air movements along the oesophagus. Although mainly a research tool at present, it is likely that this technique will supersede oesophageal pH monitoring over the next decade.

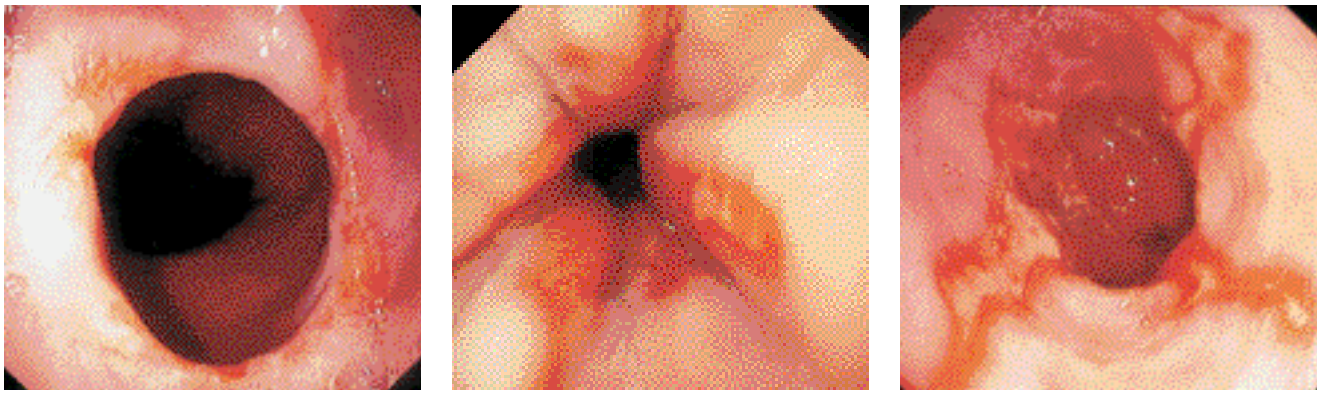
Gastrointestinal endoscopy

Upper gastrointestinal endoscopy is the most useful procedure in the investigation of upper abdominal pain, dysphagia, vomiting or haematemesis. A gastroscopy can be safely performed in infants and children under general anaesthesia. Gastroscopy allows visualisation of the mucosa in the oesophagus, stomach and duodenum (Figures 1a to c).

Oesophageal biopsies can be examined for signs of oesophagitis. Mucosal eosinophils counts of below 10 to 15 per high power field in lower oesophageal biopsies may be seen in patients with reflux oesophagitis; whereas higher eosinophil counts in specimens from the upper and lower oesophagus are suggestive of eosinophilic oesophagitis.

Differential diagnoses

As a first diagnostic step it should be ascertained whether GOR episodes are likely to be physiological or associated with adverse manifestations – that is, reflux disease. Clinicians should also try to differentiate between vomiting and GOR. Vomiting involves active expulsion of gastric and duodenal contents through retrograde peristalsis. This is mediated via the emetic reflex and is usually preceded by vagal symptoms, including nausea and pallor. By contrast, GOR is a passive event that is not preceded by nausea. In infants it may be difficult to distinguish between vomiting



PHOTOS COURTESY OF DR CHRIS POKORNY, SYDNEY

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

and GOR. Vomiting is associated with a broad range of paediatric conditions, including gastroenteritis, urinary tract infection, sepsis, food allergy, metabolic diseases or raised intracranial pressure.

Eosinophilic oesophagitis

Over the past decade, eosinophilic oesophagitis has emerged as a form of oesophagitis. It is closely associated with food allergy and atopic disorders, such as asthma or eczema. It can occur in any age group but typically affects children and young adults.

Patients with eosinophilic oesophagitis have symptoms that are indistinguishable from GORD; however, they fail to respond to medical antireflux treatment or fundoplication. In school-aged children and young adults, oesophageal food bolus impaction is a typical presentation of eosinophilic oesophagitis, whereas in infants and young children, aversive feeding behaviours and failure to thrive are common presentations.

The diagnosis of eosinophilic oesophagitis is made by oesophageal biopsy and demonstration of mucosal eosinophil counts of more than 15 to 20 per high power field in upper and lower oesophageal biopsies. Treatment relies on hypoallergenic elimination diets or swallowed corticosteroid aerosols.

Food protein-induced GORD

A small proportion of infants with food allergies may present with features of GORD. The most common food allergen causing infantile GORD is cow's milk protein. Infants with this allergy present with GORD within the first few weeks of life, often in association with feeding difficulties, diarrhoea, eczema or failure to thrive. Cow's milk allergy may occur in exclusively breastfed infants due to the presence of intact cow's milk protein of maternal dietary origin in breast milk. The food allergy is usually non-IgE-mediated, and skin prick testing or specific serum IgE-antibodies are negative.

The diagnosis of food protein-induced GORD is made by strict cow's milk protein elimination, usually by use of a hypoallergenic formula (extensively hydrolysed or amino acid-based formulas), and then later rechallenge. In breastfed infants, a maternal elimination diet may be effective.

The prognosis of infants with food protein-induced GORD is usually excellent. In infants who have responded to an elimination diet, cow's milk-containing formulas or foods can be cautiously reintroduced within one to two months of the clinical resolution of GOR symptoms, as tolerated.

Treatment

The treatment of GORD should be based on the clinical manifestations and possible complications (Table 2). It is important to establish if the degree of GOR in each patient requires medical treatment.

In infancy, simple measures may help to reduce the frequency or volume of reflux episodes. These include head-up posturing of the infant. For this purpose, the head end of the cot should be elevated to a 30° angle. Prone posturing is no longer recommended due to the increased risk of sudden infant death syndrome. In addition to posturing, thickening of infant formula, using for example corn starch, may decrease overt regurgitation and improve weight gain. In infants with unexplained crying or persistent irritability without significant regurgitation, there is no evidence to support the use of acid-suppressive medications.

Pharmacotherapy

In older children and adults, treatment of GORD relies mainly on pharmacotherapy. Acid-suppressive treatment in infants and young children usually involves a proton pump inhibitor – e.g. omeprazole. Other proton pump inhibitors that have also been used in children with GORD are esomeprazole, lansoprazole and pantoprazole. In patients with mild GORD, a H_2-receptor antagonist (e.g. ranitidine or famotidine) may be suitable, although levels of acid suppression are much lower than those in patients who take a proton pump inhibitor. Antacids have a limited role in children due to possible aluminium toxicity. It is important to highlight

continued

Table 2. Management of gastro-oesophageal reflux disease (GORD) in infants and children

Age group	Clinical presentation	Considerations	Management
Infants (0 to 12 months)	Infrequent regurgitation, but otherwise well and normal weight gain	Likely to be physiological GOR	Reassure parents Monitor growth Head-up supine posturing No specific treatment required
	Frequent regurgitation and/or haematemesis	Reflux oesophagitis Consider gastritis	Refer patient to a gastroenterologist for gastroscopy Treat reflux oesophagitis with omeprazole 1 mg/kg (max dose 10 mg) once daily
	Frequent regurgitation and poor weight gain	May be caused by loss of nutrients through recurrent regurgitation, insufficient oral intake or both	Organise dietetic review of oral intake Advise fortification of formula/nutritional supplementation Advise thickening of formula feeds (e.g. corn starch)
	Unsettled behaviour, and feeding difficulties or refusal	GOR unlikely cause of persistent crying, therefore, consider cow's milk protein intolerance or eosinophilic oesophagitis	Trial maternal hypoallergenic elimination diet or hypoallergenic formula (extensively hydrolysed formula) Involve dietitian and monitor nutritional progress
Children and adolescents (12 months and older)	Epigastric or retrosternal pain Regurgitation of gastric contents Halitosis Dental erosions	Likely reflux oesophagitis Consider eosinophilic oesophagitis if patient does not improve in response to standard medical antireflux treatment	Refer patient to a gastroenterologist for gastroscopy Prescribe omeprazole 1 mg/kg (max dose 20 mg) once daily
	Pulmonary aspiration or other respiratory manifestations of GORD	May present as persistent wheeze or chronic pneumonia Common in children with cerebral palsy or dysphagia Aspiration may occur during oral feeding (oropharyngeal inco-ordination) or after GOR episode Can be oligosymptomatic in children with significant neurological impairment	Refer patient to a respiratory medicine, gastroenterology and/or speech pathology specialist Patient may require video fluoroscopy, nuclear medicine studies, gastroscopy and/or bronchoalveolar lavage Consider enteral tube feeding (nasogastric tube or gastrostomy; postpyloric feeding in gastroparesis) or fundoplication

to parents that the frequency of regurgitation will not significantly change while children are taking acid-suppressive therapy. Symptomatic improvement usually occurs within two to four weeks of therapy. Patients' responses to treatment should be reviewed within four to six weeks, and discontinuation of the medication attempted, as tolerated. In patients with significant persistent or relapsing symptoms, referral for further diagnostic evaluation should be considered.

The role of prokinetic agents (e.g. domperidone or metoclopramide) in the treatment of paediatric GORD is limited. Prokinetic agents are sometimes used in combination with acid-suppressive medications, particularly if delayed gastric emptying is suspected. However, their use is generally not recommended in the first-line treatment of GORD in children.

