Peptic ulcer disease
an update on diagnosis and treatment

The two major causes of peptic ulcer disease are H. pylori infection and NSAID use. Treatment involves combination therapy for eradication of H. pylori and acid suppression therapy. In patients who need to continue NSAID therapy, maintenance antiulcer therapy should be co-prescribed.

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Peptic ulcer disease is an important differential diagnosis in the patient with dyspepsia (upper abdominal discomfort or pain often associated with bloating). Uncomplicated peptic ulcer disease classically presents as epigastric burning pain one to three hours after meals or when the person is hungry, which is relieved by antacids or eating. The pain is often nocturnal. Symptoms tend to persist for weeks to months, and recur over months to years.

It is important to obtain a careful history of nonsteroidal anti-inflammatory drug (NSAID) use, including low dose aspirin and over-the-counter medications. It is not possible to discriminate between duodenal and gastric ulcers on the basis of symptoms alone. Abdominal tenderness has little diagnostic value.

The main differential diagnoses of dyspepsia are:
- functional (or nonulcer) dyspepsia
- peptic ulcer disease
- gastro-oesophageal reflux disease
- biliary disease
- malignancy
- cardiac ischaemia.

Gastro-oesophageal reflux disease usually presents with heartburn and regurgitation, often worse with recumbency or straining. Table 1 lists alarm symptoms for cancer, which necessitate referral for early endoscopy (Figure 1).

Complications of ulcer disease include minor or major bleeding, ulcer perforation and gastric outlet obstruction.

IN SUMMARY

- **Peptic ulceration requires eradication of *H. pylori* if present. Follow up with an investigation such as the urea breath test is necessary to ensure eradication.**
- **Endoscopy is indicated in older patients with dyspepsia, patients with alarm symptoms or those taking NSAIDs.**
- **Endoscopy should also be considered in younger patients with dyspepsia of more than two weeks in spite of antacid treatment or a short course of H_2-receptor antagonists.**
- **Patients who have had complicated ulcer disease should have a follow up endoscopy to assess ulcer healing.**
- **Even low dose aspirin can cause gastroduodenal ulceration. In the setting of cardiovascular or cerebrovascular prophylaxis, less ulcerogenic medications should be considered.**
- **For prevention of NSAID ulceration in the setting of continued NSAID therapy, co-prescription of a proton pump inhibitor or misoprostol is necessary.**
- **Maintenance therapy of H_2-receptor antagonists at half dosage at night or proton pump inhibitors before breakfast should be considered in patients with a high risk of ulcer.**

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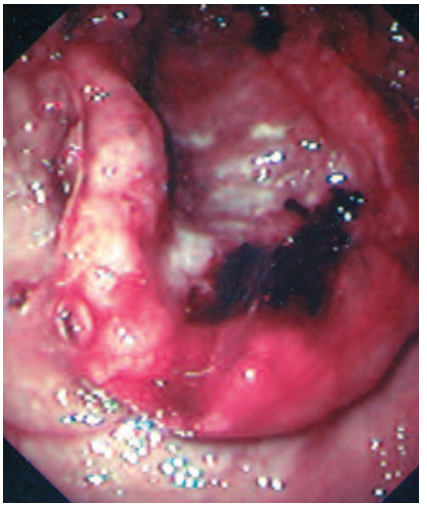

Figure 1. Malignant gastric ulcer in a patient presenting with dyspepsia and weight loss. Patients with alarm symptoms should have early endoscopy.

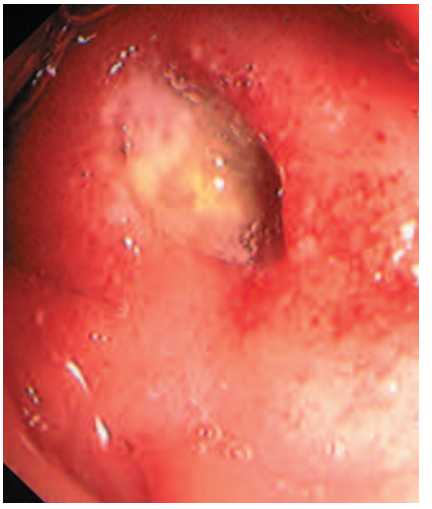

Figure 2. Duodenal ulcer and duodenitis due to *Helicobacter pylori* infection. Eradication therapy has prevented recurrent ulceration.

