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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?

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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

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 (ie. 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.**

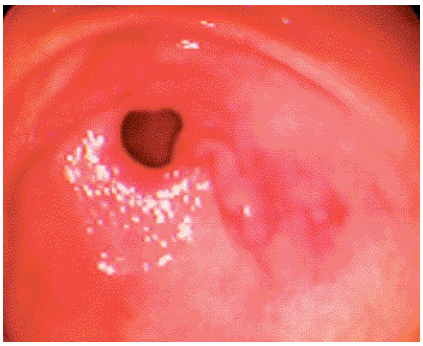


Figure. Antral erythema and erosions in a patient with functional dyspepsia. These endoscopic findings do not cause symptoms.

H. pylori is much lower than 20% in young adults 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

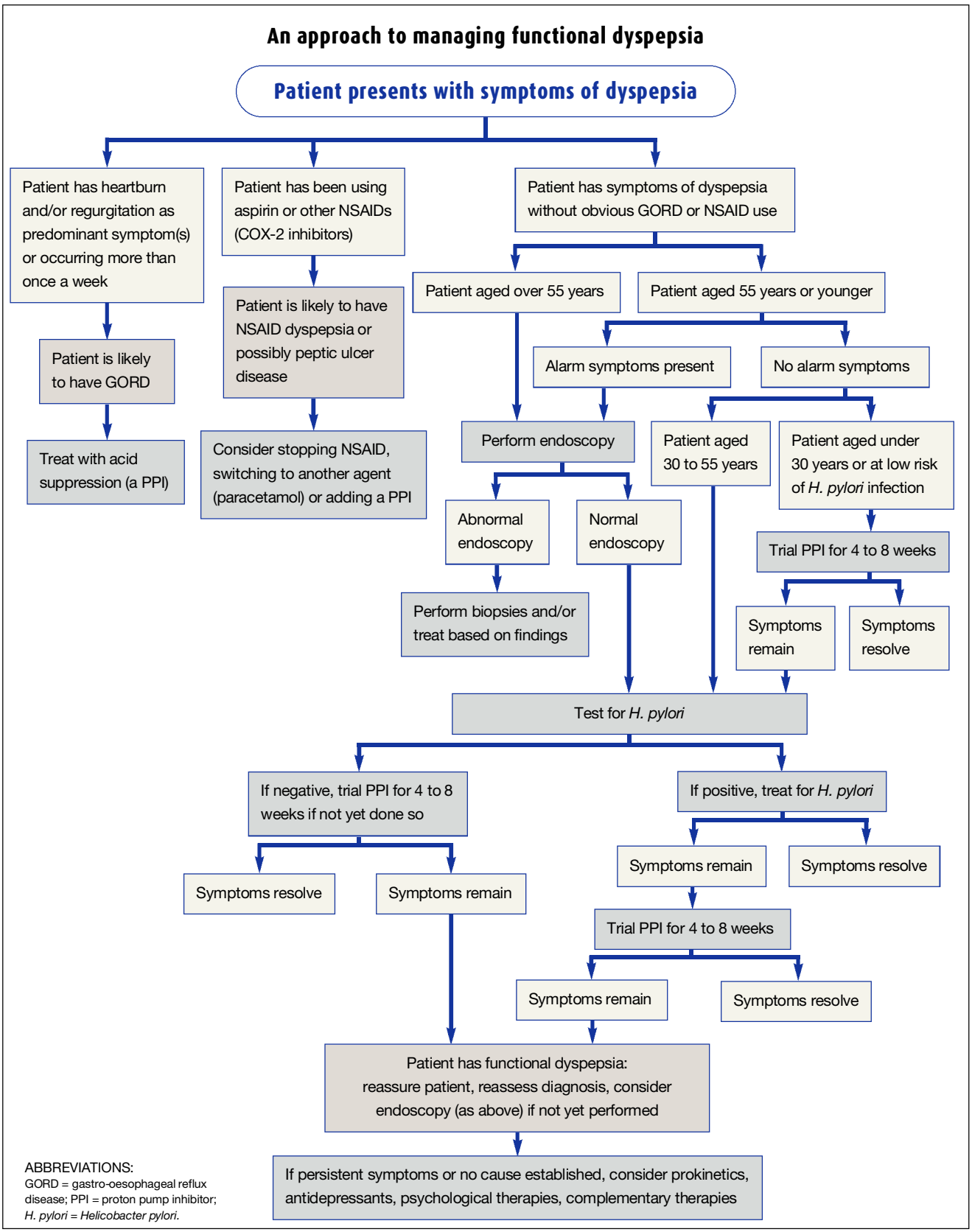
About 10% of upper gastrointestinal symptoms are due to peptic ulcers but an ulcer may be missed if a patient is already on empirical antisecretory therapy. *H. pylori* infection is the main cause of peptic ulcers not associated with NSAIDs (including low-dose aspirin), being responsible for up to 90% 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 without heartburn in some cases, and

An approach to managing functional dyspepsia



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

continued

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 (Nexium HP7)
Amoxycillin plus clarithromycin plus omeprazole (Klacid HP 7)
Acid suppression – proton pump inhibitors
Esomeprazole (Nexium)
Lansoprazole (Zoton)
Omeprazole magnesium (Acimax Tablets, Losec Tablets, Omepral Tablets)
Omeprazole (Meprazol, Probitor)
Pantoprazole (Somac)
Rabeprazole (Pariet)

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 47 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 severe early satiation (inability to finish a normal-sized meal), postprandial fullness or persistent nausea and vomiting; here, an empirical trial of prokinetic therapy (e.g. domperidone [Motilium]) 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 endoscopy, and eradication therapy offered to those who are infected. Endoscopy has the advantages over upper gastrointestinal

continued

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

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 47). 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. 10mg 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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Further reading

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