Review of diet

In infants with persistent crying and symptoms of GOR, acid-suppressive therapy is often ineffective. In these infants, gastrointestinal cow's milk protein allergy should be suspected. These patients should trial an extensively hydrolysed formula for two to four weeks. In infants with ongoing significant GOR symptoms who have failed to respond to extensively hydrolysed formula, an amino acid-based

formula may be tried. Alternatively, a maternal hypoallergenic elimination diet can be attempted in breastfed infants with GORD. Use of these elimination diets should be supervised by a paediatric dietitian to safeguard the nutritional adequacy of the diet for the mother and infant.

Thickened formula has been shown to reduce regurgitation in infants with mild to moderate GOR. Similarly, casein-predominant antiregurgitation formulas have been marketed for infants with regurgitant GOR. Although these formulas appear to reduce the frequency of overt regurgitation, their efficacy in reducing acid reflux and preventing reflux oesophagitis has not been proven.

Fundoplication

In infants and children, fundoplication is the treatment of choice for refractory, erosive oesophagitis or significant reflux aspiration. Fundoplication creates a high pressure zone at the gastro-oesophageal junction and thus prevents GOR episodes. Fundoplication can be performed as an open procedure or via laparoscopy. In children with neurological impairment and significant GORD, fundoplication may be required, sometimes in conjunction with a gastrostomy. Complications of fundoplication include dysphagia, gas bloat syndrome, wrap herniation and dumping syndrome.

Conclusion and recommendation for specialist referral

GOR is a common and generally benign condition in infants and young children. Infants with mild or moderate GOR will generally improve without treatment and do not require diagnostic investigation. However, patients with severe GORD, presenting with haematemesis, failure to thrive, aversive feeding behaviours, respiratory manifestations or hypoxic episodes, should be referred for specialist assessment.

Infants with GORD who have failed to respond to a trial of acid-suppressive therapy may have a cow's milk protein intolerance or eosinophilic oesophagitis. Early recognition of underlying food allergies is important to prevent nutritional or behavioural complications in infants and young children.

Most infants will outgrow their GOR symptoms by 12 to 18 months of age. Those with persistent regurgitation beyond 18 months of age may require further specialist evaluation if their symptoms appear significant. MT

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COMPETING INTERESTS: None.

GESA Gastroenterological Society of Australia
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Dealing with reflux in pregnancy

CHRIS RAYNER MB BS, PhD, FRACP

Most women experience symptoms of gastro-oesophageal reflux during pregnancy. Here, Associate Professor Chris Rayner outlines an approach to this common complaint.

Remember

- Up to two-thirds of women report daily heartburn during pregnancy. The symptom is most troublesome in the third trimester and impacts on quality of life. It can aggravate nausea and vomiting of pregnancy.
- For most women, heartburn is a new symptom that begins in pregnancy and resolves with delivery. However, it may be a risk factor for reflux later in life.
- Pregnancy is associated with a progressive decline in basal lower oesophageal sphincter pressure, possibly due to the effects of oestrogen and progesterone on smooth muscle. Raised intra-abdominal pressure and impaired oesophageal peristalsis may contribute. The role of transient sphincter relaxations (the major mechanism of most reflux disease) has not been studied in pregnant women.

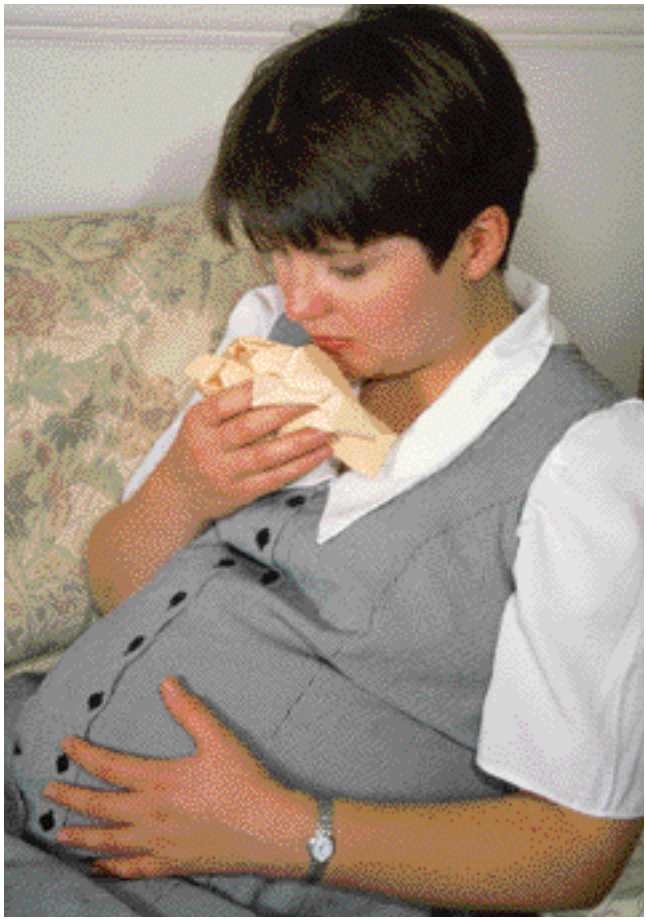

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Figure. Not all the drugs used to treat reflux in the general population are safe for use in pregnant women.

Assessment

- A history of retrosternal burning, worse after meals or when recumbent, is highly sensitive and specific for reflux disease.
- Complications of reflux (bleeding, stricture) are infrequent in pregnancy because of the short duration of excessive acid exposure.
- Endoscopy with conscious sedation is probably safe, especially after the first trimester. However, only a minority of women will have mucosal erosions, and endoscopy should be reserved for reflux disease that is refractory to medical treatment or associated with severe complications.
- Manometry and pH studies can be performed safely but are rarely indicated. A 'normal range' of acid exposure has not been established in pregnant women.

Associate Professor Rayner is Gwendolyn Michell Associate Professor, Discipline of Medicine, University of Adelaide, and Consultant Gastroenterologist, Royal Adelaide Hospital, Adelaide, SA.

Management

- Reflux in pregnancy is best managed by a step-up approach.
- Mild reflux symptoms may respond to lifestyle modifications. These include raising the head of the bed by 15 cm and avoiding late night meals, foods that precipitate heartburn, smoking and alcohol.
- Antacids are used by up to 50% of pregnant women and are safe in pregnancy (Table).[1] Antacids that contain calcium might also help prevent hypertension and pre-eclampsia. Sodium bicarbonate should be avoided because of the potential for metabolic alkalosis and fluid overload. Any long term therapy affecting gastric acidity can impair iron absorption.
- Sucralfate, a minimally absorbed mucosal protectant, may also be helpful.
- The H_2-receptor antagonists cimetidine, famotidine and ranitidine and have been widely used in pregnancy for reflux that is refractory to antacids, and appear to be safe. Famotidine has the lowest excretion in breast milk of the H_2-receptor antagonists and may, therefore, be the drug of choice if therapy is required during lactation.[2]
- Metoclopramide potentially enhances lower oesophageal sphincter pressure and improves acid clearance and gastric emptying. It offers symptom relief equivalent to H_2-receptor antagonists in mild reflux disease, but is less effective at healing oesophagitis and has more side effects.
- Proton pump inhibitors represent the most effective medical therapy for reflux symptoms and healing of oesophagitis in the general population. In pregnancy, they have not been used as widely as H_2-receptor antagonists and, therefore, safety data are more limited (most data apply to omeprazole and lansoprazole). However, a recent meta-analysis found no increased risk of congenital malformations, spontaneous abortion or preterm delivery.[3] In pregnancy, this class of drugs should be restricted to severe or complicated reflux disease unresponsive to H_2-receptor antagonists. MT

Table. Safety of drugs used to treat reflux in pregnant and lactating women[1]

Drug	ADEC pregnancy category*	Safety in lactation†
Antacids	A	Safe
Sucralfate	B1	Safe
H_2-receptor antagonists:		
– cimetidine, famotidine, ranitidine	B1	Safe
– nizatidine	B3	Not recommended
Metoclopramide	A	Safe
Proton pump inhibitors:		
– esomeprazole, omeprazole, pantoprazole	B3	Excreted in breast milk, effects uncertain
– lansoprazole	B3	Unknown
– rabeprazole	B1	Unknown

*Australian Drug Evaluation Committee (ADEC) pregnancy categories:
Category A: Drugs that have been taken by a large number of pregnant women without any proven increase in the frequency of malformations or other harmful effects on the fetus.
Category B: Drugs that have been taken by only a limited number of pregnant women, without an increase in the frequency of malformation or other harmful effects on the human fetus. B1 – Studies in animals have not shown evidence of an increased occurrence of fetal damage. B3 – Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
†As reflux symptoms arising in pregnancy tend to resolve with delivery, drugs can usually be stopped postpartum.

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COMPETING INTERESTS: None.

Helicobacter pylori infection

when to search for it and how to diagnose it

The discovery of *Helicobacter pylori* in the mid-1980s sparked ongoing interest in its role in health and disease. *H. pylori* infection is associated with many other conditions and it is important to know when to diagnose and treat the infection.

