Gastro-oesophageal reflux disease

mechanisms and management

Gastro-oesophageal reflux disease is common and its symptoms often have a significant impact on an individual's quality of life. Management generally involves attention to lifestyle factors and individualised medical treatment. Surgery may be required for a small number of cases.

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Gastro-oesophageal reflux is a normal physiological event. However, excessive exposure of the oesophagus to contents of the stomach can lead to symptoms or complications – this is gastro-oesophageal reflux disease (GORD).

Mechanisms of GORD

The main mechanism responsible for GORD is failure of the antireflux barrier, which is primarily composed of the lower oesophageal sphincter and the crural diaphragm. Transient relaxations of the lower oesophageal sphincter appear to account for the majority of reflux episodes and are most commonly caused by gastric distension in the postprandial period. Decreased pressure of this sphincter may also be caused by nicotine, fatty foods, caffeine, alcohol and various medications. Other contributing factors include delayed gastric emptying, impaired oesophageal clearance and decreased salivary production (saliva helps to neutralise acid).

Hiatus hernia and GORD

A hiatus hernia results when part of the stomach protrudes through the oesophageal hiatus in the diaphragm. The most common type is a sliding

IN SUMMARY

- **Gastro-oesophageal reflux disease (GORD) is common and tends to run a chronic and relapsing course.**
- **The most common symptoms of GORD are heartburn and regurgitation. Atypical presentations include a chronic cough, hoarseness, sore throat, asthma and atypical chest pain.**
- ***Helicobacter pylori* does not cause GORD.**
- **Treatment of GORD, including endoscopy-negative reflux, involves attention to lifestyle modification and acid suppressant therapy.**
- **Therapy is best commenced with a proton pump inhibitor and a step-down approach should then be adopted. In the long term, maintenance treatment can be given on either a continuous or on-demand basis.**
- **Antireflux surgery should be considered for patients who have failed medical therapy and patients who have regurgitation as a predominant symptom. It should also be considered as an alternative to lifelong medical therapy in young patients with severe oesophagitis.**

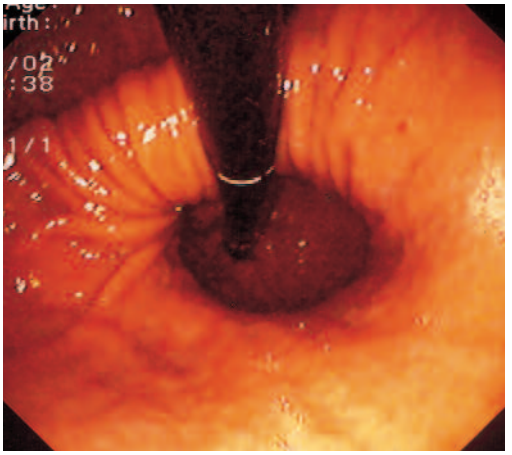

Figure 1. A large sliding (direct) hiatus hernia, as seen at endoscopy.

hiatus hernia, which occurs when the gastro-oesophageal junction passes directly through the oesophageal hiatus into the chest (Figure 1). A para-oesophageal or rolling hernia is produced when a part of the gastric fundus herniates through the oesophageal hiatus and lies next to the lower part of the oesophagus, with the gastro-oesophageal junction remaining in the normal position below the diaphragm. Rolling hernias are much less common than sliding hernias.

Although the vast majority of hiatus hernias are asymptomatic, they are particularly common in patients with GORD: more than 80% of such patients have a hiatus hernia compared with approximately 30% of the general population. Hiatus hernias impair lower oesophageal sphincter function and thereby increase the likelihood of reflux. The resultant oesophagitis tends to be more severe when the hernia is large.

Gastro-oesophageal reflux disease

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Although gastro-oesophageal reflux is a normal physiological event, excessive exposure of the oesophagus to gastric contents can lead to GORD. Hiatus hernias, which are common in patients with this condition, impair lower oesophageal sphincter function and thereby increase the likelihood of reflux. The degree of oesophagitis that may result varies greatly in severity and is poorly correlated with symptom severity.

