33 Dyspepsia and peptic ulcer disease

THE SPECTRUM OF DISEASE

Dyspepsia is the term used for a group of symptoms that arise from the upper gastrointestinal tract. They include heartburn, abdominal pain or discomfort, fullness, bloating, early satiety, belching and nausea. Dyspepsia can occur alone (nonulcer dyspepsia) or in association with various upper gastrointestinal disorders such as gastritis, peptic ulcer disease or gastro-oesophageal reflux disease (GORD).

NONULCER DYSPEPSIA

Nonulcer dyspepsia is probably caused by a combination of abnormalities in gastrointestinal motility, increased gastroduodenal sensitivity to mechanical distention and increased acid sensitivity in the duodenum.

PEPTIC ULCER DISEASE

Peptic ulceration describes both gastric and duodenal ulcers. The characteristic symptom of peptic ulceration is epigastric pain, but other dyspeptic symptoms also occur. Symptoms are not a reliable guide to the location of an ulcer. However, pain with duodenal ulceration is usually worse during fasting and at night and is relieved by antacids or by food. By contrast, pain with gastric ulcer may be made worse by food and gastric ulcer is more likely than duodenal ulcer to be associated with weight loss, anorexia and nausea. Chronic ulcers at either site can also be asymptomatic. Complications of peptic ulcers include bleeding, perforation and, if close to the pylorus, scarring with gastric outlet obstruction.

Mechanisms of protection of gastric and duodenal mucosa

The healthy gastric mucosa is able to resist acid digestion. There is an adherent layer of viscoelastic mucus that acts as a physical barrier to acid, and HCO_3^- is secreted into the mucus to neutralise acid locally. In addition, there is a high electrical resistance of, and tight junctions between, gastric mucosal cells, which make the mucosa relatively impermeable to luminal contents. Gastric mucosal blood flow provides an extra layer of defence, delivering HCO_3^- to buffer any H^+ ions that penetrate the mucosa and also regulating acid secretion. Many of these protective functions are dependent on synthesis of the prostaglandins PGE_2 and PGI_2 by gastric mucosal cells (see Chapter 29; Table 33.1).

The duodenal mucosa is protected by a layer of viscoelastic mucus, but the mucosal cells are highly permeable, permitting absorption of luminal nutrients. The mucosal cells secrete HCO_3^-, which accumulates in the mucus layer and buffers the pulses of gastric acid released from the stomach.

Aetiology of peptic ulceration

The aetiology of peptic ulceration is not fully understood, but many contributory factors have been identified. Gastric acid

Table 33.1 Factors associated with protection and damage of the intestinal mucosa

Factors associated with peptic ulcer disease	Factors associated with peptic ulcer protection and healing
Thin or breached mucus layer	Intact mucus layer
Helicobacter pylori and host immune response	Adequate blood flow
Reduced bicarbonate secretion	Bicarbonate in mucus layer
Reduced mucosal blood flow	Prostaglandins (generated by COX-1 and COX-2 isoenzymes)
Stress	Hydrophobicity of phospholipid layer of epithelial cells
Smoking	Regrowth of epithelial cell layer following damage (restitution)
Alcohol	Growth factors
Acid	Nitric oxide
Pepsin	
Iatrogenic (e.g. NSAIDs)	

NSAIDs, nonsteroidal antiinflammatory drugs.

is essential for ulceration to arise, and there is often failure of the normal luminal acid concentration to inhibit further gastric acid secretion. Pepsin secretion is also enhanced in people with peptic ulceration. Accelerated gastric emptying is a factor in promoting duodenal ulceration, with entry of gastric contents at a lower pH into the duodenum. Prostaglandins enhance mucosal protection against ulceration, and deficient production of prostaglandin E_1 is a factor in reducing resistance to mucosal erosion in both the stomach and duodenum.

Helicobacter pylori *and peptic ulceration*

A major risk factor associated with peptic ulceration is gastric and duodenal infection with the Gram-negative bacterium *Helicobacter pylori*. The incidence of *H. pylori* colonisation in the gastric mucosa varies widely in the adult population in different countries, being highest in those who have poorer living conditions. About 10–15% of the United Kingdom population is infected. Infection is usually acquired in childhood and persists unless it is treated. Infection with *H. pylori* is a risk factor for gastritis, peptic ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. However, only a small percentage of those who carry the bacterium develop *H. pylori*-associated disease, perhaps reflecting different host responses to the infection and whether the infecting strain carries particular factors for high virulence. *H. pylori* penetrates the mucus lining of the stomach and attaches to epithelial cells. It secretes the enzyme urease, which contributes to its survival during exposure to gastric acid by producing ammonia from urea. Ammonia is toxic to mucosal cells, and an immune response to the bacterial proteins also contributes to development of chronic inflammation.

Helicobacter pylori *and gastric ulceration*

Gastric ulceration is associated in about 70% of cases with *H. pylori* infection of the corpus of the stomach or both the corpus and antrum. In contrast to duodenal ulceration, there is no excess gastric acid secretion and often a reduction. *H. pylori* infection of the corpus is associated with the atrophy of acid-secreting cells and metaplasia of the gastric mucosa, which predisposes to gastric ulceration and gastric cancer.

Helicobacter pylori *and duodenal ulceration*

Infection with *H. pylori* is present in about 80% of people with duodenal ulcer, in whom it is predominantly found in the stomach but confined to the antral mucosa. The infection impairs secretion of somatostatin and therefore promotes secretion of gastrin from antral mucosal cells, which stimulates excess acid secretion from the body of the stomach. Exposure of duodenal cells to excess acid makes them more like gastric mucosal cells (gastric metaplasia) and allows duodenal colonisation by *H. pylori*.