LAY T. GAN
MB BS

ANNE DUGGAN
BMed, FRACP, MHP, PhD

Dr Gan is an Advanced Trainee in Gastroenterology and General Medicine at John Hunter Hospital. Professor Duggan is a Senior Staff Specialist in Gastroenterology at John Hunter Hospital, and Newcastle, Conjoint Associate Professor at the University of Newcastle, NSW.

The complete story about *Helicobacter pylori* is yet to evolve. Recent data indicate that the discovery of its association with peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) tumour may be just the first chapter in a complex story of its relation with humans. Since the turn of the century, *H. pylori* has dramatically reduced in incidence in most Western countries, and in some areas of the USA less than 10% of 10-year-old children have evidence of infection.

With the decline of *H. pylori* infection there has been an increase in rates of asthma, allergies, gastro-oesophageal reflux disease (GORD), adenocarcinoma of the oesophagus and obesity. The significance of this observation is not yet fully understood but is of sufficient interest for some researchers to suggest that *H. pylori* plays a pivotal role in determining susceptibility to these diseases. Some have also speculated that, in the future, children may be deliberately colonised with benign strains of *H. pylori* to protect them from these diseases and the diseases associated with more virulent strains of *H. pylori* .[1]

H. pylori is a bacterium that causes chronic gastritis in humans. The Australian researchers Barry J. Marshall and J. Robin Warren noted the presence of chronic gastritis and it was this that led to the recognition that in some individuals chronic

IN SUMMARY

- ***Helicobacter pylori* is usually acquired in early childhood through close contact with an infected person, and the infection persists for life unless treated.**
- ***H. pylori* infection accounts for up to 90% of duodenal ulcers and about 70% of gastric ulcers.**
- **Most individuals infected with *H. pylori* do not develop clinically significant disease during their lifetime.**
- **Proton pump inhibitor (PPI)-based triple therapy for seven days is highly effective and successfully eradicates *H. pylori* infection in more than 90% of cases.**
- **In most cases of ulcer disease, long-term PPI therapy is not warranted once *H. pylori* infection has been eradicated.**

infection with *H. pylori* causes peptic ulcer disease, distal gastric cancer and the rarer MALT lymphoma. Experience tells us that depending on the frequency of prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, *H. pylori* infection accounts for up to 90% of duodenal ulcers and about 70% of gastric ulcers. Fortunately, most individuals infected with *H. pylori* develop no clinically significant disease in their lifetime.

This article addresses the pathogenesis of *H. pylori* in causing disease, indications for diagnosis and treatment, tests available for *H. pylori* diagnosis and treatment options, and summarises the recommendations for the management of *H. pylori*-related disease.

Pathogenesis

H. pylori is usually acquired, possibly by the faecal–oral or oral–oral route, in early childhood through close contact with an infected person, and the infection persists for life unless treated. Once successfully treated, re-infection is rare. *H. pylori* is a Gram-negative spiral rod bacterium with flagella at one end, and is well adapted to evade the primary immune response mechanisms of the host. The organism produces urease, which breaks down endogenous urea to carbon dioxide and ammonia. This raises the gastric pH and allows *H. pylori* to survive in an otherwise acidic stomach.

H. pylori infection induces a vigorous systemic and mucosal response. This rarely leads to its eradication but does contribute to tissue damage and chronic gastritis, the severity and sequelae of which is determined by the toxogenicity of the *H. pylori* strains acquired.

A brief overview of *H. pylori* infection and its clinical outcome is shown in the flowchart on page 20.

Indications for diagnosis and treatment of *Helicobacter pylori*

Duodenal ulcer disease

H. pylori is the cause of between 70 and 90% of duodenal ulcers, depending on the background prevalence of infection and NSAID use. Diagnosis is usually by gastroscopy, which also allows gastric biopsies to be obtained for rapid urease testing (CLO testing) for *H. pylori* infection.

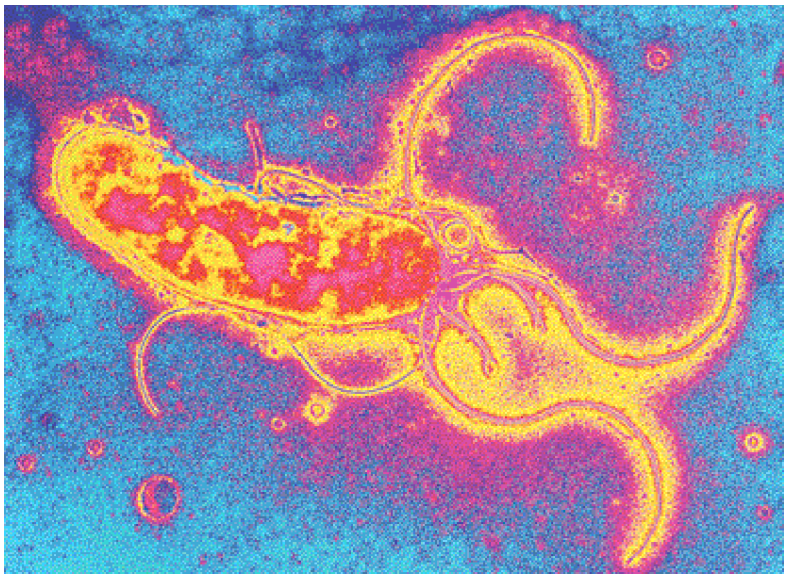

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Figure. *Helicobacter pylori* (coloured transmission electron micrograph).

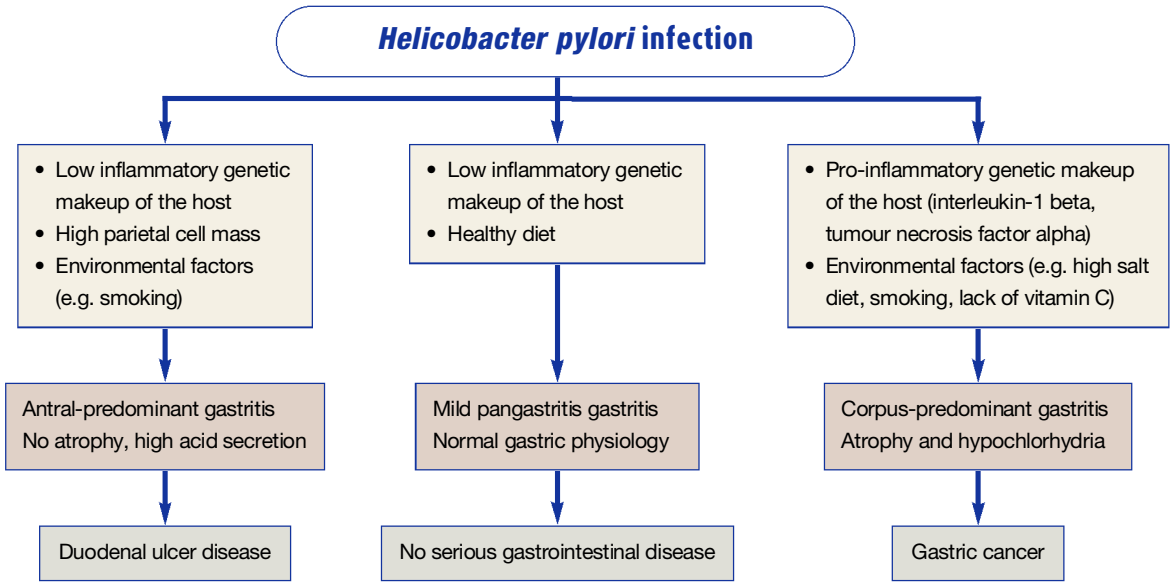
The eradication of *H. pylori* provides faster ulcer healing and reduced ulcer recurrence compared with acid-suppression therapy alone (Table 1). Uncomplicated duodenal ulcers heal quickly after triple therapy alone (Table 1). Current international recommendations are for a four-week course of acid-suppression therapy after a one-week course of *H. pylori* eradication therapy.

Symptoms that persist in patients after *H. pylori* eradication therapy are usually due to coexistent GORD. In these cases, symptom resolution with proton pump inhibitor (PPI) therapy after eradication therapy and rapid recurrence of symptoms after cessation of PPIs is diagnostic of GORD. In the absence of PPI therapy no symptoms at six months is a good indicator of successful treatment of ulcer diathesis.

Duodenal ulcers complicated by bleeding or perforation are uncommon but are associated with increased morbidity and mortality, particularly in the elderly and those with major comorbidities.

Confirmation of *H. pylori* eradication is not cost-effective in all patients because treatment is usually effective in more than 90% of cases. In patients who are at high risk of significant complications or death from peptic ulcer bleeding (e.g. those with multiple medical comorbidities) and those causing diagnostic uncertainty, confirmation of *H. pylori* eradication with a urea breath test is recommended.

Distribution of gastritis and clinical outcome of *Helicobacter pylori* infection



Eradication of *H. pylori* infection markedly reduces but does not entirely eliminate the risk of ulcer recurrence. Lifelong maintenance therapy with a PPI is indicated in the following groups:

- high-risk patients, with coprescription of NSAIDs or aspirin
- patients in whom *H. pylori* eradication has failed despite reasonable attempts, for example, with second- and third-line therapy.