Symptoms

The symptoms of GORD are listed in Table 1. Patients typically complain of heartburn (retro - sternal burning) and regurgitation within three hours after eating or when lying flat. Excessive belching as well as burning epigastric pain may also occur. The atypical symptoms include chronic cough, hoarseness, sore throat, asthma and ischaemic-like chest pain. Painful swallowing (odynophagia) is suggestive of ulcerative oesophagitis.

Symptom severity correlates poorly with the degree of oesophagitis. For example, in at least 50% of patients who undergo endoscopy for reflux symptoms the oesophagus appears normal, without macroscopic evidence of mucosal damage (i.e. they have 'endoscopy-negative' reflux).

Complications

The major complications related to GORD are listed in Table 2. These include oesophageal ulceration, which varies in severity (see Figures 2a to c).

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Barrett's oesophagus develops in up to 10% of patients with significant reflux symptoms (Figures 3a and b). It is caused by severe prolonged exposure of the oesophagus to acid and possibly from duodenogastro-oesophageal reflux of potentially carcinogenic agents such as bile salts, resulting in replacement of the normal squamous mucosa of the lower oesophagus by metaplastic columnar epithelium. Barrett's oesophagus is a pre-malignant condition that is estimated to increase the risk of oesophageal adenocarcinoma up to 125-fold. This risk is greater if the segment of Barrett's oesophagus is long, rather than short.

Another complication is oesophageal stricture, which can lead to progressive dysphagia (initially for solids). In addition, bleeding, either overt or occult, can occur as a result of oesophagitis and lead to anaemia.

Diagnosis

In the majority of cases, GORD can be diagnosed on the history alone. In the absence of anaemia and any symptoms suggesting a complication or other alarm symptoms (e.g. weight loss or anorexia), it is appropriate to give a trial of medical therapy – if the patient fails to respond to treatment with, for example, an H_2-receptor antagonist or proton pump inhibitor, investigation is warranted. Likewise, investigation is indicated for patients with symptoms suggesting oesophageal ulceration (such as odynophagia) or an oesophageal stricture (dysphagia), and for those with other alarm symptoms (see Table 1).

Table 1. Symptoms of GORD

Typical symptoms
- Heartburn
- Regurgitation
- Belching
- Waterbrash
- Burning epigastric pain

Atypical symptoms
- Chronic cough
- Hoarseness
- Sore throat
- Asthma
- Angina-like chest pain

Alarm symptoms
- Anorexia
- Weight loss
- Dysphagia
- Odynophagia (pain on swallowing)
- Anaemia

Table 2. Complications of GORD

- Oesophageal ulceration
- Barrett's oesophagus
- Oesophageal stricture
- Bleeding (occult or overt)

Investigations

A number of investigations are available for cases of suspected GORD.

