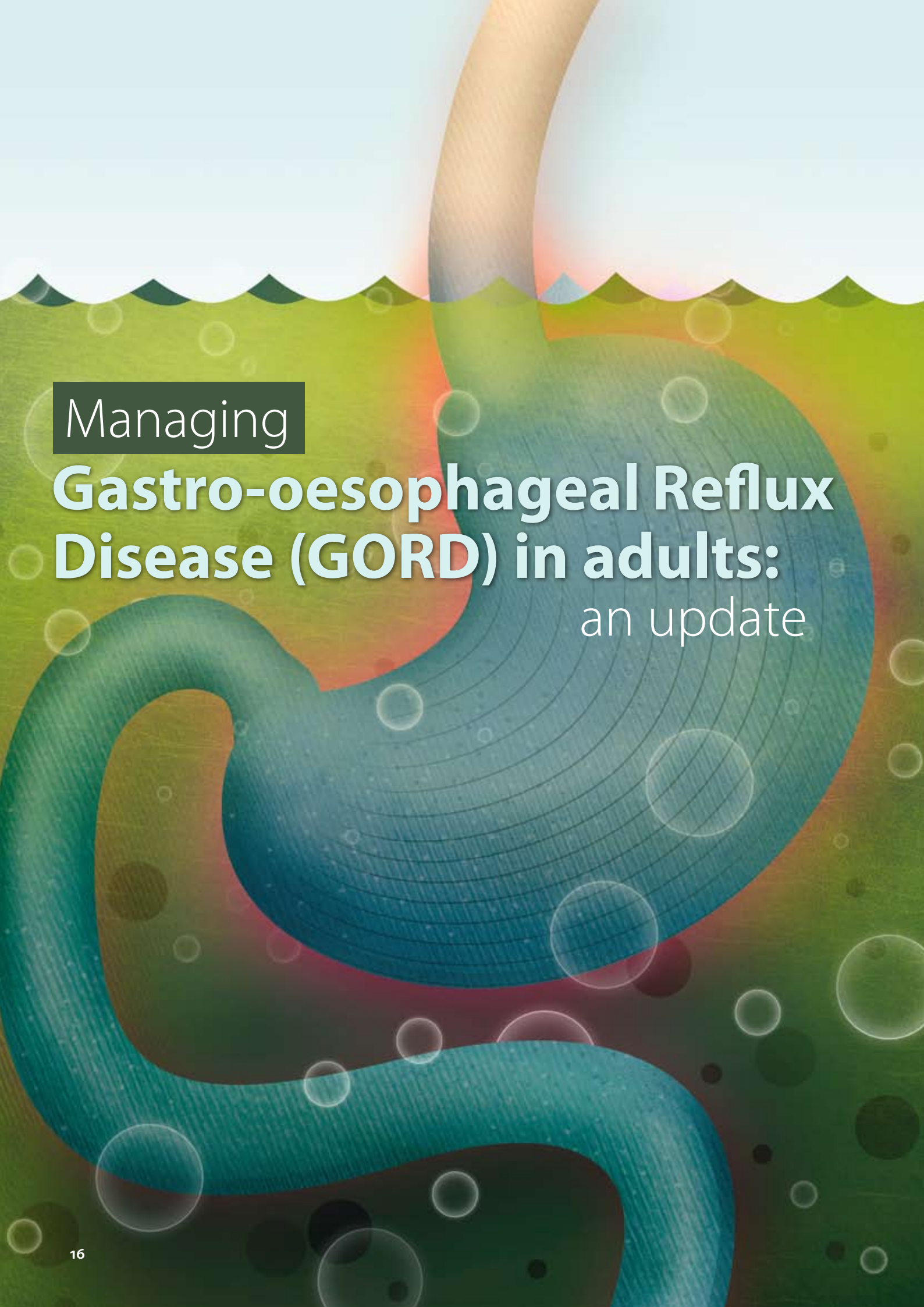

Managing Gastro-oesophageal Reflux Disease (GORD) in adults: an update

Heartburn, the cardinal symptom of gastro-oesophageal reflux disease, is experienced by 15 – 20% of adults at least once a week.[1] The patient's history and their response to an empiric trial with a proton pump inhibitor (PPI) are used to diagnose GORD in primary care. Endoscopy often provides limited diagnostic information as the majority of patients with GORD will not have visible lesions. The role of endoscopy is therefore limited to investigating patients with possible complications of GORD, e.g. erosive oesophagitis or Barrett's oesophagus. PPIs are the mainstay of treatment for GORD, but should be prescribed at the lowest effective dose or "as needed" for patients with mild to moderate forms of GORD. Fundoplication is currently the most effective treatment for patients with severe or complicated GORD.