Causes of peptic ulcer disease

By far, the two major causes of peptic ulcer disease are *Helicobacter pylori* infection and NSAID use. There are also idiopathic causes and, less commonly, Zollinger–Ellison syndrome (hypergastrinaemia), Crohn's disease, malignancy, viral infection, radiation therapy, chemotherapy and vascular insufficiency.

H. pylori infection

H. pylori is a spiral shaped, Gram-negative bacillus which has a long history of asymptomatic infection, with only a minority of individuals progressing to peptic ulceration. Up to 95% of duodenal ulcers (Figure 2) and 70% of gastric ulcers are caused by the organism, although the percentage of '*H. pylori* negative' ulcers is increasing.

H. pylori colonises the gastric mucosa and causes a mucosal inflammatory infiltrate of mostly neutrophils in response to increased interleukin-8, produced from direct contact with the gastric epithelium. It is thought that different strains have different ulcerogenicity, those with the *cag A* gene inducing a more severe inflammatory mucosal response. *H. pylori* infection is also associated with elevated gastrin levels and, in patients with duodenal ulcer, increased acid secretion, which plays an important role in the cause of duodenal ulceration. Additionally *H. pylori* impairs basal and acid-stimulated bicarbonate secretion, which is a major protective factor in the duodenum.

NSAID use

NSAIDs can cause gastrointestinal complications at any stage during their use, although most ulcers occur with high doses and in the first month of therapy. Abnormalities can persist even after one year of cessation. Even low dose aspirin carries a significant risk of gastrointestinal bleeding; studies have shown aspirin to be the NSAID most commonly taken in the setting of upper gastrointestinal tract complications, and most implicated in ulcer relapse after healing. Rectally administered NSAIDs can cause ulcers because of their systemic action. Risk factors for NSAID-related gastrotoxicity are listed in Table 2.

NSAID ulcers are often silent in nature, and their first presentation may be complicated peptic ulcer disease such as bleeding. Ulcers are often antral in location and may be multiple. Anticoagulants and corticosteroids act synergistically with NSAIDs to cause gastric injury. Alendronate has been associated with gastric ulcers, and its use with NSAIDs increases the relative risk of developing ulceration. Some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) combined with NSAIDs increases bleeding risk.

Table 1. Alarm symptoms in patients with dyspepsia

- Anorexia
- Dysphagia
- Gastrointestinal bleeding
- New symptoms in people aged >45 years
- Unexplained anaemia
- Weight loss
- Vomiting

Investigation

Prompt endoscopy is the investigation of choice in older patients with dyspepsia, patients with alarm symptoms (Table 1) or those taking NSAIDs. Endoscopy should also be considered in younger patients with dyspepsia that has persisted for more than two weeks in spite of antacid treatment or a short course of H_2-receptor antagonists. An alternative strategy in younger patients involves noninvasive screening for *H. pylori* (see the box on page 35) with the intention to treat if it is present. Prolonged empirical therapy of dyspeptic patients with acid-lowering treatment is to be discouraged because most of these patients come to have an endoscopy at a later date and the initial diagnosis may have been obscured by such treatment.

It is helpful to reassure the patients before endoscopy that their symptoms

are unlikely to be due to cancer and that the symptoms may be due to 'nonulcer dyspepsia' or 'nervous dyspepsia'. A normal endoscopy generates more anxiety in some patients than an abnormal one, and 'pretest counselling' often helps the later difficult questions resulting from the expectancy of an ulcer being found.

Patients with persistent heartburn due to reflux should also have endoscopy to look for oesophagitis (50% of patients with reflux) or Barrett's oesophagus (in up to 10% of patients with chronic reflux). A small percentage will have coexisting peptic ulceration.

Patients with gastric ulcers require a biopsy to exclude malignancy and endoscopic follow up for healing, except in those with obviously benign antral ulcers. Gastric biopsies for *H. pylori* should always be taken when peptic ulceration is present (see the box on this page).

Barium studies for the assessment of dyspepsia and heartburn are obsolete.

Treatment

General principles

In general, duodenal ulcers should be treated for four weeks and gastric ulcers for eight weeks with either an H_2-receptor antagonist administered between the evening meal and bedtime or proton pump inhibitors before breakfast. *H. pylori* should be eradicated if present.