Drugs and peptic ulceration

There is a higher incidence of peptic ulcer in people who use nonsteroidal antiinflammatory drugs (NSAIDs), including low-dose aspirin (see Chapter 29). NSAIDs are the most frequent cause of peptic ulceration in the absence of *H. pylori* infection. However, the prevalence of non-*H. pylori*, non-NSAID-associated gastric ulcers appears to be increasing in Western societies. Other drugs that are much less commonly associated with peptic ulcers include bisphosphonates, selective serotonin reuptake inhibitors (SSRIs) and spironolactone. Smoking and a high alcohol intake delay the healing of peptic ulcers, but there is less evidence that they are involved in the genesis of the ulcer.

GASTRO-OESOPHAGEAL REFLUX DISEASE

GORD can produce heartburn from regurgitation of gastric contents into the oesophagus (reflux), pain or difficulty in swallowing and even the regurgitation of gastric contents into the mouth. If reflux produces inflammation of the oesophageal mucosa (oesophagitis), there may be more prolonged chest pain and even chronic bleeding. Symptoms in GORD are usually chronic and relapsing, with at least two-thirds of those diagnosed still taking continuous or intermittent treatment after 10 years. GORD can precipitate asthma through the micro-aspiration of gastric contents into the lungs and triggering of vagal oesophago-bronchial reflexes. Micro-aspiration is also associated with chronic cough.

It is now believed that there are three distinct clinical groups of GORD rather than a steady progression of severity. These are possibly determined by genetic factors and the immunological response to reflux. The groups are

- Nonerosive reflux disease.
- Erosive oesophagitis, an acute inflammatory T-helper cell 1 (Th1) response (see Chapter 38).

- Barrett's oesophagus (intestinal metaplasia of oesophageal mucosal cells) with increased risk of cancer; this is a Th2-type immunological response (see Chapter 38).

Gastro-oesophageal reflux is produced by the generation of transient lower oesophageal sphincter relaxations (TLOSRs) in the absence of swallowing. TLSORs arise from stimulation of gastric vagal mechanoreceptors and allow gastric acid, pepsin and bile to come into contact with the vulnerable epithelium of the oesophagus. Oesophageal hypomotility and abnormal patterns of oesophageal contractility often coexist with GORD, which reduces the clearance of refluxed material. The disturbance of motility may reflect a sensory abnormality in the oesophageal mucosa. There is little correlation between the extent of oesophagitis at endoscopy and the severity of symptoms. Up to 50% of people with symptoms of GORD have no apparent oesophagitis, whereas severe oesophagitis can be asymptomatic unless complications such as stricture or anaemia arise.

The relationship of *H. pylori* infection to GORD is not straightforward. Antral infection predisposes to GORD by promoting greater amounts of gastric acid secretion, while corporal gastritis is protective partly because the acid content of the stomach may be reduced.

OESOPHAGEAL SPASM

Oesophageal spasm is a distinct disorder in which oesophageal pain is often not accompanied by any change in luminal pH. However, acid can induce spasm in some people with symptoms of reflux. The pain frequently occurs without evidence of oesophageal dysmotility, when the symptoms arise from a combination of local mucosal sensory disturbances and psychological factors.

CONTROL OF GASTRIC ACID SECRETION

Acid secretion into the canaliculi of gastric parietal cells is initiated by the activity of a membrane-bound proton pump that exchanges H^+ and K^+ across the cell membrane (H^+/K^+-ATPase). Hydrogen ions are obtained from carbonic acid (H_2CO_3) by carbonic anhydrase, and HCO_3^- enters the plasma in exchange for Cl^- ions. Chloride ions are then secreted into the stomach lumen with H^+ via a symport carrier. The activity of the proton pump is enhanced by several mediators, including histamine, gastrin and acetylcholine (Fig. 33.1).

DRUGS FOR TREATING DYSPEPSIA, PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE

ANTISECRETORY DRUGS

Antisecretory drugs reduce production of gastric acid. It is only necessary to raise intragastric pH above 3 for a few hours each day to promote healing of most peptic ulcers. However, rapid healing requires acid suppression for a minimum of 18–20 hours/day. The duration of acid suppression determines the rate of healing but not the eventual proportion of ulcers healed. Several classes of drug have antisecretory actions on the gastric mucosa.

Proton pump inhibitors

Examples

esomeprazole, lansoprazole, omeprazole, pantoprazole

Mechanism of action

The proton pump (H^+/K^+-ATPase) is the final common pathway for acid secretion in gastric parietal cells, and inhibition of the pump blocks acid secretion almost completely (see Fig. 33.1). Proton pump inhibitors are pro-drugs that are rapidly absorbed from the small intestine. As weak bases, they are selectively concentrated from the circulation into the acid environment of the secretory canaliculi of the gastric parietal cells. The drugs are then converted to active derivatives by protonation and covalently bind to and irreversibly inhibit the proton pump. The return of acid secretion is dependent on the synthesis of new proton pumps. Because protonation only takes place at acid pH, these drugs have a selective action on gastric parietal cells, and proton pumps elsewhere in the body are not inhibited. A single dose of a proton pump inhibitor inhibits acid production by up to 90% for approximately 24 hours.