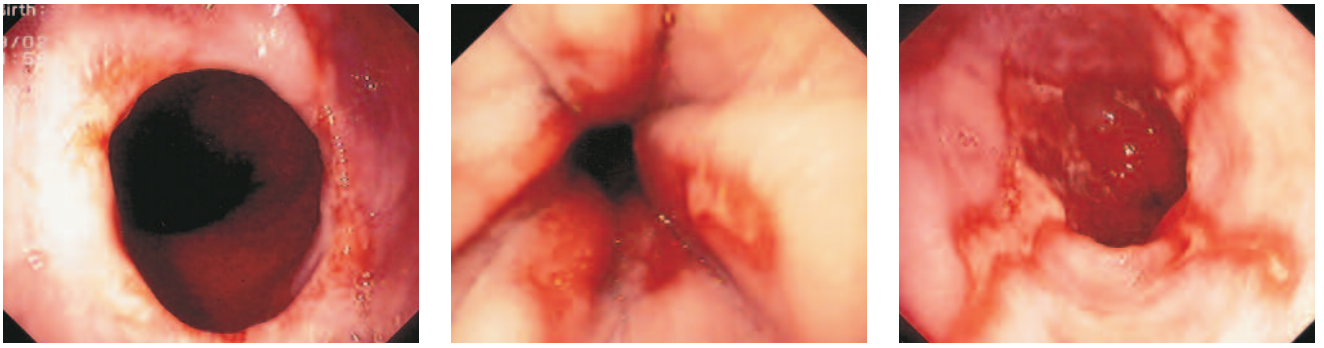
Primary investigations

Upper gastrointestinal endoscopy is the procedure of choice for investigating patients with suspected GORD because it allows direct visualisation of the mucosa. The extent and severity of oesophagitis can be assessed and the presence of complications such as Barrett's oesophagus can be established. Also biopsy specimens can be taken from areas of suspected malignancy as well as from areas of Barrett's oesophagus to check for dysplasia.

Barium swallows and barium meals are insensitive methods for diagnosing oesophagitis. However, oesophageal strictures may be detected and hiatus hernias may be seen (but note that these can also be diagnosed at endoscopy – see Figures 4a and b).

Secondary investigations

Secondary investigations that are used in patients with suspected GORD include 24-hour ambulatory oesophageal pH monitoring and oesophageal manometry. In the diagnosis of endoscopy-negative reflux, atypical chest pain, chronic cough and other symptoms suspected of being secondary to oesophageal reflux, however, an alternative and more practical approach is to give an empirical trial of therapy with a proton pump inhibitor and then assess the response. Symptoms



Figures 2a to c. Examples of mild (left), moderate (centre), and severe (right) ulcerative oesophagitis, as seen at endoscopy.

should abate quickly if reflux is the cause – the exception is a reflux-associated cough, which can take up to three months to resolve with such treatment, even with high doses of therapy.

Oesophageal pH monitoring is useful when symptoms persist and the diagnosis remains unclear. Oesophageal manometry may be invaluable in cases of noncardiac chest pain; in addition, it should be performed to exclude a motility disorder if fundoplication is being contemplated. However, although oesophageal pH monitoring and manometry can provide important diagnostic information, they are not widely available and are unpleasant for the patient. Also, in order to provide reliable data, these investigations should be conducted in a unit that has recognised expertise.

Management

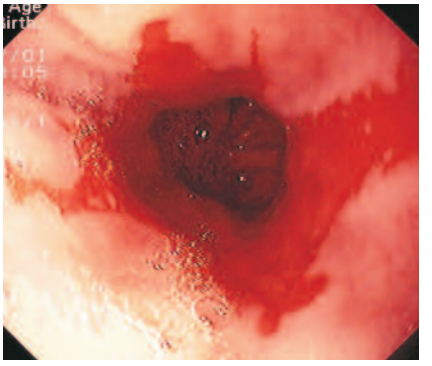
The management of GORD depends on the frequency and severity of symptoms as well as the findings at endoscopy. An approach is outlined in the flowchart on page 23.

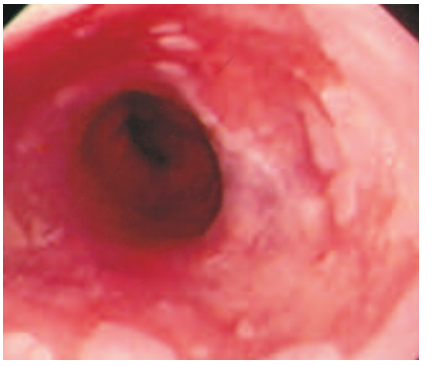
Lifestyle modifications

It is essential that patients with GORD be advised about appropriate lifestyle modifications – although these measures have little effect on oesophagitis, patients often find that their symptoms improve. The handout on page 27 may be of assistance in this regard.

