

UNIT NO. 2

GASTRITIS AND PEPTIC ULCER DISEASE

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ABSTRACT

Gastritis is often used to describe dyspeptic symptoms when it is a histological diagnosis and usually asymptomatic. Peptic ulcer disease has been decreasing due to increased use of acid suppressant drugs and eradication of *H.pylori*. NSAID induced ulcer bleeding in elderly patients is however on the rise. *H.pylori* is a significant cause of both duodenal and gastric ulcers. Eradication of *H.pylori* infection is the key to ulcer healing and prevention of relapse. The usual cause for failure of *H.pylori* eradication is antibiotic resistance of the *H.pylori* strain to metronidazole. Peptic ulcer not caused by *H.pylori* are almost always caused by NSAIDs. Both barium meal and endoscopy are appropriate investigations for dyspepsia. Various drugs such as PPI, H2 receptor antagonist, antacids, prostaglandin analogues and mucosal protective agents can be used to treat peptic ulcer. The complications of peptic ulcer are bleeding, perforation, peritonitis and gastric outlet obstruction.

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GASTROPATHY AND GASTRITIS

Gastropathy refers to epithelial cell damage and regeneration of the gastric mucosa and little or no accompanying inflammation. It is usually caused by aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). These drugs inhibit the cyclo-oxygenase (COX1) pathway in the intestinal mucosa resulting in depletion of prostaglandins and subsequent damage. Other causes include infections, e.g. cytomegalovirus and herpes simplex virus, and alcohol in high concentration.

Gastric erosions are also associated with severe stress (stress ulcer), burns (Curling's ulcer) and in renal and liver disease. Symptoms include indigestion, vomiting and haemorrhage. Erosions (superficial mucosal breaks < 3mm) and subepithelial haemorrhage are usually seen at endoscopy. Treatment is with a proton pump inhibitor (PPI) and removal of the offending cause if possible. In patients who continue to take aspirin or NSAIDs, prophylactic PPI should be considered.

Inflammation of the gastric mucosa (gastritis) is commonly caused by *Helicobacter pylori* (*H.pylori*) (identified in 1983) infection. Less common causes include viruses, duodenogastric reflux and autoimmune gastritis (with pernicious anaemia

associated with antibodies to gastric parietal cells and intrinsic factor). Gastritis is a histological diagnosis and is usually discovered incidentally when a gastric mucosal biopsy is taken for histology at endoscopy. It is classified as acute (predominantly neutrophilic infiltration) or chronic (with predominant infiltration by lymphocytes, plasma cells and macrophages). Gastritis is usually asymptomatic; whether *H.pylori* gastritis itself produces functional dyspepsia is controversial. At endoscopy the mucosa may appear reddened or normal. No specific treatment is required although eradication treatment for *H.pylori* is often given.

Gastritis is often used to describe dyspeptic symptoms as well as endoscopic or radiological appearance of the gastric mucosa thus giving rise to considerable confusion.

PEPTIC ULCER DISEASE

H.pylori is responsible for over 95% of duodenal ulcers and up to 80% of gastric ulcers. Most *H.pylori* negative ulcers are caused by NSAIDs. Duodenal Crohn's disease and the Zollinger-Ellison Syndrome (gastrinoma induced gastric acid hypersecretion) are rare causes. Peptic ulcer disease have been decreasing, due to increased use of acid-suppressive drugs and the eradication of *H.pylori*. NSAID induced ulcer bleeding in elderly patients is however on the rise.

Diagnosis**History**

Pain is typically epigastric, but can occur in the lower chest or upper abdomen. It is sometimes described as a discomfort or burning and is usually meal related: occurring 1 to 3 hours after meals, waking the patient up at night and is relieved by food (hunger pain), antacids and vomiting. Severe pain usually radiates to the back. Back pain can also be caused by pancreatic penetration of a posterior wall ulcer. Remissions and exacerbations of pain is characteristic

Post prandial vomiting may be due to gastric outlet obstruction caused by oedema and spasm around an acute pyloric canal ulcer or by scarring from chronic prepyloric or duodenal ulcers.