Gastro-oesophageal reflux disease (GORD) and its complications

Reflux of the contents of the stomach into the oesophagus is a normal physiological event that occurs in many people after eating. When gastric reflux causes a person to have symptoms and/or complications, they are said to have gastro-oesophageal reflux disease (GORD); the Montreal definition.[2] This is a patient-centred definition that frames GORD as a range of disorders, including non-erosive reflux disease, erosive oesophagitis, Barrett's oesophagus and, most seriously, oesophageal adenocarcinoma.

Between 15 – 20% of adults experience heartburn, the cardinal symptom of GORD, at least once a week.[1] GORD is considered to be clinically significant when symptoms are present on two or more days a week.[1] Proton pump inhibitors (PPIs) are used in the short-term to help diagnose GORD and to allow healing of erosive lesions, as well as providing long-term symptom control on an "as needed" or daily basis. If a patient has an uncertain diagnosis or symptoms that do not respond to treatment, they may need to be referred for further investigation (Page 19).

The pathophysiology of GORD

The most common cause of gastric reflux is periodic relaxation of the lower oesophageal sphincter.[1] This exposes the easily damaged squamous mucosa of the oesophagus to acid, proteolytic enzymes (e.g. pepsin and trypsin) and bile salts.[3]

Repeated exposure to gastric reflux can cause oesophagitis that is visible on endoscopy in some people, although approximately two-thirds of people with GORD will not have visible signs of this.[1] For many people the symptoms of GORD result from the presence of abnormal spaces in the epithelium of the mucosa, causing excessive stimulation of nerve endings and peripheral sensitisation.[4] Gas reflux, without any reflux of gastric fluid, can also be experienced as heartburn.[5] In people with GORD symptoms that do not respond to PPI treatment it is possible that gas reflux may be causing distension of mechanoceptors in the oesophageal wall.[5]

Acid production by the stomach is highest when it is empty, but patients often experience GORD after a meal, when acid production is lowest. This is because after eating an unbuffered volume of acid is formed in the proximal region of the stomach, referred to as the acid pocket.[3]

GORD can be caused or exacerbated by:[3, 5]

- Hiatus hernia; which occurs when the oesophageal junction is displaced. Nearly all patients with severe GORD have a hiatus hernia which can be diagnosed on endoscopy.
- Central obesity; which increases the pressure gradient between the abdomen and thorax, increasing the number of reflux episodes and the likelihood of hiatus hernia occurring
- Impaired oesophageal or gastric clearance; which slows the movement of material down the digestive tract

Stress is reported to be a causative factor for symptoms by 60% of people with GORD.[5] Symptoms of GORD may be aggravated by diet and lifestyle, e.g. high-fat foods, spicy foods, caffeine, alcohol and smoking.[1]

Risk factors for GORD

The risk of GORD is increased in people who consume more than seven standard alcoholic drinks per week. The risk is also increased in people who have a first-degree relative with a history of heartburn.[1] The genetics of GORD are poorly understood and multiple genes are likely to be involved.[5] Up to half of pregnant women will experience symptoms related to GORD (see: "GORD during pregnancy", Page 22).[6] GORD is also more prevalent in people who are confined to bed for extended periods of time.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs), some antibiotics (e.g. tetracyclines), iron supplements and potassium supplements can irritate the oesophagus and cause heartburn. The likelihood of GORD and its complications (see below) is increased in people who are obese, have chronic respiratory disease (e.g. asthma), or connective tissue disease (e.g. scleroderma).[1] In people with systemic sclerosis, atrophy of the muscularis mucosa and submucosal fibrosis result in oesophageal and gastrointestinal dysfunction.[7] The relationship between GORD and asthma is less clear and a review on the subject was unable to conclude whether GORD precedes asthma, or asthma triggers GORD.[8]

The complications of GORD

Chronic exposure of the oesophagus to gastric reflux can result in a number of complications requiring long-term management.