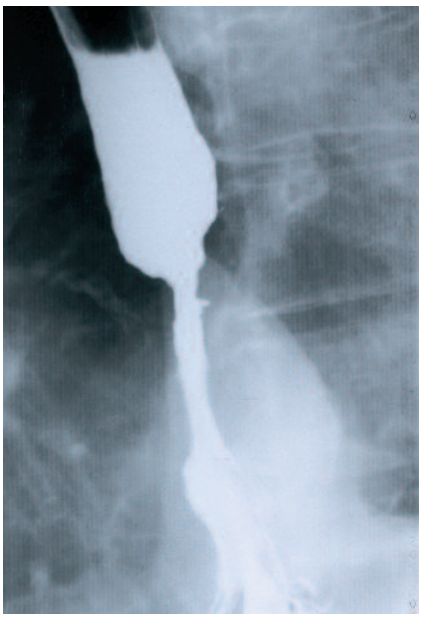
Lifestyle modifications include ceasing smoking, reducing alcohol intake, and avoiding fatty foods, caffeine and medications that can reduce lower oesophageal sphincter pressure (e.g. calcium channel blockers, anticholinergic agents, sedatives and theophylline). Foods that aggravate reflux symptoms should be avoided, and losing weight may also provide benefit.

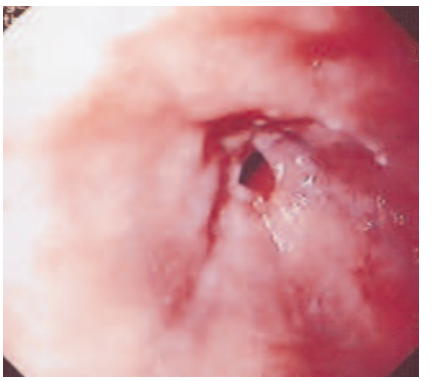
Avoiding large meals and recumbency for three hours after eating will reduce gastric distension that predisposes to transient lower oesophageal sphincter relaxations. Patients should be informed that their symptoms may be aggravated by lying on their right side, as well as by bending and heavy lifting.





Figures 3a and b. Two examples of Barrett's oesophagus (columnar metaplasia of the oesophagus).





Figures 4a and b. a (left). A barium swallow of a patient investigated for dysphagia for solid food. The appearance suggests a malignancy, but biopsies revealed it to be a benign peptic stricture. b (above). The stricture shown in Figure 4a, as seen at endoscopy.

Medical therapy

Medical treatment must be individualised according to symptoms and endoscopic findings. The goals of therapy are to:

- provide symptom relief
- heal oesophagitis
- prevent relapse and complications.

Further information regarding the use of acid suppression therapies for GORD is given in Table 3. The treatment of *Helicobacter pylori* infection in patients with GORD remains controversial; this is discussed further in the box on page 27.

Antacids

Mild and infrequent symptoms may be controlled with antacids. These should be used in conjunction with appropriate lifestyle modifications.

Acid suppression therapies

Acid suppression medication is generally indicated in patients who experience symptoms more than three times per week. Two approaches may be used:

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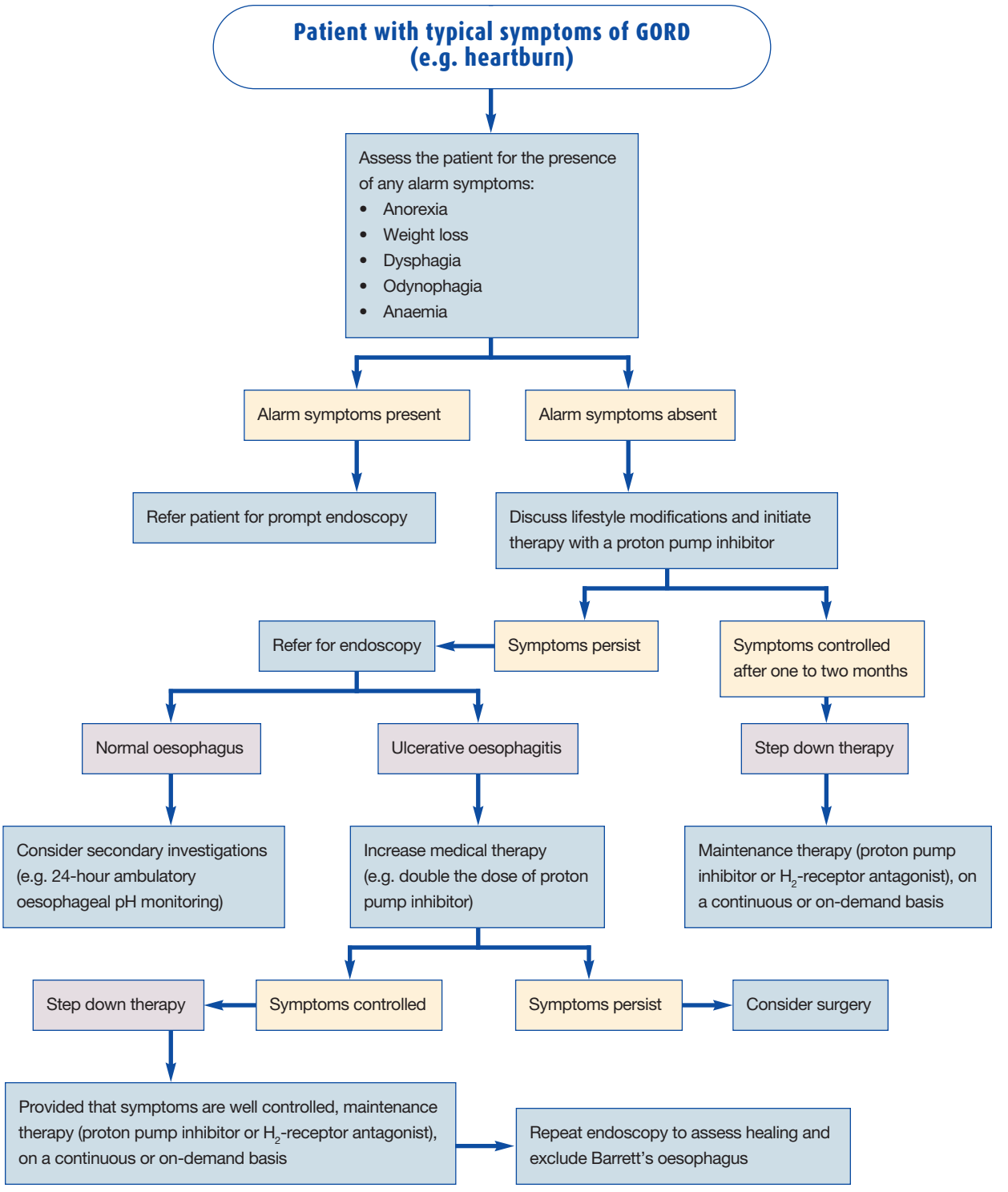
A guide to the management of GORD (step down approach)



- initiating treatment with an H_2-receptor antagonist and then 'stepping up' to more powerful medications if symptoms are not controlled
- initiating treatment with a proton pump inhibitor and then 'stepping down' therapy, provided that symptoms are controlled.

The second approach is becoming more popular for managing GORD and is appropriate for most patients. With this approach, symptom control is generally achieved rapidly and oesophagitis will usually heal within four weeks; in addition, drug exposure and costs are minimised.

Maintenance treatment must take into account the chronic relapsing nature of GORD and needs to be individualised accordingly. Medication can be used continuously or intermittently (i.e. on an on-demand basis, with the dose and class of agent selected and the duration of therapy being guided by symptoms). Use of on-demand therapy is particularly beneficial to patients whose symptoms occur infrequently.

For patients requiring continuous treatment, nocturnal acid breakthrough may occur, resulting in poor symptom control. Combining an H_2-receptor antagonist at bedtime and a proton pump inhibitor twice daily is often of benefit in this group, although tolerance to H_2-receptor antagonists may develop rapidly.