Failure of ulcer healing is usually due to noncompliance, antibiotic resistance or ongoing NSAID/aspirin use rather than the rarer causes of peptic ulcer disease, such as Zollinger Ellison syndrome.

Gastric ulcer disease

H. pylori infection is associated with about 70% of gastric ulcers. NSAID use in patients with or without *H. pylori* infection accounts for most other gastric ulcers, with gastric cancer being an increasingly rare cause. Nevertheless, diagnostic endoscopy and biopsy with repeat endoscopy at six weeks to confirm healing and exclude malignancy remains the gold standard.

Ulcer disease in association with NSAID or aspirin use

The relation between NSAID use and *H. pylori* infection remains controversial. Current management recommendations are based on a combination of evidence and consensus guidelines.[3,4] NSAID use and *H. pylori* infection are the major causes of ulcers, and ulcers are more frequent among patients who use NSAIDs and have *H. pylori* infection than among those who do not have *H. pylori* infection.

NSAID use and *H. pylori* infection are thought to cause ulcer disease via different mechanisms but work synergistically to cause ulcers and ulcer complications such as bleeding.[5] Patients who do not use NSAIDs appear to benefit from *H. pylori* eradication before starting NSAID use, with reduced occurrence of ulcers and ulcer bleeding. The evidence is not strong and current guidelines do not recommend screening all patients before starting NSAIDs.[6]

A reasonable approach is to eradicate *H. pylori* in patients with a higher risk of NSAID-associated ulcer complications because of older age and comorbidities (e.g. severe cardiorespiratory disease, severe chronic kidney disease). There is less evidence of benefit from *H. pylori* eradication in patients who use NSAIDs and have a history of ulcers. Nevertheless, current recommendations are that *H. pylori* infection if present be eradicated in high-risk patients and they be given cotherapy with a PPI.

In the presence of an ulcer, patients who use NSAIDs should have four to six weeks of PPI-based acid suppression before restarting NSAIDs if still indicated. Less toxic NSAIDs, such as ibuprofen or diclofenac, should be considered; as should also low-dose aspirin, which has a cardioprotective effect and is safer than higher doses. Aspirin and standard or selective NSAIDs should not be administered at the same time.

Gastric cancer

In 1994, the evidence for a causal relation between *H. pylori* infection and gastric cancer led the World Health Organization's

Internal Agency for Research on Cancer to classify *H. pylori* as a group-one carcinogen.[7] Gastric cancer has a high incidence in areas where *H. pylori* infection is endemic because acute gastritis can lead to chronic then atrophic gastritis, intestinal metaplasia, dysplasia and gastric carcinoma.

It may appear logical to recommend secondary prevention of gastric cancer by eradicating *H. pylori* infection, especially in those with a family history of gastric cancer. However, there are no data on when eradication would be effective, although eradication before development of preneoplastic lesions (atrophic gastritis and intestinal metaplasia) would seem essential.[8] Current recommendations are to eradicate *H. pylori* infection if present in those with a personal or family history of gastric cancer.

In countries such as Australia, where the prevalence of *H. pylori* infection is low and gastric cancer is uncommon, enthusiasm for primary prevention has understandably waned.

Gastric MALT lymphoma

The relation between *H. pylori* infection and MALT lymphoma is interesting. Localised and low-grade lymphomas regress with *H. pylori* eradication in up to 90% of patients.[9] In contrast, advanced MALT lymphoma requires treatment with traditional chemotherapeutic agents.[10] Eradication of *H. pylori* infection seems a logical additional step.

Functional dyspepsia

Functional dyspepsia is dyspepsia in the absence of an identifiable cause and is extremely common. Less than half of patients who experience symptoms seek medical attention, but dyspepsia still accounts for 5% of all visits to the GP. There is no clear relation between *H. pylori* infection and functional dyspepsia. Guidelines from the American Gastroenterology Association recommend a 'test-and-treat' strategy (testing for *H. pylori* infection and treating infection if present with triple therapy) for patients with dyspepsia because it is less expensive than endoscopy and a proportion of patients treated would have peptic ulcer disease.[3,11]

However, with the falling prevalence of *H. pylori* infection this strategy unnecessarily exposes an increasing number of patients to testing. Where prevalence of *H. pylori* infection is low and there are no risk factors for ulcer disease, such as past or family history, smoking or current NSAID or aspirin use, current recommendations for the management of uninvestigated dyspepsia are for a trial of PPI therapy. This will both diagnose and treat GORD. Endoscopy still has a role when there are alarming symptoms, such as bleeding, anaemia, early satiety, unexplained weight lost, progressive dysphagia or odynophagia, recurrent vomiting, family history of gastrointestinal cancer or previous oesophagogastric malignancy (Table 2). Endoscopy is also still appropriate when risk factors for ulcer disease or symptoms do not respond to PPI therapy.

Table 1. *Helicobacter pylori* eradication treatment regimens[2]

	Drug	Dose	Duration
First-line therapy – no penicillin allergy*	PPI†	20 mg bd	7 days
	Amoxycillin	1 g bd	7 days
	Clarithromycin	500 mg bd	7 days
First-line therapy – penicillin hypersensitivity	PPI†	20 mg bd	7 days
	Metronidazole	400 mg bd	7 days
	Clarithromycin	500 mg bd	7 days
Second-line therapy if failure of eradication – first-line therapy	PPI†	bd	10 to 14 days
	Colloidal bismuth‡	120 mg qid	7 to 14 days
	Tetracycline‡	500 mg qid	7 to 14 days
	Metronidazole	400 mg tds	7 to 14 days
	OR		
	PPI†	bd	10 days
	Amoxycillin	1 g bd	10 days
	Rifabutin	150 mg bd	10 days

* Triple therapy is available as a combination treatment.
† PPIs available include esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.
‡ Available on the Special Access Scheme.

Gastro-oesophageal reflux disease

Several epidemiological studies[3,12,13] have shown a lower prevalence of *H. pylori* infection in patients with GORD and some authors have speculated that the relation is mechanistic. Patients with antral-predominant (distal stomach) gastritis exhibit increased acid secretion, with an increased risk of duodenal ulcers. Conversely, patients who have corpus-predominant (body of stomach) gastritis

Table 2. When the use of the test-and-treat strategy would not be appropriate[4]

- Age ⩾50 years
- Anorexia or weight lost
- Dysphagia or odynophagia
- Vomiting
- Anaemia or positive faecal occult blood test
- Jaundice
- Failure of several treatments
- Strong history of familial cancer

Table 3. Diagnostic testing for *Helicobacter pylori* infection[3,15]

Diagnostic testing	Advantages	Disadvantages
Endoscopic		
Histology*	Excellent sensitivity Allows mucosal assessment	Expensive Invasive with a variable specificity
Rapid urease testing* (CLO testing)	Inexpensive and provides rapid results Excellent specificity	Sensitivity reduced after antibiotic use, upper gastrointestinal bleeding, recent PPI therapy and gastric atrophy
Culture*	Allows determination of antibiotic sensitivity	Expensive Difficult to perform Not widely available
Nonendoscopic		
Antibody testing (quantitative and qualitative)	Inexpensive Widely available Good NPV	PPV dependent on *H. pylori* prevalence Unable to differentiate between past and current infection
Urea breath test (^{13}C or ^{14}C)*†	Detects current *H. pylori* infection Excellent PPV and NPV Gold standard before and after *H. pylori* treatment	^{14}C is radioactive and contraindicated in pregnancy and ^{13}C is not radioactive Antibiotics and PPI therapy should be ceased two weeks before testing
Faecal antigen test*	Identifies active infection Excellent PPV and NPV	Need to collect stool specimen

*Sensitivity of these tests in identifying active *H. pylori* infection is reduced by recent use of a PPI, bismuth or antibiotics. Apart from for serobgical testing, PPIs and antibiotics should be stopped a minimum of two weeks before testing.
† Urea breath testing is currently reimbursable under the Medicare Benefit Scheme for either confirmation of *H. pylori* colonisation or monitoring of success of eradication.
ABBREVIATIONS: NPV = negative predictive value, PPI = proton pump inhibitors, PPV = positive predictive value.

have reduced acid secretion and are at a greater risk of developing gastric cancer. Theoretically, reversal of corpus-predominant *H. pylori* gastritis can lead to increased gastric acid secretion and reflux, but there is insufficient evidence that this is clinically relevant.[3,14] There is currently no clear evidence to implicate *H. pylori* eradication in the development of reflux symptoms and *H. pylori* eradication is not indicated in the treatment of GORD.

Other indications

Studies have suggested that *H. pylori* infection causes iron-deficiency anaemia and idiopathic thrombocytopenic purpura, and its eradication reverses anaemia and improves oral iron absorption. It has been claimed that *H. pylori* eradication induces a positive platelet response; however, in the case of both iron-deficiency anaemia and idiopathic thrombocytopenic purpura the data are inconclusive.[12]

Epidemiological data have revealed an increase in prevalence of asthma, hay fever and other atopic disorders in industrialised nations. Some cross-sectional studies have shown an inverse relation between asthma, atopic disorders and *H. pylori* seropositivity. Hypotheses to explain this observation include that *H. pylori* infection affects the balance between T helper 1 and T helper 2 cell immune responses. The results are inconclusive and the determination will be interesting.