Erosive oesophagitis occurs when excessive gastric reflux causes necrosis of the oesophageal mucosa, resulting in erosions and ulcers. This is diagnosed with endoscopy and graded A to D (least to most severe) according to the Los Angeles classification.[9] People with erosive oesophagitis are reported to have a greater than five-fold risk of progressing to Barrett's oesophagus.[9]

Barrett's oesophagus is a complication of chronic GORD involving metaplasia of the lining of the lower oesophagus following exposure to gastric reflux.[9] This results in the squamous epithelium being replaced by a specialised columnar-lined epithelium.[9] The risk of Barrett's oesophagus increases with age and it is more likely in males and in people who are obese, have a poor diet or who smoke.[9] The prevalence of Barrett's oesophagus in the general population has been estimated at 1.6%.[9] The lifetime risk of a person with Barrett's oesophagus developing oesophageal adenocarcinoma is less than 2%.[1]

A peptic stricture is a narrowing of the oesophagus that results from healing and fibrosis of inflammatory lesions following long-term exposure to gastric reflux.[9] There has been a substantial decline in the prevalence of peptic strictures due to the use of PPIs.[9] The likelihood of a peptic stricture is higher in older people with chronic GORD or in people with dysphagia. Peptic strictures are classified as simple or complex, depending on their length and degree of contraction.[9] They are generally treated using invasive techniques that physically dilate the oesophagus.

The risk of oesophageal adenocarcinoma is correlated with the frequency, severity and duration of symptoms. People with frequent symptoms of GORD, i.e. more than three times per week, are approximately 17 times more likely to develop oesophageal adenocarcinoma compared with people without GORD.[10] People with severe symptoms occurring for more than 20 years are over 40 times more likely to develop adenocarcinoma compared with people without GORD.[10]

People with Barrett's oesophagus have a significantly increased risk of developing adenocarcinoma, but very few people with Barrett's oesophagus die from this form of cancer.[1]

Diagnosing GORD

The characteristic features of GORD are heartburn and regurgitation. The meaning of heartburn may not be clear to all patients and providing a description is known to increase GORD detection rates.[1] Heartburn is a burning feeling that rises from the stomach or lower chest towards the neck and frequently occurs after eating.[1] It may also be associated with bending, lying down or straining. Upper abdominal pain or discomfort are reported by approximately two-thirds of people with GORD.[1] Regurgitated food is generally swallowed, but can sometimes be of sufficient quantity to be mistaken as vomit. Patients may also experience water brash. This is a sudden and rapid production of saliva that fills the mouth and may be associated with nausea.[1] The patient's history may reveal triggers for GORD symptoms, which can then be avoided.

Atypical symptoms of GORD include angina-like chest pain, cough, hoarseness or throat changes, wheeze, frequent belching and nausea.[1] Several other conditions can cause gastrointestinal symptoms that may be mistaken for GORD. These include gastric ulcer disease, functional dyspepsia (dyspepsia without an obvious cause), and approximately 40% of patients with irritable bowel syndrome will have regurgitation.[1] *Helicobacter pylori* infection should be considered in patients who present with dyspepsia. The possibility of medicine-induced symptoms should also be considered if the patient is taking medicines that cause

dyspepsia or that have a mechanism of action that is more likely to result in reflux, e.g. theophylline, nitrates, calcium-channel blockers, beta-blockers, alpha-blockers, benzodiazepines, tricyclic antidepressants and anticholinergics, which can all reduce oesophageal sphincter pressure and exacerbate the symptoms of GORD.[11]

Low, or absent, gastric acid production (achlorhydria) impairs protein digestion and can cause symptoms similar to GORD, and is more common in older people.[12]

Red flags of GORD

The complications of GORD are more likely in patients with red flags; these patients should be referred promptly for endoscopy. Empirical treatment with a PPI can be initiated for symptom control but should not delay the timing of referral.