Occasionally, patients with duodenal ulcer gain weight because eating relieves their pain. Gastric ulcer patients sometimes lose weight because of inadequate intake to avoid post prandial pain.

Bleeding or perforation are sometimes the only presentation in the elderly and in patients taking NSAIDs.

Physical examination

Epigastric tenderness may be present but clinical examination is usually normal. A palpable upper abdominal mass and/or the presence of cervical lymphadenopathy raises the possibility of gastric cancer. A positive gastric succussion splash more than 5 hours after intake of food or drink suggests gastric outlet obstruction.

Investigations

Both barium meal and endoscopy are appropriate investigations, depending on availability, cost and patient preference.

A gastric ulcer appears as a niche on a barium meal study and radiological features can usually distinguish a benign from a malignant ulcer. It is often difficult to distinguish duodenal ulcers from deformity due to spasm or scarring and duodenal ulcer healing cannot be confirmed radiologically. If an ulcer is diagnosed radiographically, the presence or absence of *H.pylori* can be determined by a non-invasive test such as the carbon-13 or carbon-14 isotope-labelled urea breath test or by serology.

Endoscopy is generally more sensitive in the diagnosis of duodenal ulcer. Gastric biopsies may also be taken during endoscopy to test for the presence of *H.pylori* by histology, culture or the urease test. Endoscopy is the preferred investigation in a patient presenting with upper gastrointestinal haemorrhage as a bleeding lesion or one that have bled can be identified easily with this procedure. Endoscopic haemostasis can also be attempted in appropriate cases.

Gastric acid secretory testing and serum gastrin estimations are not generally indicated.

Treatment

Eradication of *H.pylori* infection is the key to ulcer healing and prevention of relapse. Attention to the type of ulcer, its cause and the presence of risk factors would help guide further management (Table 1). Because of the possibility of cancer, gastric ulcers should be biopsied and followed up to healing.

If healing does not occur within twelve weeks gastric surgery is indicated. Healing of a painless bleeding ulcer should be documented (by endoscopy).

Treatment of the acute ulcer

Peptic ulcer associated with *H.pylori* infection

A one week triple therapy regimen is successful in eradicating *H.pylori* (non-detection of *H.pylori* one month after completion of therapy) in over 90% of cases. Eradication should be confirmed, especially in patients with complicated ulcers. The recommended method to confirm treatment outcome is the non-invasive urea breath test, one month after completion of therapy. Serology is not useful as antibody titres may not fall for several months after eradication and may remain above the threshold for a positive test.

If symptoms have resolved by the end of triple therapy, no further treatment may be required for uncomplicated ulcers (majority of patients). Patients who presented with bleeding or who have persisting symptoms may be continued on 4 to 6 weeks of proton-pump inhibitors (PPI).

The usual cause for failure of *H.pylori* eradication in a patient who has been compliant in completing the course is antibiotic resistance of the *H.pylori* strain. The commonest cause is resistance to metronidazole. There is great variation in the population and geographic prevalence of metronidazole resistance which has been reported to be as high as 60-70% in some populations. Resistance to clarithromycin and amoxycillin is generally low although the former is rising. In populations known to have a high prevalence of metronidazole resistance (e.g. above 40%), it is advisable to select a regime which does not include the latter. For failures of triple therapy, the recommendation is to prescribe quadruple therapy for one week (Table 2) or, if the first course of triple therapy included metronidazole, to repeat the treatment regime substituting amoxycillin in place of metronidazole.