Table 3. Using acid suppression therapies for GORD*

The decision to use acid suppressants to treat GORD will depend on the severity and frequency of a patient's symptoms as well as any findings on endoscopy. Dosages must be individualised. If initial therapy fails to control symptoms or severe ulcerative oesophagitis is present the dosage may need to be increased. In the long term, maintenance treatment can be given on a continuous or on-demand basis using the lowest dose that continues to control symptoms. If symptoms are well controlled with current therapy there is no need to change to a new medication.

Proton pump inhibitors	Typical dosages
Esomeprazole (Nexium)	Initial therapy: 40 mg once daily Maintenance therapy: 20 mg once daily
Lansoprazole (Zoton)	Initial therapy: 30 mg once daily Maintenance therapy: 15 to 30 mg once daily
Omeprazole (Acimax, Losec, Maxor)	Initial therapy: 20 mg once daily Maintenance therapy: 10 to 20 mg once daily
Pantoprazole (Somac)	Initial therapy: 40 mg once daily Maintenance therapy: 20 to 40 mg once daily
Rabeprazole (Pariet)	Initial therapy: 20 mg once daily Maintenance therapy: 10 to 20 mg once daily
H_2-receptor antagonists	
Cimetidine	200 mg once daily to 800 mg twice daily
Famotidine (Amfamox, Pepcid, Pepcidine)	20 mg once daily to 40 mg twice daily
Nizatidine (Tazac)	150 mg once or twice daily
Ranitidine	150 mg once daily to 300 mg twice daily

* The above medications are listed alphabetically, with no preference being implied.

Prokinetic agents

Prokinetic agents act by increasing the tone of the lower oesophageal sphincter, improving oesophageal peristalsis and clearance and promoting gastric emptying. Accordingly, they are of most benefit when regurgitation is the predominant symptom. However, the efficacy of these agents is low, and side effects and noncompliance present problems.

The currently available prokinetic agents are domperidone (Motilium), metoclopramide (Maxolon, Pramin) and cisapride (Prepulsid); some dosage information is provided in Table 4. Common side effects of domperidone are a dry mouth and headaches, and there have been reports of adverse effects related to elevated serum prolactin (e.g. galactorrhoea) during long term use. The common side effects of metoclopramide include restlessness, drowsiness, fatigue and lassitude. Cisapride is no longer widely used in view of potential cardiotoxicity.

New forms of medical therapy

As transient relaxations of the lower oesophageal sphincter are the main mechanism underlying GORD, they provide a potential target for new therapies. A number of agents have already shown promise, including baclofen, a γ-aminobutyric acid agonist. Results from large trials are awaited.

Surgery

Antireflux surgery

The need for antireflux surgery has decreased since proton pump inhibitors were introduced. However, it is indicated in patients who fail to respond to appropriate medical therapy and it should be considered when regurgitation is a major symptom because medical therapy is often ineffective. The surgical option also needs to be discussed with young patients as an alternative to lifelong medical treatment.

Antireflux surgery, which is now frequently performed via laparoscopy, carries a low but not insignificant mortality

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rate, and complications (e.g. dysphagia, bloating, inability to belch and vomit) occur in up to 10% of patients. It should be performed only by surgeons who have extensive experience and skills in the procedure. At present there are no long term studies comparing medical therapy to laparoscopic surgery for treating patients with GORD. Finally, at least 20 to 30% of patients treated by fundoplication resume some form of medical therapy one to three years after surgery.

Hernia repair

Surgical repair is often required for rolling hernias, particularly large ones because of the risk of gastric volvulus. In patients who have a sliding hiatus hernia, treatment is directed at the associated reflux symptoms and surgery is generally not required.

Endoscopic procedures

Over the past few years, several endoscopic antireflux procedures have been developed. These have involved suturing, injecting a synthetic polymer or microspheres, or delivering radiofrequency energy (Stretta procedure) to the gastro-oesophageal junction. These procedures should be regarded as experimental, and they need to be subjected to large placebo-controlled trials so that they can be evaluated properly before they can be recommended.