Red flags for patients with GORD requiring endoscopy include:[1]

- Dysphagia (difficulty with swallowing); which may be caused by inflammation, abnormal peristalsis or oesophageal hypersensitivity. If dysphagia and globus pharyngeus (the sensation of a "lump in the throat") are present then peptic stricture should be suspected.
- Odynophagia (pain with swallowing); which is generally associated with severe oesophagitis
- Haematemesis
- Weight loss with no obvious explanation
- Patients aged 55 years or older with unexplained and persistent dyspepsia of recent onset; these patients are at increased risk of gastric and oesophageal cancer.[13]

A therapeutic trial can be used to diagnose GORD

A therapeutic trial of PPIs (Page 20) in a patient with symptoms suggestive of GORD has a comparable sensitivity and specificity for diagnosing GORD as measuring the presence of oesophageal acid directly with a pH monitor in a secondary care setting.[1] This approach is suitable for younger patients with no red flags and mild, long-term symptoms.[1] It is unlikely that prescribing a higher dose of a PPI will provide any benefit to patients with uncomplicated GORD as in a primary care setting omeprazole 20 mg, daily, is generally considered to be as effective as omeprazole 40 mg, daily.[14]

The role of endoscopy

The role of endoscopy is limited in the diagnosis of GORD as the majority of patients with GORD will not have oesophageal abnormalities on endoscopy.[1] However, endoscopy is the investigation with the highest specificity for oesophagitis caused by GORD as it is able to differentiate between mucosal lesions caused by infective oesophagitis, peptic ulcer disease, malignancy and other abnormalities of the gut.[1] Endoscopy is also the most sensitive technique for diagnosing Barrett's oesophagus and is used to identify peptic strictures.[1]

Endoscopic assessment is indicated:[1, 11]

- Promptly in patients with red flags whether or not empiric treatment is initiated
- Where there is diagnostic uncertainty, e.g. non-specific or atypical symptoms, or when other diagnoses are being considered, e.g. infective or medicine-induced oesophagitis or malignancy
- When the patients symptoms do not respond to PPI treatment, or worsen despite treatment
- Prior to surgical intervention for GORD, e.g. fundoplication

Endoscopy may also be appropriate for patients with GORD who have multiple risk factors for oesophageal adenocarcinoma, e.g. chronic GORD, frequent symptoms, age over 55 years (local guidelines may vary), males, European ethnicity, a history of smoking, hiatus hernia, increased body mass index and intra-abdominal distribution of fat.[9, 10, 13, 15]

Managing patients with GORD

The management of GORD is determined by the severity of the patient's symptoms and the likelihood of complications. If the patient's symptoms are mild, lifestyle changes and antacids may provide benefit before a diagnostic trial with PPIs is tried (see below). However, there is no evidence that changes in lifestyle alone will allowing healing of established oesophagitis.[1]

Lifestyle treatment strategies include:[1, 11]

- Avoiding foods that cause symptoms, e.g. alcohol, coffee and spicy, fatty or acidic foods
- Avoiding eating three to four hours before sleeping
- Weight loss for obese or overweight patients
- Smoking cessation
- Raising the head of the bed, if this can be done safely. Extra pillows should not be used as they may increase abdominal pressure.

Discussing the patient's stress or anxiety levels and suggesting relaxation techniques may improve symptoms or assist the patient in avoiding triggers for GORD, e.g. alcohol.[11]

Review the use of any medicines which may be contributing to symptoms (Page 19).

Over-the-counter antacids can be used for the occasional treatment of patients with mild or intermittent symptoms of GORD, due to their rapid onset. However, these are not appropriate for the long-term management of GORD.[1]

Proton pump inhibitors are the first-line treatment for GORD

Multiple studies have found PPIs to be the most potent class of acid-suppressive medicine and the most effective class of medicine in the treatment of GORD.[1] For example, a meta-analysis found that PPIs were more effective than H_2-receptor antagonists at treating erosive oesophagitis, especially in patients with severe disease.[16]

When initiating PPI treatment it is a good idea to discuss with patients the expected duration of treatment. For patients with mild GORD the regimen should be regularly reviewed with the goal of treatment being lifestyle control of symptoms with minimal reliance on medicines. Patients with severe GORD are likely to require long-term treatment with PPIs and may require surgery.

The age of the patient should be considered when recommending a treatment regimen as younger patients may be exposed to a greater lifetime risk of adverse effects from long-term PPI use. The possibility of the patient developing rebound acid secretion following treatment withdrawal should also be discussed. This occurs due to increased production of gastrin, which is released to compensate for the decreased acidity of the stomach when PPIs are taken.

PPIs can be purchased in limited quantities, without a prescription, as a "Pharmacist only" medicine. Patients should be asked about any use of medicines for their GORD symptoms before PPIs are prescribed. Patients who self-administer PPIs could potentially develop rebound acid secretion which would complicate the clinical picture.[17]

For further information, see: "Proton pump inhibitors: When is enough, enough? Page 8.