Pharmacokinetics

Proton pump inhibitors are unstable in acid and are given orally as enteric-coated formulations. Esomeprazole, omeprazole and pantoprazole are also available as intravenous formulations. Elimination is by hepatic metabolism. They have short plasma half-lives, but because of the irreversible mechanism of action, these bear no relationship to the long duration of action.

Unwanted effects

- Gastrointestinal upset, such as nausea, vomiting, abdominal pain, diarrhoea, constipation.
- Headache.
- All proton pump inhibitors inhibit CYP2C9 and CYP2C19 in the liver to varying extents. This can give rise to drug interactions with other substrates of these isoenzymes – for example, decreasing the metabolism and increasing the clinical effects of warfarin, clopidogrel, phenytoin and several antiviral drugs (see Table 2.7). Esomeprazole may be less likely to cause such interactions than other proton pump inhibitors.

Concerns that substantial reductions of gastric acid, and the associated rise in gastrin secretion, might increase the risk of gastric cancer (comparable to the increased risk in pernicious anaemia) are unfounded. Proton pump inhibitors do not completely abolish acid secretion, and intragastric pH can still fall below 4 during part of the day, the critical pH below which bacterial populations that predispose to cancer cannot become established. However, symptomatic improvement following treatment with a proton pump inhibitor can mask the symptoms of pre-existing gastric cancer.

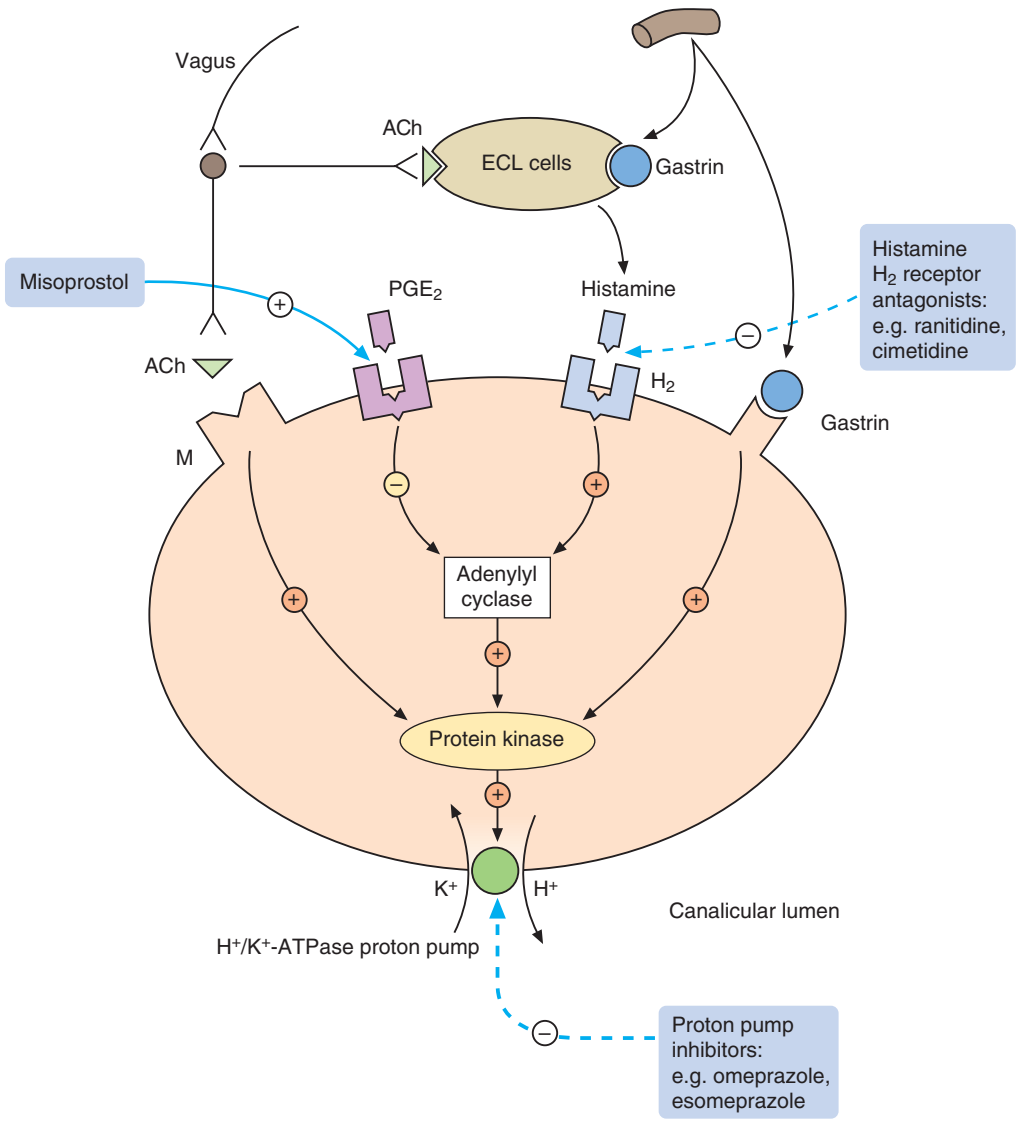

Fig. 33.1 **Control of gastric acid secretion from the parietal cell.** Acid secretion from the parietal cell is stimulated by acetylcholine (ACh), histamine and gastrin. Gastrin and ACh also reinforce acid secretion by causing the release of histamine from the enterochromaffin-like (ECL) cells, which lie close to the parietal cells in the gastric pits. Prostaglandin E_2 (PGE_2) reduces acid secretion. The sites of action of the main drugs used to inhibit acid secretion from the parietal cell are shown. There are no useful inhibitors of gastrin action, and the gastric-selective muscarinic receptor (M_1) antagonist pirenzepine is no longer available in the United Kingdom. *H_2*, Histamine type 2 receptor.

