

## Acute Gastrointestinal Bleeding: Part I.

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### ABSTRACT

**Objective:** *To review the management of acute gastrointestinal bleeding in the critically ill patient in a two part presentation.*

**Data sources:** *Articles and a review of studies reported from 1991 to 2001 and identified through a MEDLINE search of the English language literature on acute gastrointestinal bleeding.*

**Summary of review:** *Gastrointestinal bleeding is a relatively frequent problem in the critically ill patient. Common causes include acute stress ulceration (ASU), peptic ulceration and bleeding oesophageal varices. Non-variceal upper gastrointestinal bleeding requires resuscitation and correction of coagulation disturbances before endoscopy is performed. If a bleeding ulcer is detected it is often managed by an adrenaline injection or electrocautery into the base of the lesion and a proton pump inhibitor (e.g. omeprazole 80 mg i.v. followed by 8 mg/hr for 72 hr then 20 mg orally for 8 weeks). Surgery is considered for all patients in whom bleeding persists despite endoscopic or medical therapy.*

*While H<sub>2</sub> receptor antagonists have been used for the management of ASU, proton pump inhibitors are currently prescribed due to their greater gastric acid suppressant effect (e.g. omeprazole 40 mg i.v. daily for ASU prophylaxis, 40 mg daily or 12-hourly for ASU with mild blood loss and 80 mg i.v. followed by 8 mg/hr for 72 hrs for ASU with severe haemorrhage). With severe haemorrhage, fibrinolytic inhibitors (e.g. tranexamic acid 3 - 6 g i.v. daily) may also be of benefit.*

*For lower gastrointestinal bleeding or if there is no obvious upper gastrointestinal lesion during endoscopy, then selective mesenteric angiography with embolisation of the bleeding point (if the bleeding is brisk, e.g. > 0.5 - 2.0 mL/min) or colonoscopy with electrocautery or adrenaline injection (for diverticular haemorrhage) may be considered as an alternative to surgery.*

**Conclusions:** *Acute upper gastrointestinal bleeding is often managed by intravenous proton pump inhibitors and endoscopy with electrocautery or adrenaline injection when a bleeding at the base of an ulcer is found. For lower gastrointestinal haemorrhage, selective mesenteric angiography with embolisation of the bleeding point is an alternative to surgery in critically ill patients. Fibrinolytic inhibitors may have added benefit. (Critical Care and Resuscitation 2001; 3: 105-116)*

**Key Words:** *Acute gastrointestinal bleeding, acute stress ulceration, peptic ulcer haemorrhage*

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The normal amount of blood lost from the gastrointestinal tract ranges from 0.5 - 1.5 mL per day and is typically not detected by faecal occult blood tests.<sup>1</sup> For guaiac-based occult blood tests to be positive, faecal haemoglobin must exceed 10 mg/g of stool (i.e.

10 mL of gastrointestinal blood loss per day or greater). Approximately 60 mL of blood is required to produce a single black stool, although for melaena to be produced consistently, 150 to 200 mL of blood per day must be lost as a gastroduodenal loss of up to 100 mL per day

may occur with stools that appear normal.<sup>1</sup>

Gastrointestinal haemorrhage is divided clinically into upper gastrointestinal bleeding (i.e. originates above the duodenojejunal flexure) and lower gastrointestinal bleeding (i.e. originates from below the duodenojejunal flexure).

### **Aetiology**

The causes of upper gastrointestinal bleeding are listed in table 1. The causes of lower gastrointestinal bleeding include anorectal disease (e.g. haemorrhoids, fissures, proctocolitis), enterocolitis (e.g. inflammatory bowel disease, infections, radiation), diverticular disease (e.g. diverticulitis, Meckel's diverticulum), polyps, carcinoma, mesenteric ischaemia, angio-dysplasia (which may be associated with aortic stenosis, or vWD), vasculitis and Dieulafoy's lesion (i.e. an unusually large submucosal artery, where bleeding occurs through a minute mucosal erosion. In most cases the lesion is found in the stomach within 6 cm of the gastro-oesophageal junction on the lesser curve of the stomach, although oesophageal, small intestine, colon, and rectal lesions have also been reported).

**Table 1. Causes of acute upper gastrointestinal bleeding**

<i>Oesophageal</i>
Oesophageal varices
Mallory-Weiss syndrome
Oesophagitis
<i>Stomach and duodenum</i>
Duodenal ulcer
Gastric ulcer
Acute stress ulceration
Gastritis (alcoholic, NSAIDs)
Hiatus hernia
Tumours (benign and malignant)
Gastric varices
Portal hypertensive gastropathy
Dieulafoy's lesion
<i>Aortoenteric haemorrhage</i>
<i>Coagulation defects</i>
Anticoagulants, thrombocytopenia
DIC, fibrinolysis

### **Clinical features**

The patient may have a history or symptoms suggestive of peptic ulcer disease, NSAID therapy, alcohol abuse or be asymptomatic (i.e. occult bleeding, which refers to gastrointestinal bleeding that is not clinically evident and only detected by tests that detect

faecal blood, although it may also refer to bleeding that is clinically evident but from an obscure source).