Begin treatment with 20 mg omeprazole, once daily, for four to six weeks. Pantoprazole 20 mg, once daily, or lansoprazole 30 mg, once daily, are alternatives if omeprazole is not tolerated. The safety and clinical efficacy of these medicines is similar.[11] A meta-analysis found there was no difference in the comparative effectiveness of PPIs in healing oesophagitis.[16]

To maximise their effect, PPIs should be taken 30 – 60 minutes before food, ideally before the first meal of the day.[1, 4] Check compliance if the patient reports that the PPI is ineffective. It may be difficult for patients to take medicines before breakfast and it is reported that as few as 10% of patients are adherent to this treatment advice.[4]

The majority of patients who have responded to a diagnostic trial with a PPI can be switched from daily to "as needed" treatment without affecting symptom control or quality of life.[11] This involves the patient waiting for symptoms to develop before taking the medicine, e.g. omeprazole 20 mg, daily, until symptoms resolve.[11] This strategy may be explained to the patient as being analogous to the use of paracetamol for headache, i.e. it is being used for short-term symptom relief. Also explain to the patient that the return of symptoms is to be expected and is reported to occur in 70% of people.[1]

Alternatively, step down treatment to the lowest effective daily dose. For example, a patient taking omeprazole 20 mg, once daily, could be prescribed omeprazole 10 mg, once daily. If the patient experiences a return of symptoms they can resume their previous dose. A small Japanese study of 70 patients with heartburn occurring at least twice a week found that after an eight week course of omeprazole 20 mg, once

daily, 80% of patients whose heartburn had decreased to once a week or less were then successfully managed with a maintenance treatment of omeprazole 10 mg, once daily.[18]

For patients who have had an incomplete response to a diagnostic trial with a PPI consider increasing the dose, e.g. from omeprazole 20 mg, once daily, to omeprazole 40 mg, once daily.[11] The patient's adherence to treatment, e.g. dosing 30 – 60 minutes before eating, should be discussed as well as revisiting any lifestyle factors that may be contributing to symptoms.[11] For patients who are experiencing adverse effects it may be appropriate to trial an alternative PPI.[11]

N.B. When increasing the dose of lansoprazole or pantoprazole it is recommended that the dose is divided to twice daily dosing, i.e. before breakfast and before dinner.[11] Omeprazole is usually dosed once daily, but a divided dose could be trialled if symptoms worsen later in the day.

H. pylori infection may need to be reconsidered as a diagnosis in patients who continue to experience gastrointestinal symptoms following a diagnostic trial with a PPI. The incidence of *H. pylori* is generally higher in the north of New Zealand than in the south. Māori, Pacific, Asian and Indian people and people born outside of New Zealand (depending on their country of origin) are more likely to have *H. pylori*.

For further information see: "The changing face of *Helicobacter pylori* testing", BT (May, 2014).

Antacids can be prescribed as "rescue" medication for rebound acid secretion

Many patients will experience reflux symptoms after PPIs are withdrawn, due to rebound acid secretion. This can be indistinguishable from ongoing symptoms of GORD. Patients can be prescribed "rescue" medication to help them manage symptoms that may arise after stopping the PPI. If symptoms are unable to be managed, or continue for longer than one or two weeks, reconsider the decision to withdraw the PPI.

Medicines that contain both an antacid and an anti-foaming agent are likely to be the most effective treatment for rebound acid secretion. Liquid preparations are often more effective, but chewable tablets may be more convenient for some patients. Some products contain significant amounts of sodium, and should be used carefully, or avoided, in patients with heart failure (see below). These medicines should not be used within two hours of taking any regular medicines for other conditions, to avoid interactions.

The following medicines are currently partially subsidised* and may be prescribed for adults:

Mylanta P or Acidex oral liquid, 10–20 mL, as required, up to four times daily, usually after meals and at night.[19] Prescribe Acidex with caution in people with heart failure.

Gaviscon Double Strength tablets, 1–2 tablets chewed as required, up to four times daily, after meals and half an hour before bed.[19] Prescribe Gaviscon Double Strength with caution in people with heart failure.