Table 1: Management of peptic ulcer

Factors :	Management Action
Type of ulcer	
Gastric ulcer	Requires biopsy to exclude malignancy Requires confirmation of healing by endoscopy
Duodenal ulcer	Endoscopic confirmation of healing generally not required if symptoms resolve after adequate treatment, except in patients who presented with bleeding
Cause of ulcer disease	
Has the patient used NSAIDs?	If yes, evaluate indication for NSAID; Stop if possible; consider non-ulcerogenic substitutes: eg cimetidine instead of aspirin for cardiovascular prophylaxis; non-NSAID analgesics such as paracetamol or codeine; cox-2 inhibitors.
Is <i>H.pylori</i> infection present?	Treat <i>H.pylori</i>
Risk factors	
Is patient a smoker?	Advise to stop smoking

Table 2: Drug regimens for treating *Helicobacter pylori*:

Recommended first-line triple therapy for eradication of *Helicobacter pylori*:

PPI bid+ clarithromycin 500 mg bid+ amoxicillin 1 g bid, for one week

PPI bid+ clarithromycin 500 mg bid+ metronidazole* 400 mg bid, for one week

If clarithromycin is not available, either of the following may be considered:

PPI bid + amoxicillin 1 g bid + metronidazole* 400 mg bid, for one week

Colloidal bismuth subcitrate 120 mg qid + metronidazole 400 mg bid + tetracycline 500 mg qid, for two weeks.

Quadruple therapy for failures after first-line treatment:

PPI bid + colloidal bismuth subcitrate 120 mg qid + metronidazole 400 mg bid + tetracycline 500 mg qid, for one week.

NB: PPI=proton pump inhibitor in standard dose

* avoid the use of metronidazole as first-line therapy in regions with a high prevalence of metronidazole resistance.

Peptic ulcers not associated with *H. pylori* infection

Peptic ulcers not associated with *H. pylori* infection are treated with a PPI for 4 (duodenal ulcers) to 8 (gastric ulcers) weeks. NSAIDs should be stopped if possible to ensure optimal ulcer healing and should not be continued in patients who present with bleeding.

Follow-up and long term treatment

The relapse rate of peptic ulcers have fallen from 80% to less than 20% with eradication of *H. pylori* infection.

For peptic ulcer disease not due to *H. pylori* infection, one of the following can be considered after initial ulcer healing:

- Intermittent therapy: Treat when ulcer symptoms recur
- Maintenance therapy: Recommended for patients with complicated ulcer disease, for the elderly and for patients with concomitant medical illnesses who might not be able to stand the stress of ulcer complications. A single nocturnal dose of a PPI / H2 receptor antagonist is given long term. Duodenal ulcers occurring during maintenance treatment usually run a benign course. Relapse and healing of gastric ulcers during maintenance therapy should be documented because of the risk of malignancy.

Drugs used in the treatment of peptic ulcer

Proton pump inhibitors

These are extremely potent acid-inhibitory agents. Four drugs are available in this class: omeprazole (Losec), 20 to 40 mg daily, lansoprazole (Prevacid), 30 to 60 mg daily, pantoprazole (Controloc) 40 mg daily, and rabeprazole (Pariet), 20 mg daily. Proton pump inhibitors heal peptic ulcers faster than H2 receptor antagonists at recommended doses. Generic preparations have resulted in the widespread use of these agents.

H2 receptor antagonists

These drugs were the mainstay of peptic ulcer treatment for two decades. Five preparations are presently available. Cimetidine can be given in one of three ways: 200 mg with

each of the three meals plus 400 mg at night, 400 mg morning and night or 800 mg at night. Ranitidine and nizatidine are given at doses of 150 mg twice daily or 300 mg once nightly. The recommended dosage for famotidine is 20 mg twice daily or 40 mg once nightly, while that for roxatidine is 75 mg twice daily or 150 mg once nightly. Maintenance treatment is given as a single nocturnal dose (cimetidine 400 mg, ranitidine or nizatidine 150 mg, famotidine 20 mg, roxatidine 75 mg). H2 receptor antagonists are remarkably safe. Uncommon side effects include gynaecomastia and mental confusion, the latter usually in elderly patients with impaired renal function. Cimetidine should not be used together with warfarin, theophylline, phenytoin or cyclosporin A as it interferes with hepatic drug metabolism.