Histamine H_2 receptor antagonists

Examples

cimetidine, ranitidine

Mechanism of action

Histamine H_2 receptor antagonists act competitively with histamine at receptors on gastric parietal cells. They reduce basal acid secretion and pepsin production and prevent the increase in secretion that occurs in response to several secretory stimuli. Overall, acid secretion is reduced by about 60% (see Fig. 33.1).

Pharmacokinetics

Cimetidine and ranitidine are mainly eliminated unchanged by the kidney and have short half-lives between 1 and 4 hours.

Unwanted effects

- Diarrhoea and other gastrointestinal disturbances.
- Headache, dizziness, tiredness.

- Rash.
- Drug interactions: cimetidine is an inhibitor of hepatic P450 isoenzymes (see Table 2.7) and can increase the plasma concentrations and actions of drugs such as warfarin, phenytoin and theophylline. Other histamine H_2 receptor antagonists do not inhibit P450 isoenzymes.

ANTACIDS

Examples

aluminium hydroxide, magnesium trisilicate

Mechanism of action

Antacids neutralise gastric acid. They have a more prolonged effect if taken after food. If used without food, the effect lasts no more than an hour because of rapid gastric emptying. Antacids rapidly relieve symptoms in peptic ulcer disease, but large doses are required to heal ulcers. Liquid preparations work more rapidly, but tablets are more convenient to use. Most antacids are relatively poorly absorbed from the gut. Simeticone is sometimes added to an antacid as an antifoaming agent. The combination may reduce flatulence or relieve hiccups in palliative care.

Unwanted effects

- Constipation can occur with aluminium salts and diarrhoea with magnesium salts; mixtures of aluminium and magnesium salts may have less effect on stool consistency.
- Systemic alkalosis can occur with very large doses.
- In advanced renal failure, retention of absorbed aluminium may contribute to metabolic bone disease and encephalopathy. Magnesium salts can also cause hypermagnesia with weakness and confusion in renal failure.
- Drug interactions: aluminium salts can bind to NSAIDs and tetracyclines in the gut and reduce their absorption.

Antacids with alginic acid

Alginic acid is an inert substance. It is claimed that it forms a raft of high-pH foam that floats on the gastric contents and protects the oesophageal mucosa during reflux. All proprietary preparations combine alginic acid with an antacid, which is probably responsible for much of the clinical effect. Some formulations contain a high Na^+ concentration, which can be undesirable in people with fluid retention or hypertension.

CYTOPROTECTIVE DRUGS

Sucralfate

Mechanism of action

Sucralfate is a complex of aluminium hydroxide and sucrose octasulfate. It dissociates in the acid environment of the stomach to its anionic form, which binds to the ulcer base. This creates a protective barrier to pepsin and bile and inhibits the diffusion of gastric acid. Sucralfate also stimulates the gastric secretion of bicarbonate and prostaglandins.

Pharmacokinetics

Sucralfate is only slightly absorbed from the gut (<2%).

Unwanted effects

- Constipation.
- Bezoar formation (a mass trapped in the gut, usually the stomach), especially if gastric emptying is delayed.

Prostaglandin analogues

Example

misoprostol

Mechanism of action

Misoprostol is an analogue of PGE_1 and has several actions that protect the gastric and duodenal mucosae. It is most widely used to prevent NSAID-associated ulcers and is available in combination products with diclofenac or naproxen (see Chapter 29).

Pharmacokinetics

Misoprostol undergoes first-pass metabolism to active misoprostolic acid. Elimination is mainly by hepatic metabolism and it has a very short half-life (<1 hour).

Unwanted effects

- Diarrhoea and abdominal cramps are common.
- Uterine contractions: therefore misprostol is to be avoided in pregnancy. It can, however, be used to induce labour (see Chapter 45).
- Menorrhagia and postmenopausal bleeding.

MANAGEMENT OF DYSPEPSIA, PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE

NONULCER DYSPEPSIA

Most people with dyspepsia do not have significant underlying disease (i.e. they have nonulcer or functional dyspepsia). In all cases, efforts should be made to remove exacerbating agents, for example smoking, excess alcohol or NSAIDs. Upper gastrointestinal endoscopy may be indicated to assess the cause of symptoms. However, younger people (especially those under 55 years of age) who do not have ALARM symptoms (**a**naemia, **l**oss of weight, **a**norexia, **r**ecent onset of progressive symptoms, **m**elaena, haematemesis or dysphagia) are often treated initially without investigation.

A proton pump inhibitor is more effective than a histamine H_2 receptor antagonist for symptom relief in nonulcer dyspepsia. Treatment should be given for 4–6 weeks, followed by clinical review with the intention of reducing

the dose of drug or moving to intermittent or on-demand therapy for symptom relief. Eradication of *H. pylori* does not usually reduce symptoms. On the occasions it is effective (about 15% of people with suspected nonulcer dyspepsia), symptoms are probably due to undiagnosed peptic ulceration. Recurrent symptoms may prompt further investigation to exclude peptic ulceration or GORD.