Upper gastrointestinal bleeding usually presents with haematemesis (vomiting of blood which may be red, brown or black i.e. 'coffee grounds' depending on the presence and duration of contact with gastric acid), signs of acute blood loss (e.g. tachycardia, hypotension, pallor, diaphoresis, anaemia) and melaena (i.e. black 'tarry' stool). When the upper gastrointestinal blood loss has stopped the melaena usually resolves within 2-3 days, although it can continue for up to 7 days.

Lower gastrointestinal bleeding usually presents with haematochezia (passage of red blood) and signs of acute blood loss. Melaena may also occur from a lower gastrointestinal blood loss associated with a prolonged gastrointestinal transit time.

### **Investigations**

The investigations performed in a patient with upper or lower gastrointestinal haemorrhage include:

*Complete blood picture, coagulation profile and plasma biochemistry.* The haematocrit may be normal (with an acute blood loss) or low with morphological features of iron deficiency anaemia (with chronic blood loss). The INR, APTT or platelet count may be abnormal suggesting primary or secondary coagulation defects. In one study of 59 patients with overt gastrointestinal haemorrhage, a urea:creatinine ratio (both measured in mmol/L) of greater than 100 was observed in 87% of patients with upper gastrointestinal bleeding and less than 100 in 95% of patients with lower gastrointestinal bleeding.<sup>2</sup>

*Gastric aspiration.* Aspiration of blood stained contents from a nasogastric tube confirms an upper gastrointestinal blood loss. The aspiration is continued until the stomach is emptied followed by a saline lavage to facilitate vision of the active bleeding site during endoscopy.

*Endoscopy.* Endoscopy is the method of choice to diagnose the site of bleeding in a patient who has haematemesis, as potential bleeding sites are identified in up to 90% of patients.<sup>3,4</sup> Treatment may also take place during the endoscopy by electrocautery or by injecting adrenaline (1/10,000) or bipolar coagulation at the base of the bleeding lesion (e.g. vessel at the base of an ulcer).

Duodenal and gastric ulcers are the commonest cause of acute upper gastrointestinal bleeding, 80% of which stop spontaneously. However, only 20% of ulcers that have active 'spurters' at the time of endoscopy stop spontaneously and ulcers that have a visible vessel at the base have about a 50% chance of rebleeding. Clean

ulcers do not rebleed.

To rule out upper gastrointestinal haemorrhage, endoscopy is also performed in a patient who presents with rectal blood loss (i.e. melaena or haematoschezia). This then is followed by sigmoidoscopy or colonoscopy if no abnormality is found. In one study of patients with severe haematochezia and diverticulosis, urgent colonoscopy (i.e. 6 - 12 hr after a 5 - 6 L polyethylene glycol bowel lavage) with endoscopic management of the diverticular haemorrhage (e.g. adrenaline injection or bipolar coagulation) prevented recurrent bleeding and reduced the need for surgery.<sup>5</sup> Haemoclipping<sup>6</sup> and use of tissue glues or fibrin<sup>7</sup> have also been used to treat diverticular bleeding.

**Angiography.** Selective mesenteric angiography is usually of value in patients with brisk haemorrhage (e.g. > 0.5 - 2 mL/min) and if the diagnosis has not been established by endoscopy (e.g. the bleeding is below the duodenojejunal flexure). In lower gastrointestinal bleeding, compared with colonoscopy, angiography (by a skilled radiologist) has the advantages of not requiring aggressive bowel preparation and allows embolisation of the offending bleeding point to be performed without delay, which can also be used to treat any bleeding lesion (not just diverticular haemorrhage). However it should be performed urgently (i.e. while the bleeding is likely to be present) and should always be followed by an elective colonoscopy, to identify a source of bleeding, particularly if it is not identified by angiography.<sup>8</sup>

**Labelled RBC scan.** This is usually performed with chromium-51 labelled red blood cells and is of value in patients with lower gastrointestinal bleeding.

**Contrast studies.** Gastrograffin or barium meal studies are now rarely performed in patients with haematemesis or melaena as they are significantly less accurate than endoscopy in the diagnosis of upper gastrointestinal lesions and will only detect potential bleeding sites in 50% of patients.<sup>9</sup>

### Treatment

The initial priority for the patient with acute gastrointestinal bleeding is resuscitation, with the pace of fluid requirement to maintain normal blood pressure and pulse rate, reflecting the speed of gastrointestinal blood loss. In approximately 85% of all patients who have acute gastrointestinal bleeding, the bleeding will stop spontaneously.<sup>4</sup> Further management depends on the lesion responsible for the bleeding.

In the critically ill patient, common causes of acute gastrointestinal haemorrhage include acute stress ulceration, exacerbation of a previous peptic ulcer, Cushing's ulcer, Curling's ulcer and bleeding oesophageal varices.