Management of complications

Proton pump inhibitors are also the treatment of choice in patients with severe ulcerative oesophagitis because they have a much higher rate of healing than H_2-receptor antagonists (Figures 5a and b). In this group, follow up endoscopy should be performed after appropriate medical treatment to exclude the presence of Barrett's oesophagus that may have been obscured on initial endoscopy by coexisting ulceration.

With regard to Barrett's oesophagus, no form of treatment, medical or surgical, has been shown to result in its regression. Endoscopic surveillance is currently recommended every two years in these patients, with multiple oesophageal biopsy specimens taken to check for development of high grade dysplasia; if this is detected, surgery (or radiotherapy in those judged to be unfit for surgery),

MedicineToday PATIENT HANDOUT

Lifestyle modifications for patients with GORD

Addressing lifestyle factors that contribute to reflux is an important part of managing gastro-oesophageal reflux disease (GORD). Adopting the following measures may lead to an improvement in your symptoms:

- Stop smoking
- Avoid caffeine (coffee, tea, chocolate, cola drinks), fatty foods and foods that aggravate symptoms
- Reduce your alcohol intake if your consumption is excessive
- Lose weight (recommended for overweight patients)
- Avoid large meals
- Avoid lying down for three hours after eating, and avoid lying on your right side
- Elevate the head of the bed (15 cm blocks can be used)
- Avoid medications that reduce lower oesophageal sphincter pressure (e.g. calcium channel blockers, anticholinergics, sedatives, theophylline) – your doctor will discuss this with you
- Be aware that bending and lifting heavy objects may aggravate symptoms

This patient handout was prepared by Dr C. Pokorny.

Helicobacter pylori infection and GORD

Is H. pylori a risk factor?

Current evidence suggests that infection with *H. pylori* is not a risk factor for GORD. In fact, several studies have shown the prevalence of *H. pylori* infection to be lower in patients with reflux than in control groups.[1] Also, reflux symptoms may develop or worsen following eradication of *H. pylori* in patients with peptic ulcers, which suggests that the infection protects against development of GORD. Similarly, erosive oesophagitis reportedly occurs most often in the absence of infection with *H. pylori*.

Should H. pylori be eradicated?

Treatment of *H. pylori* infection in patients with GORD remains controversial. Concerns have been raised that the acid lowering capacity of the proton pump inhibitors may be impaired in those infected with this organism, but clinical trial data suggest that the presence of *H. pylori* in patients with GORD has little effect on the antisecretory efficacy of these agents. In addition, treatment of GORD with proton pump inhibitors in *H. pylori* infected patients has been reported to accelerate the development of atrophic gastritis, suggesting that the organism should be eradicated in these patients. Recent evidence does not support this concept.[2] Hopefully further studies will provide clearer direction in the near future.

References

1. Richter JE. *H. pylori:* the bug is not all bad. Gut 2001; 49: 319-320.
2. Lundell L. Gastro-oesophageal reflux disease and *Helicobacter pylori* or gastro-oesophageal reflux disease from *Helicobacter pylori*? Eur J Gastroenterol Hepatol 2001; 13 (Suppl 1): 23-27.

needs to be considered. Recent evidence suggests that NSAIDs and COX-2 specific inhibitors may reduce the incidence of oesophageal adenocarcinoma in patients with Barrett's oesophagus; however, these agents should not be prescribed for this purpose at this stage. Results of properly conducted studies are awaited.

For patients with benign strictures, oesophageal dilatation is indicated and, if successful, should be followed by aggressive acid suppressant therapy. The best agents in this situation are proton pump inhibitors, which should be continued lifelong because they have been shown to reduce the need for repeat oesophageal dilatation.

Management of GORD in pregnancy

GORD is common in pregnancy and may result in significant discomfort. Heartburn and regurgitation are the major presenting symptoms, and endoscopy is rarely required unless a complication occurs. Heartburn occurs in up to 80% of pregnant women – at least 25% experience it on a daily basis and the severity and frequency increase throughout pregnancy.