Antacids

Antacid preparations delivering 30 mEq of buffering capacity taken four times daily (i.e. 120 mEq buffering capacity daily) are effective in healing duodenal ulcers. Such high doses invariably give rise to bowel disturbances: diarrhoea in magnesium-containing preparations, constipation in aluminium-containing preparations. Standard doses relieve ulcer pain without healing the ulcer. Antacids are generally very safe. Several formulations e.g. magnesium trisilicate BP, have high sodium contents and should be avoided in some patients. There numerous antacid preparations and no single formulation is clearly superior. Antacids in tablet form should be thoroughly chewed before swallowing. Most antacid preparations contain simethicone which is useful for flatulence.

Prostaglandin analogues

Misoprostol reduces gastric acid secretion and is cytoprotective. It is less effective than H2 receptor antagonists, causes diarrhoea and because of its effects on uterine muscle is not recommended for women who may be pregnant. It is useful for the prevention of gastric ulcer in patients taking NSAIDs. The usual dose is 200 ug four times daily or 400 ug twice daily.

Mucosal protective agents

Colloidal bismuth does not affect gastric acid secretion but is

as effective as H₂ receptor antagonists in healing ulcers. Ulcers healed with bismuth have a lower relapse rate and this has been attributed to its bactericidal effect against *H. pylori*. The usual dose is two tablets twice daily. Disadvantages include darkening of stools (indistinguishable from melaenic stools) and occasional exacerbations of ulcer pain.

Sucralfate also has no effect against acid production and works by coating the ulcer surface. Constipation is a frequent side-effect.

Surgery

In the era of powerful acid-inhibitory drugs and *H. pylori* eradication therapy, elective surgery for duodenal ulcers is now obsolete. Elective partial gastrectomy is appropriate for the gastric ulcer suspected of being malignant.

Other considerations

Smoking delays ulcer healing and increases recurrence and should be discouraged. There is no evidence that alcohol has an adverse effect on peptic ulcers. Chillies, spices and sour foods often aggravate the pain of peptic ulcer (non-ulcer dyspepsia) although there is no evidence that they are harmful to ulcer disease. Available evidence of stress being important in the aetiology of ulcer disease is conflicting.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND PEPTIC ULCER

NSAIDs cause mucosal injury of the gastrointestinal tract. Most people taking full doses of NSAIDs develop superficial mucosal injury in the form of petechiae or erosions while 10-25% develop endoscopic ulcers. A considerably lower proportion of people develop clinical symptoms of ulcer disease or complications including hemorrhage and perforation. NSAIDs have been shown to increase the risk of peptic ulcer complications by 3 to 10 times, and for some specific NSAIDs the risk is higher. Even low dose aspirin taken for cardiovascular or cerebrovascular prophylaxis increases the chance of ulcer hemorrhage or perforation by 2 to 4 times. Complicated ulcers are more likely in elderly females, smokers and those with a history of ulcer.

NSAIDs and *H. pylori* infection are independent and additive risk factors for ulcer disease and complications. For patients with a history of ulcer disease or complications, testing and eradication of *H. pylori* is recommended before starting NSAID medication including aspirin for cardioprotection,

Reducing the risk of NSAID induced ulcers.

- Use alternative analgesics when appropriate e.g. paracetamol or codeine.
- Use 'safer' NSAIDs e.g. ibuprofen which has been found to have the least risk of gastrointestinal bleeding.

- Use the lowest effective dose of any NSAIDs.
- Use formulations which reduce local gastric damage e.g. soluble, enteric-coated or slow-release aspirin and slow-release ketoprofen, rectal or parenteral preparations (e.g. indomethacin suppositories, ketoprofen injection), but it is not known whether they produce less gastric damage than oral preparations.
- Use COX-2 inhibiting NSAIDs e.g. celecoxib, rofecoxib and meloxicam which have been demonstrated to have a lower incidence of gastrointestinal complications and adverse reactions than conventional NSAIDs. Anti-inflammatory actions of NSAIDs are mediated via inhibition of COX-2, whereas gastric injury is mediated by blockage of COX-1.
- Coadministration of proton pump inhibitors or misoprostol reduces the risk of development of NSAID-related ulcers. Concurrent usage of antacids have not been found to be beneficial.