CONFIRMED PEPTIC ULCERATION

Proton pump inhibitors produce the fastest rate of ulcer healing (over 90% of ulcers heal within 4 weeks). Histamine H_2 receptor antagonists usually give symptomatic relief for both gastric and duodenal ulcers within a week, but healing of the ulcer is much slower, requiring up to 8 weeks for duodenal ulcer or 12 weeks for gastric ulcer. Other agents such as sucralfate will heal ulcers in a similar proportion of people but are used less often, since they do not improve symptoms as quickly.

Eradication of *H. pylori* infection enhances ulcer healing and reduces relapse, so that maintenance therapy with acid-suppressing drugs is often unnecessary for uncomplicated ulcers. If *H. pylori* is not eradicated, 80% of ulcers will reoccur within a year; following successful eradication, the recurrence is less than 20%.

ERADICATION OF *HELICOBACTER PYLORI* INFECTION

Several indications for *H. pylori* eradication have been proposed based on acid suppression and antibacterial treatment (Box 33.1). Many eradication regimens are available: the most widely used is a high dose of proton pump inhibitor combined with two antibacterials (to maximise efficacy and minimise resistance) given for 1 week. The first choice antibacterials are clarithromycin with either amoxicillin or metronidazole, but it is important to avoid an antibacterial that has been used recently for treatment of other infections. Treatment for 2 weeks has a higher eradication rate, but unwanted effects often reduce adherence to the regimen, which limits the success rate. The incidence of in vitro resistance of *H. pylori* to metronidazole and clarithromycin is increasing. If in vitro clarithromycin resistance is detected, it is always reflected in a reduced ability to eliminate the bacterium clinically. By contrast, eradication may be successful even when laboratory resistance to metronidazole is demonstrated.

Box 33.1 Indications for eradication of *Helicobacter pylori*

Eradication recommended
Proven peptic ulcer
Low-grade mucosa-associated lymphoid tissue gastric lymphoma
Severe gastritis
After resection of early gastric cancer

Eradication suggested (less certain indications)
Functional dyspepsia
Family history of gastric cancer
Nonsteroidal antiinflammatory drug therapy
Intended long-term proton pump inhibitor therapy

Resistance to amoxicillin is less common, and resistance to tinidazole is currently lower than to metronidazole. Concurrent use of probiotic yoghurts can improve both tolerability and the outcome of eradication therapy.

H. pylori eradication with a triple regimen is successful in about 85% of cases in the United Kingdom and reinfection is rare. Testing to confirm eradication is required only if the indication for treatment was MALT lymphoma or peptic ulcer disease. Failure of eradication usually reflects antibacterial resistance or poor adherence to treatment. However, resistance to standard triple therapy is more common in some parts of the world, with a failure to eradicate *H. pylori* in up to 20% of people adherent to treatment. Further treatment should then be guided by the results of microbiological sensitivity tests on biopsy specimens or a third antimicrobial drug may be considered as part of the regimen.

After *H. pylori* eradication, it is usually possible to stop acid-suppression treatment for peptic ulcers, although it is normally continued for up to 3 weeks if the ulcer is large, has bled or has perforated. Longer-term therapy with acid-suppressant treatment is required only if symptoms continue and after exclusion of more serious conditions.

BLEEDING FROM PEPTIC ULCERS

Active bleeding from a peptic ulcer is a medical emergency. Endoscopic treatment applied to a visible vessel in the ulcer base using diathermy, clipping, laser coagulation or injection with adrenaline may stop the bleeding. Even after achieving haemostasis, recurrent bleeding occurs in up to 20% of cases. Endoscopic treatment should be followed by intravenous infusion of a high dose of proton pump inhibitor for 72 hours before changing to oral therapy. This reduces the rebleeding rate and the need for surgery by 30–40%. Proton pump inhibitors reverse the deactivation of the coagulation system and platelet aggregation in the gut mucosa that occurs when the local pH falls below 4.

PEPTIC ULCERATION ASSOCIATED WITH NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Ideally, the NSAID should be stopped. If continued treatment is essential, then NSAID-associated ulcers will usually heal if an ulcer-healing agent is co-prescribed. Continued use of NSAIDs can slow ulcer healing by histamine H_2 receptor antagonists but probably not by proton pump inhibitors. Eradication of *H. pylori* infection is recommended if an NSAID must be continued in someone who has had previous peptic ulceration, although this may prevent further ulcers only early in treatment with NSAIDs and is less effective during long-term use.

When an NSAID is first used, careful assessment is recommended to determine whether prophylaxis against ulceration should be given in the absence of upper gastrointestinal symptoms. Those at higher risk of NSAID-induced ulceration include people over 65 years of age, smokers, heavy alcohol users and those taking concomitant treatment with medicines that cause gastrointestinal irritation, such as corticosteroids. There is also an increased risk in people with a history of previous ulceration or those who have serious comorbidities, such as cardiovascular disease, diabetes mellitus or renal or hepatic impairment.

Misoprostol provides effective prophylaxis against NSAID-induced gastric or duodenal ulceration. However, a high dosage is necessary for prevention of ulcer recurrence, and this is often poorly tolerated because of colic or diarrhoea. Standard doses of a histamine H_2 receptor antagonist protect against NSAID-induced duodenal ulcers but not against gastric ulceration. Double the usual doses of a histamine H_2 receptor antagonist or standard doses of a proton pump inhibitor protects against both gastric and duodenal ulceration; these are better tolerated than misoprostol. There is limited evidence to support the use of a cyclo-oxygenase-2 (COX-2)-selective inhibitor with a proton pump inhibitor as a strategy to further reduce the risk of peptic ulceration in people at highest risk of ulceration. The combination of a COX-2-selective inhibitor with low-dose aspirin carries the same risk of ulceration as a conventional NSAID and should be avoided.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Initial measures for GORD include avoidance of tight clothing around the waist, smoking, and the use of alcohol and caffeine and encouraging weight loss. Raising the head of the bed on wooden blocks by 15 cm can promote symptom relief and mucosal healing. For mild persistent symptoms, reduction of gastric acid with antacids, with or without the addition of an alginate to provide a mechanical barrier, is often helpful. Alginates should be taken after meals to reduce their clearance by rapid gastric emptying. Eradication of *H. pylori* in GORD has no effect on symptoms.