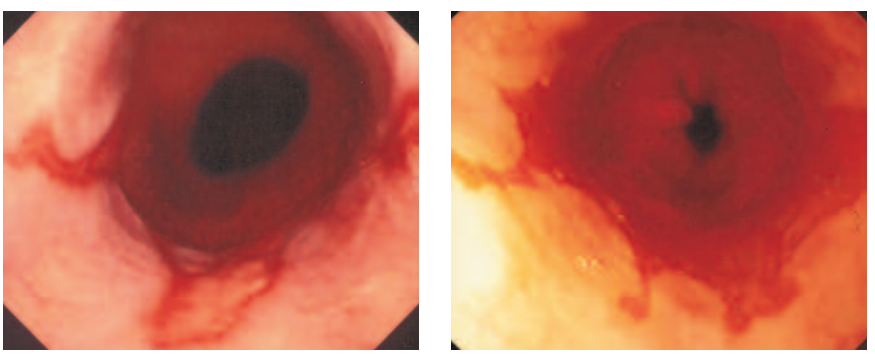
Initial management should be directed at lifestyle modification and changes to the patients diet. If medication is required, antacids, antacid/alginate combinations or sucralfate (Carafate, Ulcyte) are the treatments of choice. These agents have little systemic absorption and thus lead to few if any adverse effects to the fetus. However, caution should be advised regarding use of antacids containing magnesium in late pregnancy because these may slow labour and precipitate seizures.

For more persistent symptoms, an H_2-receptor antagonist should be considered (nizatidine is an exception because it is potentially teratogenic), although no large studies have been performed in pregnancy with these drugs. Prokinetic agents are not recommended in view of their side effects and possibly fetal toxicity. Proton pump inhibitors are best avoided unless absolutely necessary because no trial data are available with regard to their safety in pregnancy.

Table 4. Using prokinetic therapies for regurgitation

Prokinetic agent	Dosage
Domperidone (Motilium)	10 to 20 mg three times daily
Metoclopramide (Maxolon, Pramin)	5 to 10 mg three times daily
Cisapride (Prepulsid)*	15 to 40 mg daily in two to four divided doses (maximum 40 mg/day)

* Prior to commencing cisapride, an ECG should be performed to look for any QT prolongation.



Figures 5a and b. a (left). A case of severe ulcerative oesophagitis. b (right). The same patient, shown six weeks after treatment with a proton pump inhibitor. The oesophagitis has healed, but Barrett's oesophagus is evident.

Summary

GORD is a common condition that tends to run a chronic and relapsing course. Empirical treatment is appropriate when symptoms are mild and infrequent. However, when symptoms are persistent and severe or when they suggest a complication, investigation is indicated. Endoscopy is the best means of assessing the extent and severity of oesophagitis as well as diagnosing complications such as Barrett's oesophagus and ulceration.

The management of GORD, including endoscopy-negative disease, involves attention to lifestyle modification and use of acid suppressants. Symptom control is best achieved with a proton pump inhibitor and a 'step down' approach can then be adopted. Medical therapy usually needs to be continued lifelong, either continuously or on a symptom-driven basis. Unfortunately, symptoms frequently recur when treatment is ceased. Antireflux surgery is an alternative, but it should be considered only when medical therapy has failed or regurgitation is a major symptom, and also in young patients. Newer therapies directed at transient lower oesophageal sphincter relaxations are currently being trialled. MT

Further reading

1. Sifrim D, Zerbib F. Gastroesophageal reflux disease. Curr Opin Gastroenterol 2002; 18: 447-453.
2. Digestive Health Foundation. Gastro-oesophageal reflux disease in adults: guidelines for clinicians. Sydney: Gastroenterological Society of Australia, 2001.
3. Katz PO. Gastroesophageal reflux disease during pregnancy. Clin Perspect Gastroenterol 2000; 3: 164-167.
4. American Gastroenterological Association. Improving the management of GERD: evidence based therapeutic strategies. Peterson WL (Chair). Consensus opinion in gastroenterology. Bethesda, MD: AGA Press, 2002.