Diagnosis of *Helicobacter pylori* infection

Population testing for *H. pylori* infection is not recommended. The 2007 American Gastroenterology Society Guidelines recommend testing in the following circumstances:[3]

- if the clinician plans to offer treatment for a positive result (this is at the clinician's discretion but should certainly be offered to high-risk patients with medical comorbidities)
- in patients with peptic ulcer disease (past or present), gastric adenocarcinoma or gastric MALT lymphoma
- for uninvestigated dyspepsia in patients under the age of 55 years with no 'alarm features', using the test-and-treat strategy rather than endoscopy, which has been shown to be less cost-effective[11] in areas where *H. pylori* is prevalent.

This strategy would only be applicable in developed countries like Australia

in cohorts where *H. pylori* infection is common, such as in some immigrant populations from countries with a high prevalence of *H. pylori* infection.

Table 3 summarises the diagnostic tests available and their advantages and disadvantages. Tests can be divided into endoscopy-based and nonendoscopy-based.

Treatment of *Helicobacter pylori* infection

PPI-based triple therapy (a PPI and two antibiotics; Table 1) for seven days is highly effective for the treatment of *H. pylori* infection, being successful in more than 90% of cases. Increasing resistance of *H. pylori* to clarithromycin and metronidazole poses a significant threat to effective *H. pylori* eradication.[16] In some countries, *H. pylori* resistance to metronidazole is reported to be as high as 40% in the USA and Europe, and clarithromycin resistance is reaching up to 15% in parts of Australia[17] and increasing in areas with a high use of macrolides. In the case of treatment failure, there are a number of options, including:

- repeat therapy with a first-line agent
- trial PPI-based quadruple therapy (Table 1)
- gastroscopy with gastric biopsy for culture to determine sensitivities
- consideration of long-term therapy with a PPI to reduce the risk of ulcer recurrence.

To prevent increasing antibiotic resistance it is essential that the initial indication for eradication is justified.

Recommended treatment regimens and their roles are provided below (Table 1).

Recommendations

The diagnosis and treatment of *H. pylori* infection is currently indicated for patients with:[3,12]

- peptic ulcer disease with or without a history of NSAID or aspirin use
- gastric MALT lymphoma, especially in the early stages of the disease
- early gastric cancer endoscopically resected
- a personal or family history of gastric cancer.

A more conservative approach to *H. pylori* infection in other clinical settings has been recommended because of the decline in the prevalence of *H. pylori* infection, the lack of evidence of harm for the majority of people infected with *H. pylori* the small risks associated with treatment (such as antibiotic-associated diarrhoea) and the controversial data suggesting an inverse relation between *H. pylori* infection and allergic diseases (such as asthma and atopy), GORD and oesophageal adenocarcinoma.

Urea breath testing is the most accurate noninvasive test for *H. pylori* diagnosis, with ^{13}C preferred over ^{14}C due to its non-radioactive properties. The concept underlying urea breath testing is basically the ingestion of labelled urea. This urea is metabolised by urease produced by *H. pylori*, resulting in labelled carbon dioxide. This is then exhaled through the lungs and the concentration of labelled carbon atoms can be determined in the exhaled air.[15]

PPI therapy and antibiotics should be stopped two weeks before all serological testing for *H. pylori*, except in children, whose co-operation may be unreliable, faecal antigen testing is acceptable.

Retesting after eradication of *H. pylori* infection is recommended in patients:

- with complicated ulcer disease (e.g. bleeding, gastric ulcers), the elderly or with significant comorbidities where ulcer recurrence would cause substantial morbidity
- with a past history of ulcer disease where it is unknown whether *H. pylori* testing and/or treatment occurred
- after endoscopic resection of early gastric cancer
- after treatment of *H. pylori* -associated early gastric MALT lymphoma
- after eradication of *H. pylori* infection where there is a recurrence of dyspeptic symptoms not thought to be due to GORD.

In all the above circumstances for retesting, serology testing should not be used for confirmation of eradication because serology can remain positive for up to 12 months after eradication.

For the compliant patient who fails first-line eradication therapy, we recommend the following options:

- repeat triple PPI-based or trial quadruple PPI-based therapy with extension of treatment from seven to 10 days
- other second-line treatment of PPI-based therapy (Table 1)
- referral to a gastroenterologist for endoscopy and biopsies for culture and sensitivity testing to guide treatment for subsequent antibiotic therapy.

In most cases of ulcer disease long-term PPI therapy is not warranted once eradication of *H. pylori* infection has occurred. It should be reserved for patients starting long-term aspirin or anti-inflammatory therapy. MT

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Towards a diagnosis of functional dyspepsia

Which patients with dyspepsia should be tested for *Helicobacter pylori* infection, given a trial of acid suppression or have endoscopy performed, and how is functional dyspepsia diagnosed?

JAMSHID S. KALANTAR
FRACP, MMedSc(ClinEpi)

NICHOLAS J. TALLEY
MD, PhD, FRCP, FRACP

Dr Kalantar is Gastroenterologist and Staff Specialist at the Nepean Hospital, Penrith, NSW. Professor Talley was formerly Professor and Chair of the Department of Internal Medicine, Mayo Clinic, Jacksonville, Florida, USA, and is currently Pro-Vice Chancellor of the Faculty of Health, University of Newcastle, Newcastle, NSW.

The term 'dyspepsia' is derived from the term for 'bad digestion' in Greek. Dyspepsia refers to pain or discomfort in the upper abdomen; key symptoms include epigastric pain, early satiation (inability to finish a normal sized meal) or fullness after eating. Most patients with dyspeptic symptoms who are investigated are not found to have an organic disease that can account for the symptoms (i.e. chronic peptic ulcer disease, gastro-oesophageal reflux or malignancy). Rather, most (60%) have unexplained symptoms, and the condition is then termed functional, or non-ulcer, dyspepsia. Those patients with an obvious cause of the key symptoms – such as abdominal wall pain – are not considered to have dyspepsia, nor are those with predominant or frequent (occurring more than once a week) reflux symptoms (i.e. heartburn or acid regurgitation), who are considered to have gastro-oesophageal reflux disease (GORD) until proven otherwise.

Helicobacter pylori infection is the main cause of chronic peptic ulcers not associated with NSAIDs (including low-dose aspirin). There has been a substantial decrease in the incidence of peptic ulcer disease and distal gastric adenocarcinoma, as well as in the prevalence of *H. pylori*, in Australia over recent decades. This is probably because of better hygiene and lower household density reducing transmission of infection within families. The prevalence of *H. pylori* infection in the general Australian population is now about 20% but this rate, like those in other Western nations, is expected to decrease in time, in part because there has been widespread detection and treatment of the infection. The prevalence of *H. pylori* is much lower than 20% in young adults

IN SUMMARY

- **Functional dyspepsia is characterised by a history of at least three months of chronic dyspeptic symptoms in the absence of any relevant organic disease.**
- **Individual dyspeptic symptoms or groups of symptoms cannot be used to help distinguish organic dyspesia (i.e. that caused by chronic peptic ulcer disease, gastro-oesophageal reflux or malignancy) from functional dyspepsia. Therefore it is often difficult to distinguish between these conditions without investigations.**
- **Empirical therapy for dyspepsia involves testing for *Helicobacter pylori* and treating if infected, followed by acid suppression with a proton pump inhibitor (PPI) if symptoms remain, or if negative for *H. pylori,* a trial of PPI therapy.**
- **Endoscopy should be performed before *H. pylori* testing and treatment in patients with new symptoms who are older than 55 years or who have alarm symptoms.**
- **If acid suppression fails in a patient in whom *H. pylori* has been excluded or eradicated, the symptoms and diagnosis should be reappraised. Prokinetics, antidepressants, psychological therapies or complementary therapies may be helpful.**
- **Alarm features (red flags) for upper gastrointestinal malignancy include onset of dyspepsia at an older age (over 55 years), a family history of upper gastrointestinal cancer or symptoms such as unexplained weight loss, recurrent vomiting or progressive dysphagia.**

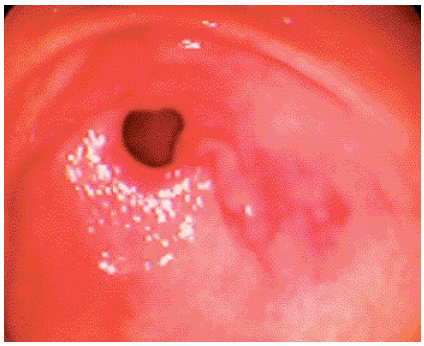


Figure. Antral erythema and erosions in a patient with functional dyspepsia. These endoscopic findings do not cause symptoms.

but is higher in the elderly (because older people acquired the infection in childhood and it persists unless treated). In certain groups, however, such as South East Asian immigrants, the rate of infection is much higher (50 to 60%).