Proton pump inhibitors are the most effective treatment for severe resistant or relapsing GORD. They will rapidly ease symptoms and heal oesophagitis within 8 weeks in up to 85% of those treated. Acid secretion can break through at night during treatment with a proton pump inhibitor. This may be important in severe erosive oesophagitis or Barrett's oesophagus; in this situation esomeprazole may be more effective than other proton pump inhibitors. Failure to heal oesophagitis with a proton pump inhibitor often indicates bile reflux rather than acid reflux.

Histamine H_2 receptor antagonists usually relieve heartburn in up to 50% of people after 4 weeks of treatment. However, oesophagitis heals in only about 20% of cases. Better healing rates can be achieved by using double the standard dosages, with healing in 70–80% of cases by 8–12 weeks.

Intermittent therapy with healing agents or the use of an alginate after healing often controls recurrent symptoms. For severe or resistant reflux disease, long-term use of a proton pump inhibitor is the only effective drug treatment, although about 60% of people will need only a low maintenance dose after healing has occurred. Laparoscopic antireflux surgery is increasingly used for resistant GORD, particularly if there is high-volume reflux.

OESOPHAGEAL SPASM

The frequency of oesophageal spasm can be reduced by regular use of a proton pump inhibitor when it is induced by oesophageal reflux. Pain due to oesophageal spasm, with or without associated reflux, can respond to smooth muscle relaxants such as calcium channel blockers (see Chapter 5), nitrates (see Chapter 5) or sildenafil (see Chapter 16). Local injection of botulinum toxin (see Chapter 24) has also been successful in limited studies.

SELF-ASSESSMENT

True/false questions

1. Histamine acts on H_1 receptors on the parietal cell to stimulate acid secretion.
2. Vagal stimulation of the parietal cell increases acid secretion.
3. An unwanted effect of antacids containing magnesium salts is diarrhoea.
4. Antacids are not effective in healing peptic ulcers.
5. Cimetidine can potentiate the effects of other drugs by inhibiting cytochrome P450 enzymes.
6. Ranitidine is associated with a lower incidence of gynaecomastia than cimetidine.
7. Cimetidine reduces acid secretion by more than 90%.
8. Esomeprazole is a prodrug.
9. The active metabolite of lansoprazole is a reversible proton pump inhibitor.
10. Omeprazole inhibits the cytochrome P450 system in the liver.
11. Prostacyclin (prostaglandin I_2, PGI_2) reduces gastric mucosal blood flow.
12. Misoprostol causes constipation.
13. Histamine H_2 receptor antagonists and proton pump inhibitors are not useful for treatment of ulcers induced by NSAIDs.
14. Sucralfate binds to the ulcer base and promotes ulcer healing.

One-best-answer (OBA) question

1. Identify the least accurate statement about *H. pylori*.
   - A. *H. pylori* infection in the gastric antrum reduces acid secretion.
   - B. *H. pylori* infection can be found in the duodenum in people with duodenal ulcers.
   - C. If *H. pylori* is not eliminated, a duodenal ulcer is likely to recur.
   - D. *H. pylori* is a risk factor for the development of gastric cancer.
   - E. *H. pylori* frequently develops resistance to antibacterial treatment.

Case-based questions

A 56-year-old man, Mr T.K., was newly appointed as headmaster of a large comprehensive school and was experiencing some difficulties with the increasing demands of the job. He increased his smoking from 5 to 20 cigarettes a day and drank 10 units of alcohol a week. He had a good, varied diet. He had suffered intermittently from dyspepsia for some years, taking proprietary antacids when required. His symptoms then increased and the pain caused him to waken most nights. He bought a supply of ranitidine from the local chemist without consultation with the pharmacist. Following 2

weeks of treatment, his symptoms were successfully relieved and he was symptom-free for 3 months. His symptoms then returned and he took further treatment with ranitidine for 2 weeks. He was symptom-free for a further month, but when symptoms returned again he consulted his general practitioner (GP).

1. Why did his symptoms return?
2. Would his symptoms have been less likely to return following a short course of a proton pump inhibitor?
3. What should be the GP's course of action?

   An endoscopic examination revealed a duodenal ulcer.
4. Why do some people infected with *H. pylori* develop gastric ulcers and some duodenal ulcers?
5. What eradication therapy for *H. pylori* should be given, and is a proton pump inhibitor beneficial when given with antibacterial therapy?

   The eradication therapy given was 7 days with omeprazole, amoxicillin and clarithromycin. Mr T.K. was symptom-free for 6 weeks but then his symptoms returned.
6. What were the possible reasons for the return of the symptoms?
7. What treatment could be given?