H_2-receptor antagonists

H_2-receptor antagonists reversibly inhibit the action of histamine on the gastric parietal cell histamine receptor. The optimal time for dosing H_2-receptor antagonists in the treatment of duodenal ulcer is before bedtime. In the absence of *H. pylori* and NSAIDs as causes of the ulcer, H_2-receptor antagonists should be prescribed for an eight week trial. They all have similar efficacy and are used in the following doses:

- ranitidine 300 mg at night or 150 mg twice a day
- nizatidine (Tazac) 300 mg at night or 150 mg twice a day
- famotidine (Amfamox, Pepcid, Pepcidine) 20 mg twice a day or 40 mg at night.

After four to six weeks of treatment approximately 80% of duodenal ulcers will have healed.

Proton pump inhibitors

Proton pump inhibitors, such as lansoprazole (Zoton), omeprazole (Acimax, Losec, Maxor), pantoprazole (Somac) and rabeprazole (Pariet), give potent acid suppression by inhibiting the gastric enzyme H^+/K^+-ATPase, and they heal gastroduodenal ulcers more rapidly than

Table 2. Risk factors for NSAID-related gastrotoxicity

- Age >65 years
- Alcoholism
- Family history of NSAID-related ulceration
- General debility
- History of previous ulcer
- Concurrent use of corticosteroids, anticoagulants or bisphosphonates
- High dose NSAIDs
- No co-therapy with antiulcer agents
- Previous NSAID complications
- Prolonged or multiple NSAID use

Testing for H. pylori

Noninvasive tests

Serological testing detects the presence of IgG antibodies to *H. pylori* and is highly sensitive (>80%) and specific (90 to 99%). It cannot be used in demonstrating eradication because antibody titres remain elevated for an indefinite period after cure. Rapid serological test kits are available and the test can be performed in the office.

Urea breath testing is the most sensitive (90 to 99%) and specific (92 to 100%) means of diagnosing current *H. pylori* infection. It can be used as follow up to an eradication regimen and in the screening of dyspeptic patients. It assesses the entire gastric mucosa and thus decreases sampling error. Orally administered urea labelled with either nonradioactive ^{13}C or radioactive ^{14}C is hydrolysed to ammonia and carbon dioxide by the urease produced by *H. pylori*. The carbon dioxide diffuses into the bloodstream and is excreted by the lungs. Urea labelled with the nonradioactive ^{13}C can be safely used in children and women of childbearing age.

Stool antigen testing involves assaying for *H. pylori* antigen in stool samples, but, despite comparable sensitivity and specificity to the urea breath test, impracticality will limit its use.

Invasive tests

Mucosal biopsy during endoscopy can detect *H. pylori* infection through histological testing, rapid urease testing and culture.

Histological testing requires three or more samples for reliable results (sensitivity 80 to 100%; specificity >95%). Haematoxylin–eosin staining is commonly used.

Rapid urease testing detects the change in pH in a medium that occurs when the urease produced by *H. pylori* liberates ammonia and carbon dioxide from urea. It is performed on a biopsy specimen taken during endoscopy. Such testing has a sensitivity of 80 to 95% and specificity of 95 to 100%.

***H. pylori* culture** has a role in determining antimicrobial susceptibilities in the research setting.

Note: With the urea breath test, histological test and rapid urease test, false negatives can arise if there has been recent treatment with proton pump inhibitors, antimicrobials or bismuth compounds.

do H_2-receptor antagonists. High risk ulcer patients – such as those with ulcer complications, those with frequent recurrences, *H. pylori*-negative patients and those in whom combination therapy has been unsuccessful – should be considered for maintenance therapy. Maintenance regimens include H_2-receptor antagonists at half the ulcer healing dose at night, or proton pump inhibitors before breakfast.

H. pylori eradication

H. pylori eradication regimens are based on combination triple or quadruple therapies. Higher eradication rates occur with 14 days of therapy, but seven to 10 days appears sufficient in duodenal ulceration in a population with a low prevalence of antibiotic resistance.

Triple therapy comprises:

- a proton pump inhibitor (omeprazole 20 mg or lansoprazole 30 mg) or ranitidine bismuth citrate 400 mg, twice a day; with
- amoxycillin 1 g twice a day; and
- clarithromycin 500 mg twice a day or metronidazole 400 mg three times a day.