Functional dyspepsia is characterised by a history of at least three months of chronic dyspeptic symptoms in the absence of any relevant organic disease. A six-month or longer history is typical, and helps exclude concerns about missing malignancy. The presence of certain endoscopic abnormalities, such as gastric erosions and oesophageal or duodenal erythema, or a hiatal hernia at gastroscopy does not exclude the diagnosis of functional dyspepsia (Figure).

Individual dyspeptic symptoms cannot be used to help identify peptic ulcer disease in uninvestigated dyspepsia. Symptom subgroups and symptom scoring systems have all failed in distinguishing organic from functional dyspepsia. Therefore it is often difficult to distinguish between these conditions in the uninvestigated patient with upper gastrointestinal symptoms in general practice.[1,2]

Epidemiology of dyspepsia

In Western countries, recurrent upper abdominal pain or discomfort has a prevalence of approximately 25%, depending on the definition used; the prevalence approaches 40% if frequent heartburn (defined as rising retrosternal burning pain or discomfort occurring weekly or more often) is included. The prevalence remains stable from year to year as the number of people developing dyspepsia seems to be matched by a similar number of people losing their symptoms.

Dyspepsia is a costly chronic condition. In many cases, the symptoms are of short duration or mild severity and are self-managed. Despite less than half of affected people seeking medical care for their dyspepsia, the management of dyspepsia is a major part of clinical practice, being responsible for some 2 to 5% of family practice consultations. Factors determining whether a patient consults a physician about their dyspepsia include symptom severity, older age, lower social class, fear of serious disease and psychological distress.

Pathophysiology of functional dyspepsia

The pathophysiology of functional dyspepsia is unclear. Postinfectious functional dyspepsia has been reported after gastroenteritis (e.g. *Salmonella* infection). In patients with peptic ulcer disease who have *H. pylori*, functional dyspepsia may develop after successful eradication of the infection and disappearance of ulcer disease endoscopically.

Approximately 25% of patients with functional dyspepsia have delayed gastric emptying, 10% have accelerated gastric emptying, and 40% have failed fundic accommodation to a meal (a 'stiff' gastric fundus). About one-third of patients have altered visceral sensation (such as increased gastric hypersensitivity to mechanical distension, or duodenal hypersensitivity to acid or mechanical distension). Eosinophilic infiltration into the duodenum has also been observed but the importance is unclear. Although gastric acid secretion is not increased, in some cases sensitivity to acid infusion may be increased, in part because of impaired duodenal acid clearance. Abuse and other psychological distress have been associated with this type of dyspepsia, but a cause-and-effect relationship has not been established.

H. pylori-induced gastritis is present in 30% of patients with documented functional dyspepsia. While no association is apparent between *H. pylori* and any specific symptom profile in functional dyspepsia, there is a small benefit in eradicating *H. pylori* in functional dyspepsia.

Differential diagnoses of functional dyspepsia

Before a diagnosis of functional dyspepsia can be made, organic causes of the symptoms have to be excluded.

Peptic ulcer disease

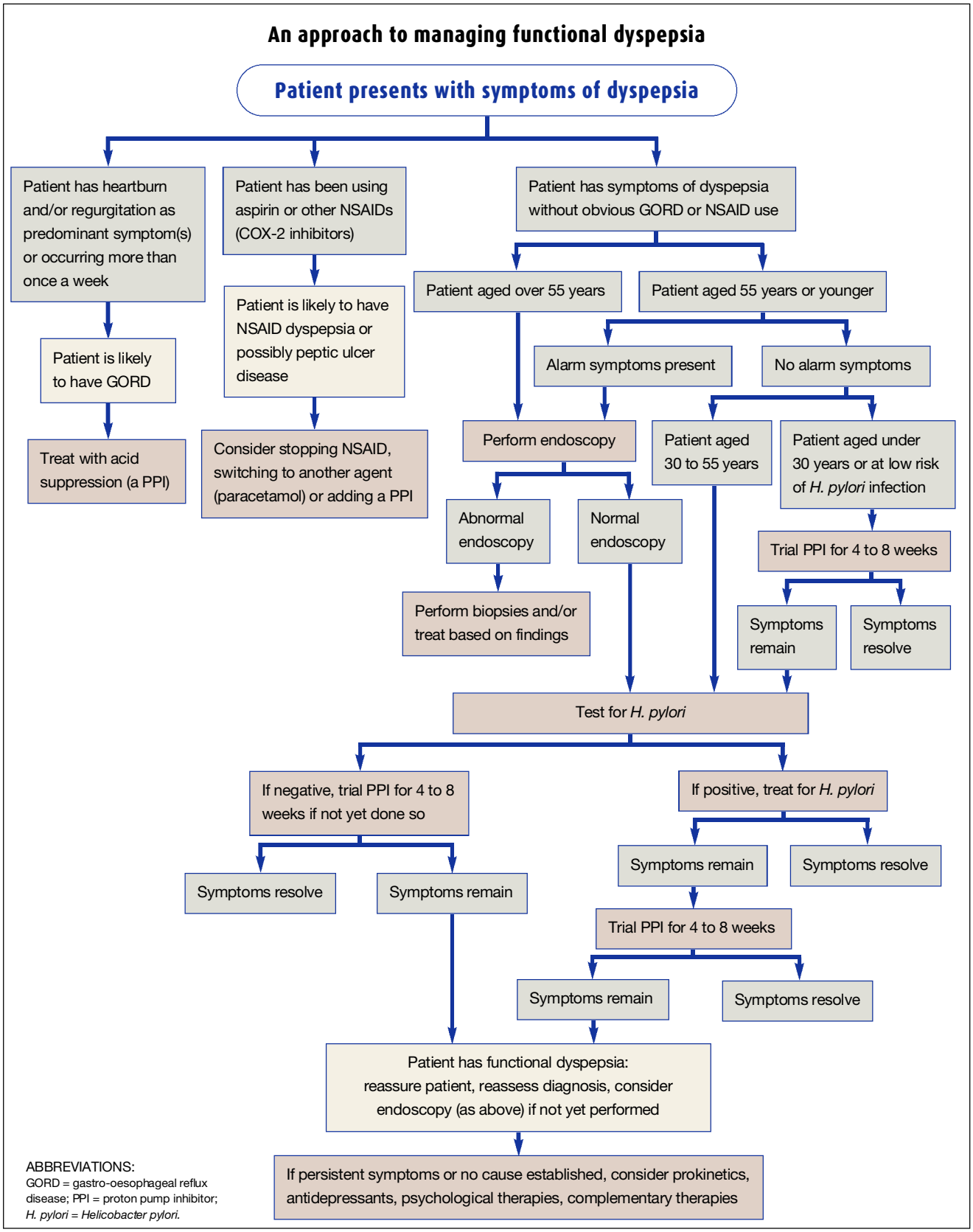
About 10% of upper gastrointestinal symptoms are due to peptic ulcers but an ulcer may be missed if a patient is already on empirical antisecretory therapy. *H. pylori* infection is the main cause of peptic ulcers not associated with NSAIDs (including low-dose aspirin), being responsible for up to 90% of chronic duodenal ulcers and about 70% of chronic gastric ulcers. Up to one-third of patients with 'cured' ulcers (i.e. in whom *H. pylori* infection has been diagnosed and successfully treated) can develop typical functional dyspepsia.

New symptoms of dyspepsia in a patient taking aspirin or another non-selective NSAID may be due to peptic ulcer disease or the NSAID. Although ulcer disease may be ruled out by endoscopy, stopping the NSAID and only performing endoscopy on those patients whose symptoms fail to resolve is considered adequate by many experts.

GORD

Patients with predominant or frequent (occurring more than once a week) reflux symptoms (i.e. heartburn or acid regurgitation) are, as mentioned earlier, considered to have GORD until proven otherwise, rather than dyspepsia. Reflux oesophagitis (defined as the presence of oesophageal mucosal breaks) can cause dyspepsia

An approach to managing functional dyspepsia



ABBREVIATIONS:
GORD = gastro-oesophageal reflux disease; PPI = proton pump inhibitor; *H. pylori* = *Helicobacter pylori*.

Table 1. *H. pylori* eradication and acid suppression treatments for dyspepsia

***H. pylori* eradication – triple therapy**
Amoxycillin
Clarithromycin
Proton pump inhibitor
Seven-day combination packs
Amoxycillin plus clarithromycin plus esomeprazole
Amoxycillin plus clarithromycin plus omeprazole
Acid suppression – proton pump inhibitors
Esomeprazole
Lansoprazole
Omeprazole magnesium
Omeprazole
Pantoprazole
Rabeprazole

without heartburn in some cases, and will be identified endoscopically in 15% of patients presenting with new onset dyspepsia.

Gastro-oesophageal malignancy

Upper gastrointestinal malignancy (gastric or oesophageal adenocarcinoma) becomes more common after the age of 55 years, and is identified in about 1% of all patients referred for endoscopy to evaluate dyspepsia. In the absence of alarm features (red flags) for this malignancy, such as onset of dyspepsia at an older age, a family history of upper gastrointestinal cancer or the presence of certain symptoms (e.g. weight loss, gastrointestinal bleeding, progressive dysphagia or persistent vomiting), curable cancer is rare.