ANSWERS

True/false answers

1. **False.** The histamine receptors on parietal cells that stimulate acid secretion are H_2 receptors, which are selectively antagonised by ranitidine and cimetidine.
2. **True.** The vagal neurotransmitter acetylcholine stimulates muscarinic receptors, which increases acid secretion.
3. **True.** Magnesium salts may cause diarrhoea, and antacids containing aluminium salts may cause constipation.
4. **False.** Antacids can heal peptic ulcers, but their effects are slower than those of proton pump inhibitors or histamine H_2 receptor antagonists.
5. **True.** Cimetidine – but not famotidine, nizatidine or ranitidine – inhibits cytochrome P450 isozymes and should be avoided in people taking warfarin, phenytoin or theophylline.
6. **True.** Cimetidine is more likely than other histamine H_2 receptor antagonists to cause galactorrhoea in women or gynaecomastia in men by inhibiting oestrogen metabolism.
7. **False.** Histamine H_2 antagonists reduce acid secretion by only about 60% because these drugs do not block other stimuli for acid secretion, such as gastrin and acetylcholine.
8. **True.** Like other proton pump inhibitors, esomeprazole is converted to its active form by protonation in acid conditions. It is therefore selectively active on the proton pump in the gastric parietal cell but not on proton pumps in other tissues that operate at higher pH.
9. **False.** The active metabolites of proton pump inhibitor prodrugs are irreversible inhibitors and fresh protein must be synthesised to replace the inhibited proton pump.
10. **True.** Omeprazole can inhibit the metabolism of drugs such as warfarin or phenytoin by both CYP2C9 and CYP2C19. Proton pump inhibitors differ in their inhibitory activity on cytochrome P450 isozymes, with pantoprazole and rabeprazole thought to have the least effect.
11. **False.** Part of the gastroprotective action of PGI_2 and PGE_2 is by increasing gastric mucosal blood flow, removing back-secreted H^+ and providing HCO_3^- to buffer the H^+ ions. They also increase mucus secretion and decrease acid secretion.
12. **False.** Misoprostol is a prostaglandin analogue. Prostaglandins can increase gastrointestinal motility and secretions and cause diarrhoea.
13. **False.** Both histamine H_2 antagonists and proton pump inhibitors can cause healing of NSAID-induced ulcers. Proton pump inhibitors may produce more rapid healing as this is probably related to the degree of acid suppression.
14. **True.** The mucosal protectants sucralfate and bismuth salts have been largely superseded, although bismuth chelates (with low bismuth content) still have a place as quadruple therapy with PPIs and antibacterial drugs when triple therapy fails.

One-best-answer (OBA) answer

1. **Answer A** is the *least accurate* statement.
   - A. **Incorrect**. Acid secretion is *enhanced* by *H. pylori* infection in the antrum, while infection in the corpus is associated with reduced or unchanged acid secretion.
   - B. Correct. Increased acid secretion caused by antral infection produces changes in the duodenal mucosa that enable duodenal colonisation by *H. pylori*.
   - C. Correct. Following healing with a proton pump inhibitor, approximately 80% of duodenal ulcers will recur within a year if *H. pylori* is not eradicated.
   - D. Correct. *H. pylori* infection increases the risk of developing gastric adenocarcinoma by five- to sixfold.
   - E. Correct. In some countries *H. pylori* resistance to metronidazole is as high as 90%.

Case-based answers

1. This man could have nonulcer dyspepsia or peptic ulceration. Ranitidine for only 2 weeks of treatment is available without prescription; if it had been continued, the symptoms would probably have been suppressed longer. If he is *H. pylori*-positive and has nonulcer dyspepsia, it is likely that he will develop peptic ulcer disease in the future. If he is *H. pylori*-positive and has peptic ulceration, failure to eradicate *H. pylori* is likely to result in a recurrence of peptic ulcer within a year.
2. If *H. pylori* is present, the symptoms will still recur in a high percentage of individuals.
3. It is recommended that any person over 55 years of age, such as Mr T.K., be referred for endoscopic examination. *H. pylori* infection can be detected noninvasively using a blood test (antibody to urease), a stool antigen test or a radiolabelled (^{13}C) urea breath test. In a gastric antral biopsy, it can be detected using bacterial culture, histopathology or a rapid urease (CLO) test. Use of

NSAIDs, tobacco and alcohol consumption should be assessed, as these are strongly contributory to ulcer disease and/or will prevent healing.

4. The reasons why some people develop gastric ulcers and others develop duodenal ulcers are imperfectly understood. If there is only antral inflammation and *H. pylori* is present, more gastrin and therefore excess acid is produced, resulting in duodenal ulcers. If a pangastritis exists, it is associated with corporal atrophy, lower levels of acid secretion and gastric ulcers.
5. Numerous treatment regimens have been evaluated. One week of therapy with a proton pump inhibitor (or ranitidine, if intolerant) plus two antimicrobials (clarithromycin and either metronidazole or amoxicillin, in a combination dictated by local sensitivities) results in a 70%–90% eradication rate.
6. It is possible that the strain of *H. pylori* was resistant to the antibiotics used. Tests should be carried out to see whether *H. pylori* is still present after treatment. If necessary, quadruple therapy or longer treatment periods should be used.
7. Culture sensitivities of the *H. pylori* in a biopsy specimen could be sought. Quadruple therapy, which has 93%–98% success, could be used; for example, a proton pump inhibitor (or histamine H_2 receptor antagonist) plus bismuth chelate plus metronidazole (or tinidazole) plus tetracycline (Fig. 33.2).