Aluminium hydroxide tablets are an alternative antacid that are fully subsidised, but do not contain an anti-foaming agent. Prescribe Alu-tab 600 mg tablets, one tablet, up to four times daily, between meals and at bedtime.[19]

H_2-receptor antagonists are second-line for patients with GORD

Patients with mild symptoms who have not responded to a four to six week trial with a PPI may be offered an H_2-receptor antagonist as an alternative, e.g. ranitidine 600 mg, daily, in two to four divided doses, for up to 12 weeks (if moderate to severe symptoms, otherwise a lower dose is more appropriate – see NZF).[19] However, the use of H_2-receptor antagonists is limited in the treatment of GORD due to tachyphylaxis (sudden pharmacologic tolerance, which can occur after a single dose) and interactions with other medicines.[4, 20] A prokinetic, e.g. domperidone 10 – 20 mg, three to four times daily, to a maximum of 80 mg, daily may be considered as an alternative to an H_2-receptor antagonist, but the results of clinical trials assessing prokinetics have failed to demonstrate a clear benefit to patients with GORD.[19]

H_2-receptor antagonists are occasionally used as an adjunctive treatment to PPIs (usually after discussion with a specialist). For example, patients with nocturnal symptoms that have not improved following morning dosing with a PPI and lifestyle interventions may gain benefit from the addition of a H_2-receptor antagonist at bedtime, e.g. ranitidine, 300 mg, at night, for up to eight weeks.[11, 19]

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* N.B. Medicines that are partially subsidised attract a standard prescription fee the first time a prescription is dispensed (but not when a repeat supply is dispensed), and a portion of the cost of the medicine per unit of medicine that is dispensed. It is therefore important to indicate on prescriptions for "as required" medicines, a suitable quantity to supply at each dispensing, or the patient may receive more medicine than is likely to be used, with unnecessary cost. For example, Mylanta Double Strength tablets have a higher part charge for the patient than the liquid preparations above; one way to reduce the cost to patients is to prescribe fewer tablets, e.g. 40 tablets, plus repeat of 40 tablets.

GORD during pregnancy

Between 30 – 50% of pregnant women experience symptoms of GORD and this is considered a normal part of pregnancy.[6] Often symptoms begin late in the first trimester or in the second trimester, with heartburn becoming more severe and frequent as gestation progresses. Heartburn during pregnancy is more likely in women who have had previous episodes or multiple pregnancies, and is inversely correlated with maternal age.[6]

The clinical features of GORD during pregnancy are the same as for the general population. Lying down is reported to aggravate heartburn in over 80% of pregnant women with GORD.[6] Complications of GORD during pregnancy are rare as the reflux is generally of short duration.[6]

The treatment of GORD during pregnancy is conservative and many women with mild or infrequent symptoms can be managed by lifestyle, dietary modifications and the use of antacids or ranitidine (Pregnancy Risk Category B1).[6] However, PPIs should not be withheld from pregnant women with symptoms of GORD that are affecting their quality of life as the overall risk of these medicines to the foetus is minimal (Pregnancy Risk Category B3).[6, 19] There is reported evidence of potential foetal toxicity due to omeprazole in animal studies, but this finding has not been reproduced in human studies.[6] As with all medicines taken during pregnancy, clinicians should assess the risks and benefits before treatment is begun, particularly for women in the first trimester, and prescribe the lowest effective dose for the shortest possible time.

Many women with GORD during pregnancy will find that their symptoms rapidly improve after giving birth and continued treatment is not necessary. Omeprazole and pantoprazole are considered compatible with breast feeding, but caution is recommended with lansoprazole due to insufficient data.[19] Levels of PPIs excreted in breast milk are low, and a large proportion of any PPI that is ingested by the infant is likely to be destroyed by the acid in their stomach.[6]

Managing patients with complications of GORD

Patients with severe oesophagitis (Los Angeles grades C or D) require long-term, daily dosing with a PPI, e.g. omeprazole 20 mg, once daily, to maintain mucosal healing.[1, 19] Severe GORD can be treated via fundoplication, where the stomach is wrapped around the oesophagus to strengthen the lower oesophageal sphincter.

The majority of patients with Barrett's oesophagus are treated with PPIs to control the symptoms of GORD. It is unclear whether PPIs reduce the risk of a patient developing oesophageal adenocarcinoma.[4, 9] Some patients with Barrett's oesophagus and additional risk factors for oesophageal adenocarcinoma may require endoscopic surveillance following the recommendation of a Gastroenterologist.

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