Others

Biliary pain can be distinguished from dyspepsia by its usually being severe, unpredictable and lasting from hours to days. The taking of a good history should reveal the nature of the pain.

Chronic pancreatitis and coeliac disease are uncommon causes of dyspepsia. Lactose intolerance may coexist with dyspepsia but is probably an uncommon cause. Several drugs other than the NSAIDs can theoretically induce dyspepsia but strong evidence for this is lacking. These drugs include digoxin, macrolide antibiotics, metronidazole, corticosteroids, oestrogens, alendronate, orlistat, acarbose, iron, potassium chloride, levodopa, theophylline, quinidine, niacin, gemfibrozil and colchicine.

Ischaemic heart disease can present with epigastric pain. Other rare causes of dyspepsia include infiltrative diseases of the stomach (such as eosinophilic gastritis, Crohn's disease and sarcoidosis), diabetic radiculopathy, metabolic disturbances (such as hypercalcaemia and heavy metals), hepatoma, steatohepatitis and intestinal angina.

Management of dyspepsia

H. pylori testing and acid suppression

Generally, the initial management of patients with chronic dyspepsia who are aged 55 years or younger and have no alarm symptoms is testing and treating for *H. pylori*, followed by acid suppression if symptoms remain (see the flowchart on page 27 and Table 1). Such patients do not need immediate endoscopy.

H. pylori testing should be performed by a ^{13}C-urea breath test or stool antigen test as serology is not sensitive or specific enough. The recommendation to test for *H. pylori* and treat if infected is based on randomised controlled trials and the impact of eradication in preventing future peptic ulcer disease and possibly gastric adenocarcinoma.

If the *H. pylori* test is negative or symptoms remain after *H. pylori* eradication, a trial of a proton pump inhibitor (PPI) is indicated. The available PPIs are probably similar in terms of efficacy in dyspepsia. In populations with a very low prevalence of *H. pylori* (10% or less), empirical PPI therapy is the most cost-effective approach, and standard care is now an empirical trial of acid suppression with a PPI for four to eight weeks before considering *H. pylori* testing; this applies to most younger Australians (i.e. those aged under 30 years). However, as most patients present with dyspepsia in their forties and fifties, *H. pylori* testing remains generally the first line strategy in clinical practice.

Patients who respond to *H. pylori* testing and treatment or PPI therapy can be managed without further investigation. A major gastroduodenal motor disorder should be suspected if there is early satiation (inability to finish a normal-sized meal), postprandial fullness, persistent nausea or frequent vomiting; here, an empirical trial of prokinetic therapy (e.g. domperidone) is worth considering. The value of gastric emptying studies is limited as abnormalities correlate very poorly with specific symptoms.

Endoscopy

There is a very low probability of finding relevant organic disease in patients aged 55 years or younger who continue to have upper gastrointestinal symptoms without alarm features despite failing *H. pylori* testing and treatment and PPI therapy. Some of these younger patients with continued symptoms may be reassured by the performing of endoscopy, but evidence suggests this is not often the case even in those who are most anxious. Endoscopy may be appropriate for some who continue to have dyspepsia, but this should be considered in the wider context of re-evaluating the symptoms and the diagnosis and assessing the need for specialist referral (Table 2).

Endoscopy is, however, recommended for patients presenting with new-onset dyspepsia who are older than 55 years of age or who have alarm symptoms. Although the yield of endoscopy is low, it may reveal disease in a minority. Biopsy specimens for *H. pylori* testing should be routinely obtained at the time of

Table 2. When to consider referring a patient with dyspepsia

- If prompt investigation is required (such as recent onset of alarm symptoms)
- Severe unexplained pain
- Failure of symptoms to resolve or substantially improve after an appropriate treatment period
- Progressive symptoms
- Fear/suspicion of cancer

endoscopy, and eradication therapy offered to those who are infected. Endoscopy has the advantages over upper gastrointestinal radiography of greater diagnostic accuracy and the opportunity to obtain biopsies of the stomach for detecting *H. pylori* infection and, if required, of the small bowel for diagnosing coeliac disease (an uncommon but important cause of dyspepsia).

Further treatment

Most patients who have normal findings on endoscopy and in whom *H. pylori* has been excluded or eradicated will have functional dyspepsia. Those who have not yet had a trial of acid suppression should be offered a PPI.

Patients of any age who continue to have symptoms despite appropriate investigations, therapy and reassurance are a difficult group to manage (see the flowchart on page 27). The symptoms should be reassessed and the diagnosis reconsidered, including an assessment for psychological disorders. Prokinetic agents, antidepressants, complementary therapies, hypnotherapy or behaviour therapy may be helpful.

The prokinetic agent of choice currently is domperidone, at a dose of, for example, 10 mg three times a day before each meal; this may help even if gastric emptying is normal. Low dose tricyclic antidepressant therapy may help some patients with difficult to control symptoms; start low (e.g. 10 mg imipramine at night time) and build up slowly if there is no response (to 50 mg at night or higher). Psychological treatments can be considered (e.g. hypnotherapy), although the benefits of these approaches are not established.

Complementary medical therapies have their place in the treatment of dyspepsia and are widely used in the community. However, these approaches have often not been tested in rigorous scientific trials controlling for the high placebo response rate. Iberogast is a herbal preparation containing extracts of nine plants, including *Iberis amara* (candytuft), peppermint and liquorice. It relaxes the gastric fundus and has been shown in a double blind placebo controlled study to be effective in functional dyspepsia.[3]

Conclusions

Functional dyspepsia is a common condition seen in the general practice setting, causing significant economic woes and impairing quality of life. It is often difficult to distinguish from GORD as the symptoms overlap considerably.

The approach to uninvestigated dyspepsia based on the best available evidence can be summarised as:

- for patients 55 years of age and younger without alarm symptoms, the management strategy of choice is *H. pylori* testing and treatment, followed by PPI therapy if the patient remains symptomatic or is not infected; endoscopy is not mandatory even in patients who remain symptomatic despite this strategy
- for patients older than 55 years and those with alarm symptoms, the preferred initial approach is early endoscopy including biopsy for *H. pylori*; targeted management is then based on the diagnosis but most patients will have functional dyspepsia.

In patients with functional dyspepsia in whom the above investigations and/or interventions prove unhelpful, the diagnosis may have to be reappraised and other treatment modalities considered. Prokinetics, antidepressants, psychological therapies and complementary therapies may be useful. MT

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Investigation and management of noncardiac chest pain

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

GEOFF HEBBARD
MB BS, PhD, FRACP

CLAUDIA KRIEGER-GRUEBEL MD

Associate Professor Hebbard is Director of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Vic. Dr Krieger-Gruebel is a Gastroenterologist at the Cantonal Hospital, St Gallen, Switzerland.

Series Editor
CHRISTOPHER S. POKORNY
FRACP, FRCP, FACG

Associate Professor Pokorny is Conjoint Associate Professor of Medicine, University of NSW, and Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.

Recurrent acute or chronic pain in the anterior chest is common, with up to 33% of the Australian adult population reporting chest pain symptoms over the previous year. Clearly not all these people seek medical attention, but for the majority of patients who do, the chest pain will be due to benign, noncardiac causes. These patients may be relieved that they have been given the 'all clear' for cardiac disease, but they will still be in pain. In a significant proportion, quality of life can be reduced, leading to increased work absenteeism and disruption of daily activities. These patients may also have a new set of concerns, having now received a different (and rather nonspecific) diagnosis for their pain.

Causes of noncardiac chest pain (NCCP)

There is a wide variety of possible contributors to NCCP. A focused history and examination are useful in narrowing the differential diagnoses.

Oesophageal causes

Conditions of the oesophagus, such as gastro-oesophageal reflux disease (GORD), spastic disorders, and the increasingly recognised syndrome of oesophageal hypersensitivity, are often implicated as causes of NCCP (Table 1). The oesophagus has very similar innervation to the heart and oesophageal pain can mimic cardiac pain. Indeed, the relation between the heart and oesophagus may be more complex than previously suspected in light of recent evidence that oesophageal acidification causes changes in cardiac blood flow in patients with syndrome X. The mechanisms behind oesophageal pain may include mucosal irritation, hypermotility and hypersensitivity, or any combination of these. The pain is mediated by nerves in the oesophageal mucosa and muscularis propria.

The most common oesophageal cause of NCCP is GORD. Symptoms of GORD are associated with NCCP, and up to 50% of patients with NCCP will have an abnormal oesophageal acid exposure on ambulatory pH testing.

The pain mechanism behind oesophageal hypermotility has not been identified but it may involve local muscle ischaemia. There are several conditions associated with oesophageal hypermotility, and some may be difficult to detect. For example, one form of oesophageal spasm may involve only the outer (longitudinal) muscle layer of the oesophagus, which can currently be detected only using intraluminal ultrasound.