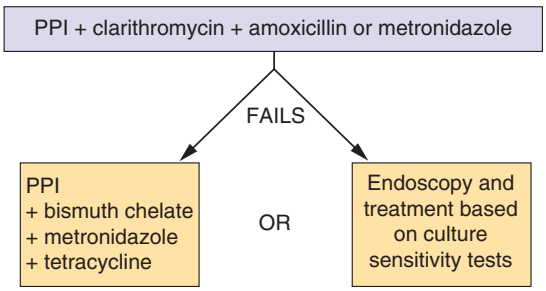

Fig. 33.2 **Recommended regimens for the eradication of *H. pylori*.** Many regimens exist, dictated by local patterns of sensitivity and resistance. Increasing resistance to metronidazole and clarithromycin is reducing the success rate of the triple regimen. If the proton pump inhibitor (PPI) is not tolerated, a histamine H_2 receptor antagonist can be substituted. If initial eradication fails, quadruple therapy with a PPI (or histamine H_2 antagonist), bismuth chelate (tripotassium dicitratobismuthate), metronidazole (or tinidazole) and tetracycline can be used, or the person can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

FURTHER READING

Bredenoord, A.J., Pandolfino, J.E., Smout, A.J.P.M., 2013. Gastro-esophageal reflux disease. Lancet 381, 1933–1942.

Ford, A.C., Moayyedi, P., 2013. Dyspepsia. Br. Med. J. 347, f5059.

Katz, P.O., Gerson, L.B., Vela, M.F., 2013. Diagnosis and management of gastroesophageal reflux disease. Am. J. Gastroenterol. 108, 308–328.

Lau, J.Y.W., Barkun, A., Fan, D.-M., et al., 2013. Challenges in the management of acute peptic ulcer bleeding. Lancet 381, 2033–2043.

Li, B.-Z., Threapleton, D.-E., Wang, J.-Y., et al., 2015. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network analysis. Br. Med. J. 351, h4052.

Malfertheiner, P., Chan, F.K.L., McColl, K.E.L., 2009. Peptic ulcer disease. Lancet 374, 1449–1461.

McColl, K.E.L., 2010. *Helicobacter pylori* infection. N. Engl. J. Med. 362, 1597–1604.

Sinha, M., Gautam, L., Shukla, P.K., et al., 2013. Current perspectives in NSAID-induced gastropathy. Mediators Inflamm. 2013, 258209.

Talley, N.J., Ford, A.C., 2015. Functional dyspepsia. N. Engl. J. Med. 373, 1853–1863.

Tutuian, R., Castell, D.O., 2006. Oesophageal spasm—diagnosis and management. Aliment. Pharmacol. Ther. 23, 1393–1402.

Compendium: drugs used for dyspepsia and peptic ulcer disease

Drug	Characteristics
Antisecretory agents	
H_2 receptor antagonists	
Cimetidine	May cause drug interactions by inhibiting cytochrome P450 enzymes. Given orally. Half-life: 1–3 h
Famotidine	Does not affect cytochrome P450 enzymes. Given orally. Half-life: 3–4 h
Nizatidine	Does not affect cytochrome P450 enzymes. Given orally or by intravenous infusion. Half-life: 1–2 h
Ranitidine	No effect on cytochrome P450 enzymes. May be given orally, by intramuscular injection, or by slow intravenous injection or infusion. Half-life: 2–3 h

Compendium: drugs used for dyspepsia and peptic ulcer disease (cont'd)

Drug	Characteristics
Proton pump inhibitors	
Because of the irreversible mechanism of action of the active metabolites, the proton pump inhibitors have much longer durations of action than indicated by the half-life of the parent compound. All may cause drug interactions by inhibiting hepatic CYP2C9 and/or CYP2C19 isoenzymes (see Table 2.7).	
Esomeprazole	The S-isomer of omeprazole; may cause fewer CYP450 drug interactions than omeprazole. Given orally, or by intravenous injection or infusion. Half-life: 1–2 h
Lansoprazole	Possibly fewer CYP450 drug interactions than omeprazole. Given orally. Half-life: 1–2 h
Omeprazole	Potent inhibition of CYP450 isoenzymes may cause drug interactions. Given orally or by slow intravenous injection (over 5 min) or infusion. Half-life: 1 h
Pantoprazole	Possibly fewer CYP450 drug interactions than omeprazole. Given orally or by slow intravenous injection (over 2 min) or infusion. Half-life: 1 h
Rabeprazole	Fewer CYP450 drug interactions than omeprazole. Given orally. Half-life: 1–2 h
Cytoprotective agents	
Given orally	
Misoprostol	Prostaglandin E_1 analogue; pro-drug of misoprostolic acid. Used to prevent NSAID-associated ulcers in the frail or very elderly from whom NSAIDs cannot be withdrawn. Half-life: 0.3 h
Sucralfate	Mucosal protectant that forms ulcer-adherent complex. Minimal absorption (<2%)
Tripotassium dicitratobismuthate	A chelate of bismuth that acts as a mucosal protectant. Low bismuth content is not associated with encephalopathy seen with older, high-bismuth preparations (no longer recommended). Used in gastric and duodenal ulcers and in *Helicobacter pylori* eradication when initial treatment fails
Other drugs	
Alginic acid	Alginates form a viscous gel ('raft') that floats on the surface of the stomach contents, reducing acid reflux. Usually combined with antacids
Antacids	Antacids include aluminium hydroxide, sodium carbonate, and magnesium trisilicate, carbonate or hydroxide. Antacids neutralise acid within the stomach. May be combined with simeticone, an antifoaming agent
Antimicrobials	Used with a PPI to eradicate *H. pylori* infection. See Chapter 51

PPI, proton pump inhibitors.