Quadruple therapy comprises:

- a proton pump inhibitor (omeprazole 20 mg or lansoprazole 30 mg) twice a day; with
- tetracycline HCl 500 mg four times a day
- ranitidine bismuth citrate 400 mg twice a day or colloidal bismuth subcitrate 107.7 mg four times a day
- amoxycillin 500 mg four times a day.

Resistance to metronidazole is common and to clarithromycin is increasing, whereas resistance to tetracycline and to amoxycillin is uncommon. Triple therapy failure warrants treatment with quadruple therapy, not re-treatment with triple therapy.

Patient compliance is essential to successful therapy. Prepackaged triple therapies are available for omeprazole with amoxycillin and clarithromycin (Klacid Hp7, Losec Hp7) or with amoxycillin and metronidazole (Losec Helicopak), as well as for bismuth compounds (Pylorid-KA Compliance Pack [ranitidine bismuth subcitrate, amoxycillin plus clarithromycin], Helidac [colloidal bismuth subcitrate, metronidazole plus tetracycline]), which allows for less complicated dosing.

Patients should be cautioned against alcohol consumption while being treated with metronidazole because it can interact with alcohol in a similar fashion to disulfiram (Antabuse). Nausea is a common side effect, which should settle after the course is completed.

Long term therapy with H_2-receptor antagonists or proton pump inhibitors should be considered in *H. pylori* treatment failures, especially in the elderly.

Confirmation of H. pylori eradication

It is necessary to confirm *H. pylori* eradication after appropriate treatment because treatment failure puts the patient at risk of ulcer recurrence. The urea breath test is the best follow up test. Antimicrobial therapy should have been completed at least four to six weeks before re-testing and proton pump inhibitors ceased at least one to two weeks beforehand. H_2-receptor antagonists have no effect on results of culture, histology or the ^{13}C urea breath test.

NSAID ulceration

Approaches to treatment of NSAID-induced ulceration include cessation of medication, medication substitution with a less ulcerogenic drug and antiulcer therapy. If *H. pylori* is present, it should be eradicated with combination therapy.

Change in drug regimen

For patients in whom it would be impractical to withdraw NSAID therapy, dose reduction or use of a less gastrotoxic NSAID may be effective. Individual NSAIDs vary greatly in their gastrotoxicity, ibuprofen being the least toxic. Diclofenac also has a low risk of toxicity.

Low dose aspirin has been associated with serious peptic ulcer complications, and in patients on aspirin for cardioprotective and cerebrovasculoprotective reasons, other less ulcerogenic antiplatelet therapies such as clopidogrel (Iscover, Plavix) should be considered.

COX-2-specific inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx), spare the COX-1 isoenzyme, which is thought to be largely responsible for the maintenance of gastrointestinal mucosal integrity. COX-1 is involved in the synthetic pathway of protective mucosal prostaglandins. A recent study comparing celecoxib to the traditional NSAIDs ibuprofen and diclofenac showed similar anti-inflammatory properties but significantly higher rates of ulcers and ulcer complications with ibuprofen and diclofenac.

Antiulcer medication

Antiulcer drug treatments promote ulcer healing and should be co-administered with continued NSAID use to prevent recurrence. Healing occurs usually within eight weeks and should be followed up with endoscopy.

Misoprostol (Cytotec), a prostaglandin analogue, prevents NSAID ulceration, but side effects such as diarrhoea can reduce compliance. The diarrhoea may be addressed by low initial dosing with gradual increase and by dosage at meal times. It has been shown that co-prescription of at least 200 μg misoprostol three times a day with NSAIDs reduces ulcer incidence.

H_2-receptor antagonists accelerate the healing and prevent the occurrence of duodenal ulcers with NSAID discontinuation. High dose H_2-receptor antagonists are effective in ulcer healing, but standard dosing has little benefit in NSAID-induced gastric ulcer prophylaxis.

As maintenance therapy, omeprazole has also been found to be superior to

misoprostol and ranitidine, and allows ulcer healing in the setting of continued NSAID use.

H. pylori eradication is advised in the setting of *H. pylori*-positive NSAID ulcers because eradication may reduce ulcer complications and ulcer recurrence.

Management of ulcer complications

The management of haemorrhage, ulcer perforation and gastric outlet obstruction is discussed below. It is recommended that patients who have had ulcer complications should have a follow up endoscopy to assess healing.