COMPLICATIONS OF PEPTIC ULCER

Over a lifetime, 15-20% of ulcer patients will experience one or more episodes of gastrointestinal haemorrhage, 1-2% will perforate while less than 1% will develop pyloric stenosis. Gastric ulcer is not a pre-malignant condition.

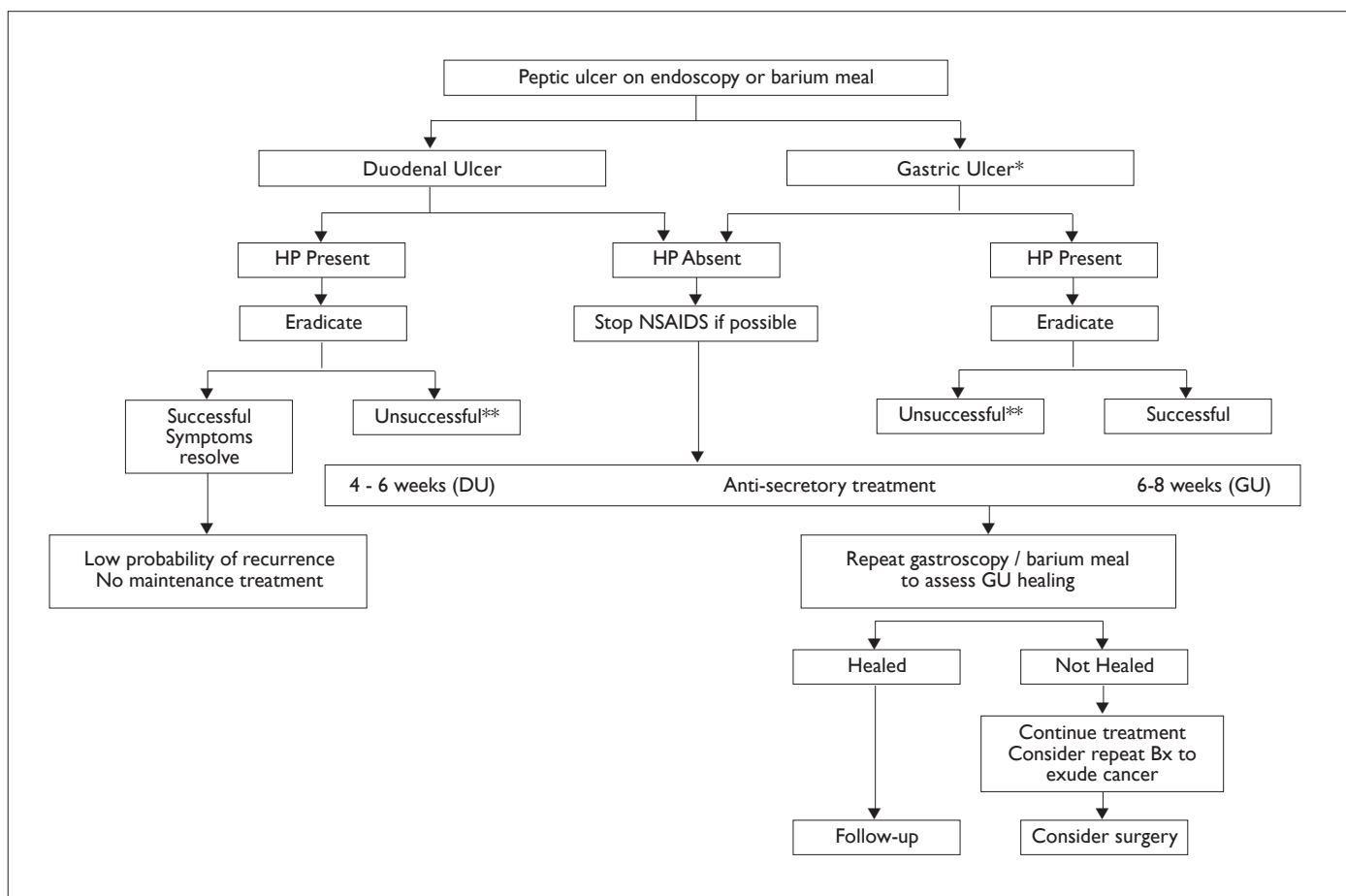
Bleeding

Patients present with haematemesis and/or melaena. The vomitus is usually coffee ground in colour (gastric acid effect), but may be bright red if bleeding is profuse. Melaenic stools are loose, sticky, tarry black and have a characteristic odour. Melaena is easily distinguishable from the greyish-greenish stool caused by ingestion of iron preparations.

Gastrointestinal bleeding is a medical emergency. An immediate assessment of the haemodynamic status should be performed and transfusion commenced if appropriate. Diagnostic gastroduodenoscopy is preferred to barium studies as:

- (1) endoscopy may help to determine which of multiple lesions have bled,
- (2) bleeding superficial mucosal lesions are very often missed on radiology,
- (3) endoscopic haemostasis may be appropriate.

During gastroduodenoscopy, actively bleeding ulcers or non-bleeding ulcers with visible vessels have the highest mortality rates, and endoscopic treatment by injection therapy (with adrenaline 1:10,000 or polidocanol), electrocoagulation or heater-probe therapy is indicated. A significant decrease in mortality has been demonstrated among patients with the above criteria who received endoscopic treatment. The two major complications of endoscopic therapy, perforation and induction of uncontrollable bleeding, are rare.

Table 3: Algorithm – Uninvestigated typical reflux symptoms

Notes: * Gastric ulcers should be biopsied to exclude malignancy

** Quadruple therapy given for failed triple therapy

Emergency surgery carries a significantly higher mortality rate, but if necessary, should be performed earlier rather than later.

Perforation