Some patients with NCCP have been shown to have oesophageal hypersensitivity to balloon

IN SUMMARY

- **Noncardiac chest pain (NCCP) is common and diagnosis can be difficult; however, in most cases the natural history is benign.**
- **The most common underlying cause of NCCP is gastro-oesophageal reflux disease. Resolution of symptoms following treatment with a proton pump inhibitor (PPI) may obviate the need for further investigations.**
- **If treatment with a PPI is not effective, other causes should be sought (using gastroscopy, manometry, barium swallow) and treated.**

Table 1. Causes of NCCP

Oesophageal causes

- Gastro-oesophageal reflux disease
- Oesophageal motility disorder (oesophageal spasm, achalasia, nutcracker oesophagus/high pressure lower oesophageal sphincter)
- Oesophageal visceral hypersensitivity (functional chest pain)

Other causes

- Musculoskeletal
- Anxiety and chronic pain syndromes
- Pulmonary pathology
  - Pulmonary embolism
  - Lung tumours
- Upper abdominal organs
  - Biliary colic
- Occult cardiac disease

distension, acid exposure or electrical stimulation of the mucosa and demonstrate increased secondary allodynia (sensitisation away from the area of stimulation). Whether oesophageal hypersensitivity represents one disorder or many has not been established, nor has the nature of the underlying pathophysiology (in particular, whether it is due to peripheral sensitisation, a central effect, or both). Nevertheless, oesophageal visceral hypersensitivity is likely to be a contributing factor in a significant proportion of patients with NCCP.

Other causes

There are various non-oesophageal causes of NCCP (Table 1), some of which have specific treatments. Such pain develops in thoracic structures other than the oesophagus and in upper abdominal organs, including the chest wall, lung, great vessels and biliary tree. The causes of chronic and recurrent pain are considerably different from those of acute pain that has not previously been experienced by the patient.

The degree to which cardiac disease has been 'excluded' also needs to be assessed as part of the overall process. One of the causes of 'NCCP' is incompletely investigated or occult cardiac disease.

The prevalence of psychological abnormalities is increased in patients with NCCP, and anxiety and depressive disorders are common. Analogous to other functional disorders such as irritable bowel syndrome, these factors may influence symptom severity and clinic attendance.

Diagnosis

Clinical features that may be helpful in differentiating NCCP include the nature and timing of the pain. An association with other gastrointestinal functions or symptoms, such as heartburn, regurgitation, postprandial pain, relief with antacid, or the presence of odynophagia (pain on swallowing) or dysphagia, suggests an oesophageal origin. Prominent odynophagia implies a mucosal inflammatory cause. A chronic aching pain is rarely cardiac or oesophageal in origin and is more likely to have a musculoskeletal or malignant cause. Changes with position or movement are particularly suggestive of a musculoskeletal problem. Chest pain that has a pleuritic component or is associated with coughing or shortness of breath should prompt pulmonary investigations or cardiac re-evaluation. Chest pain that is part of a constellation of pain symptoms suggests a rheumatological cause or a chronic pain syndrome.

Examination

Examination should focus on the areas where the pain is felt, and sites of local tenderness and trigger points should be carefully sought. Pain relief after injection of these areas with analgesic is diagnostic of a local cause. General examination may reveal other points of tenderness, which suggests a rheumatological cause or chronic pain syndrome. The upper abdomen, lymph node fields, and cardiac and pulmonary systems should be examined for other potential causes of the pain.

Investigations

Investigations to consider for patients with NCCP are listed in Table 2; however, they are often unrewarding unless a specific cause is suspected. Upper gastrointestinal endoscopy is indicated only in the presence of alarm symptoms, as it is an insensitive test for GORD. Acid suppression using proton pump inhibitors can assess the contribution of oesophageal acidification (see management below). Ambulatory pH and stationary or ambulatory manometry studies may be of value for assessing the severity of GORD or the efficacy of acid suppression in those with refractory or unusual symptoms. They should be carried out in specialised units. Stationary oesophageal manometry (Figure) may demonstrate oesophageal spasm, nutcracker oesophagus or, occasionally, achalasia. Suspect achalasia if the patient has a history of dysphagia and regurgitation. However, the relation between the manometric findings and symptoms may not be clear if patients do not report symptoms experienced at the time of the 'spasm'. Ambulatory studies increase the chance of detecting a relation between abnormalities and symptoms.

Investigation for non-oesophageal causes for NCCP needs to be tailored to the likely conditions based on the history and examination. Biliary disease is an important differential diagnosis with a specific treatment. Patients with intermittent severe chest pain should be investigated with an upper abdominal ultrasound to exclude biliary disease, particularly if liver function tests are abnormal during or shortly after the pain.

Table 2. Investigations to consider for NCCP

- Trial of high dose acid suppression
- Upper gastrointestinal endoscopy (especially if red flag symptoms present)
- Injection of site of local tenderness (e.g. xiphisternal joint)
- Upper abdominal ultrasound
- CT scan of the chest
- Bone scan
- Oesophageal manometry and/or ambulatory pH study
- Barium swallow

Management

Management of NCCP is determined by the hierarchy of probabilities following the history and examination.

As GORD is the most common cause of NCCP, especially when other features of gastro-oesophageal reflux are present, it is reasonable to institute a therapeutic trial of acid suppression. Potent acid suppression should be used, such as a proton pump inhibitor twice daily. This treatment usually needs to be continued for at least a month before the effect can be adequately assessed. A longer assessment period may be required if symptoms are infrequent. If acid suppression is effective, the dose should be reduced to the lowest level that provides adequate symptom control.

The role of fundoplication in NCCP believed to be due to GORD has not been well examined and no controlled trials have been undertaken yet to address this issue. Fundoplication should be reserved for patients who have prominent features of reflux disease, pathological values on 24h pH-impedance testing and an incomplete response to treatment.

The intermittent use of glyceryl trinitrate spray may relieve pain in patients with oesophageal spasm. If the spasms are frequent, patients may benefit from a calcium antagonist, although the therapeutic response to this medication may be disappointing. Doses that are high enough to have a significant effect on the oesophagus may also induce hypotension. Botulinum toxin injected into the lower oesophagus has been reported in uncontrolled trials to be effective in up to 70% of subjects with documented oesophageal spasm.

Visceral analgesics such as the tricyclic antidepressants (e.g. amitriptyline 20 to 50 mg at night) can be a useful treatment adjunct for patients with troublesome NCCP. How these analgesics work in NCCP is unclear but the therapeutic effect can be prolonged. Treatment is commenced at a low dose and gradually increased until a therapeutic response is obtained, which often occurs in the low 'therapeutic range'. There is little information on the effect of selective serotonin reuptake inhibitors for NCCP. Recently, theophylline, a nonspecific adenosine receptor antagonist, improved biomechanical and sensory properties of the oesophageal wall and chest pain frequency, severity and duration in patients with NCCP.

In patients with longstanding pain and multiple somatic symptoms, the contribution of psychological factors such as depression, anxiety or panic disorder may be significant. These disorders should be actively sought and treated, possibly in association with a psychologist or psychiatrist. Some patients may need to be managed for a chronic pain syndrome, which often requires specialist assistance. Hypnotherapy may be an effective treatment in patients with NCCP. Follow up of patients over two years showed prolonged beneficial effects following completion of treatment.

Possible musculoskeletal causes for the pain should be investigated and managed appropriately. Trigger points (e.g. xiphisternal joint) can be injected with a combination of local anaesthetic and a corticosteroid. This combination has diagnostic as well as therapeutic value.

Patients should be reassured that, in most cases, the prognosis of their condition is benign. In a follow up study, only 4.3% of patients with NCCP died from a cardiovascular related event over an 11-year period, although 75% continued to report chest pain. Providing patients with an acceptable explanation for their chest pain is associated with reduced future use of medical resources. MT

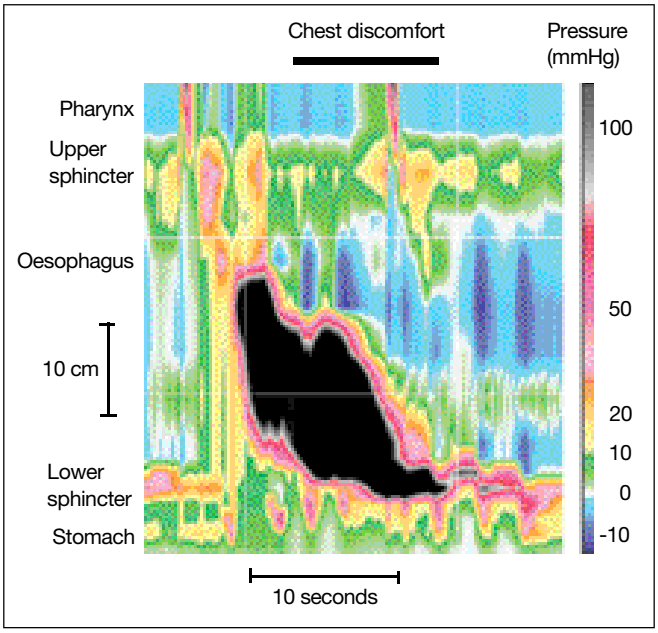

Figure. Spatio-temporal plot of oesophageal motility in a patient with chest pain. Pressure is represented as a colour (see scale on the right) and plotted against time (x-axis) and position (y-axis). The central black area is a synchronous, high amplitude (>300 mmHg), prolonged oesophageal contraction.

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