Haemorrhage

Patients presenting with haematemesis or melaena are best assessed in the hospital setting. Symptoms and signs of haemodynamic compromise should be sought: dizziness, syncope, chest pain, tachycardia, hypotension or postural hypotension. Signs of liver disease should be looked for to help rule out the possibility of variceal bleeding. A per-rectum examination should be done to look for melaena and determine its freshness. Melaena is black, not dark brown, stools. Iron and bismuth also cause black stools.

Upper gastrointestinal endoscopy should be performed early. Therapeutic endoscopy, including thermocoagulation, bipolar coagulation, ulcer injection therapy, clip therapy and argon plasma coagulation, is used in actively bleeding ulcers and with ulcers that have visible vessels (Figure 3).

Despite endoscopic therapy, rebleeding can occur in 15 to 20% of patients. High dose intravenous omeprazole infusion has been shown to reduce the rate of recurrent bleeding, decrease the need for endoscopic treatment and blood transfusions, and shorten hospital stay. An 80 mg omeprazole bolus is given, followed by an infusion of 8 mg per hour for 72 hours. This maintains a high intragastric pH, which has been shown *in vitro* to facilitate platelet aggregation and therefore stabilise clots.

PHOTOGRAPH COURTESY OF DR CHRIS POKORNY, SYDNEY

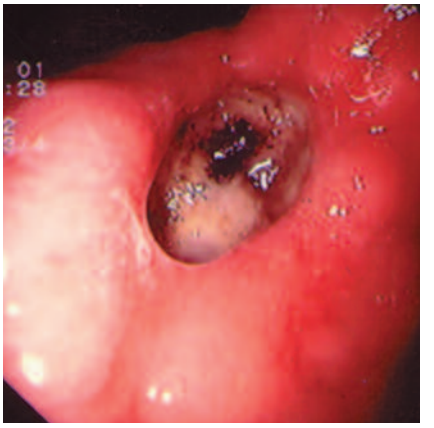

Figure 3. Gastric ulcer with a visible vessel in a patient presenting with life threatening haematemesis. The patient was taking low dose aspirin. A visible vessel denotes a high risk of rebleeding.

Ulcer perforation

Ulcer perforation is an uncommon complication, but it tends to occur in NSAID ulceration more than in any other type of ulceration probably because of the silent nature of NSAID ulcers.

Perforation may present with sudden abdominal pain, pyrexia, anorexia or confusion, with signs of an acute abdomen as well as tachycardia, hypotension and lack of bowel sounds. Symptoms and signs may be masked by corticosteroids, opiates, old age or serious comorbidity.

Plain abdominal x-rays may show a pneumoperitoneum or ileus.

Without delay, the patient with ulcer perforation should be resuscitated aggressively with intravenous fluids, made nil by mouth, given antibiotics and taken to the operating theatre for perforation closure.

Gastric outlet obstruction

Gastric outlet obstruction may present with bloating, early satiety, anorexia, nausea and vomiting. The diagnosis is made on endoscopy. The patient may need resuscitation with intravenous fluids and electrolytes; nasogastric decompression and intravenous proton pump inhibitors should be commenced. If conservative therapy fails, endoscopic balloon dilation then surgery are used.

Ulcer prevention

NSAIDS should be prescribed with care, using the lowest possible dose and the least gastrotoxic agent. Patients should also be educated about the risks of ulceration and the attendant complications when taking NSAIDs. In long term NSAID users, haemoglobin levels should be monitored to aid in the detection of asymptomatic ulcers.

Smoking cessation should be advised.

Conclusion

Peptic ulcer disease is an important differential diagnosis in the dyspeptic patient. Treatment is aimed at the two major causes – *H. pylori* infection and NSAID use – and involves combination therapy for eradication of *H. pylori* and acid suppression therapy.

In the patient who must continue NSAID therapy, maintenance therapy consisting of a proton pump inhibitor or misoprostol should be co-prescribed. H_2-receptor antagonists and proton pump inhibitors may be considered in patients who are at high risk of ulcer recurrence.

COX-2-selective NSAIDs have been shown to significantly decrease the rate of ulcer incidence while retaining their anti-inflammatory properties and so may well decrease the incidence of NSAID-related ulceration in the future. MT

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