Ulcer perforation presents with severe unremitting pain and features of peritonitis. Treatment is surgical.

Gastric outlet obstruction

Wasting, dehydration and electrolyte disturbances indicate severity. A trial of supportive therapy with gastric decompression, parenteral rehydration and anti-secretory drugs is indicated as obstruction may be due to oedema and spasm which would resolve with ulcer healing. Surgery is indicated if adequate supportive therapy fails.

THE REFRACTORY ULCER

Most ulcer patients become asymptomatic within a few days of initiation of treatment. About 95% of all ulcers will heal if therapy is continued for up to 12 weeks. The term 'refractory ulcer' applies to ulcers which persist beyond this.

Consider the following:

- Are medicine dosages adequate and optimal?
- Was the patient compliant?
- Is the diagnosis correct? Consider Irritable bowel OR Gastric Cancer. Endoscopy is indicated if the initial diagnosis has been made radiologically. Does the patient have a gastrinoma? Estimation of serum gastrin and calcium levels and gastric secretory testing may be indicated.
- Is the patient a heavy smoker and has he stopped smoking?
- Is the patient on NSAIDs?

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LEARNING POINTS

- **Gastritis is a histological diagnosis. It often used to describe dyspeptic symptoms as well as endoscopic or radiological appearance of the gastric mucosa thus giving rise to considerable confusion.**
 - **Gastritis and Peptic ulcer is usually caused by *Helicobacter pylori* infection.**
 - **Endoscopy is the investigation of choice for dyspepsia.**
 - **Gastric cancer can masquerade as a gastric ulcer, and when seen the latter must be biopsied and followed to healing.**
 - **Peptic ulcers not caused by *Helicobacter pylori* are almost always due to NSAIDs although both can be independent aetiologies.**
 - **Peptic ulcer relapse can be prevented by *Helicobacter pylori* elimination.**
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