### ACUTE STRESS ULCERATION (STRESS EROSIVE GASTRITIS)

Acute stress ulceration has an increased incidence in patients with respiratory failure, coagulopathy, sepsis, shock, multiple trauma, renal failure, hepatic failure, severe burns, or head injuries. It was once a common lesion in the critically ill patient, with an endoscopically verified incidence approaching 100%,<sup>10,11</sup> and clinical signs of bleeding in up to 5% - 7%.<sup>12</sup> However, contemporary studies suggest that the incidence has decreased with clinically important bleeding occurring in less than 5% of critically ill patients.<sup>13</sup>

The earliest lesion is a generalised mucosal hyperaemia with focal areas of pallor. Small petechiae and shallow erosions develop within 24 hr which may become large and confluent and involve the mucosal and submucosal blood vessels to cause haemorrhage.<sup>14</sup> These lesions can be found from the oesophagus to the duodenum, although during the early phase they are most commonly found in the fundus of the stomach.<sup>15</sup> While bleeding can occur early from the superficial proximal gastric lesions, it commonly occurs as a late complication of critical illness (e.g. after 2 weeks of hospitalisation) from deeper and more distal lesions (i.e. ulcers) in the duodenum.<sup>16</sup> The pathophysiology is multifactorial and is believed to include:

**Gastroduodenal ischaemia.** This is probably the initiating event and is caused by TNF- $\alpha$  (which causes thrombosis within the gastric mucosal vessels), endothelin-1 (a potent endothelial derived vasoconstrictor that has a long duration of action) and sympathetic vasoconstriction causing redistribution of blood away from the splanchnic bed.<sup>17</sup> Use of vasopressin in hypotensive patients may also increase the risk of acute stress ulceration.<sup>18</sup>

**Gastric acid and pepsin.** Gastric acid and pepsin are necessary for stress ulceration,<sup>19,20</sup> as the lesions do not occur if the gastric pH is > 7.0.<sup>21</sup> However, there is no evidence that hypersecretion of gastric acid or pepsin is responsible.<sup>22,23</sup>

**Bile salt disruption of the mucosal barrier.** In experimental studies, prevention of duodenal reflux of bile salts is associated with significant reduction in acute gastric ulceration.<sup>24</sup>

**Helicobacter pylori.** In one study of critically ill patients, a high *Helicobacter pylori* seropositivity rate was recorded with a trend toward increased macroscopic gastric bleeding in the seropositive patients.<sup>25</sup>

### Treatment

Management of acute gastric erosions is either preventative (i.e. prophylactic) or definitive. The latter

is often divided into management of minor (e.g. 'coffee grounds') bleeding requiring < 1 unit in 4 hr, moderate bleeding requiring 2 - 4 units in 4 hr, or severe bleeding requiring 5 or more units in 4 hr (or 10 or more units in 24 hr).

#### *Prophylactic treatment*

The fact that stress ulceration occurs only in the presence of acid,<sup>20</sup> and does not occur when the gastric pH is greater than 7.0,<sup>21</sup> has been the basis for prophylactic treatment of acute stress ulceration with antacids, H<sub>2</sub>-receptor antagonists and proton pump inhibitors. These are often used to maintain the gastric pH value above 3.5 or 4.0.<sup>26</sup>

In one prospective multicentred study of critically ill patients, clinically important gastrointestinal bleeding only occurred in patients who had a coagulopathy (i.e. platelet count < 50,000, INR > 1.5 or an APTT > 2.0 x control value) or respiratory failure, and they suggested that prophylaxis against stress ulcers could be safely withheld unless respiratory failure requiring mechanical ventilation for more than 48 hr or coagulopathy existed.<sup>27</sup> In another study, prolonged nasogastric intubation, alcoholism, acute hepatic failure and increased *Helicobacter pylori* IgA antibody concentrations were found to be independently correlated with an increased incidence of acute gastrointestinal bleeding in intensive care patients.<sup>28</sup>

As routine prophylaxis for stress ulceration using antacids, H<sub>2</sub>-receptor antagonists or sucralfate has not been shown to improve the survival in all critically ill patients,<sup>15,29,30</sup> and as antacids, H<sub>2</sub>-receptor antagonists and sucralfate are all equally effective in producing a 50% reduction in relative risk of clinically important bleeding,<sup>31-33</sup> treatment with these agents has been recommended only in at risk patients or when there is evidence of established stress ulcer haemorrhage (usually determined when blood or 'coffee grounds' appear in the nasogastric tube).

One meta-analysis concluded that sucralfate may be the agent of choice (if prophylaxis was deemed necessary) as it was associated with a reduced mortality rate, relative to antacids and H<sub>2</sub>-receptor antagonists.<sup>31</sup> However, a prospective randomised, blinded, placebo-controlled, multicentred, trial comparing sucralfate (1 g orally 6-hourly) and ranitidine (50 mg i.v. 8-hourly) in 1200 critically ill patients who required ventilation for 48 hr or longer, found that ranitidine was associated with a significantly lower rate of clinically important gastrointestinal bleeding when compared to sucralfate (with no significant difference in mortality rates or rates of ventilator associated pneumonia) and that it was possible that sucralfate had no effect on clinically important gastrointestinal bleeding.<sup>34</sup>

In a recent prospective and randomised study of critically ill patients with at least one risk factor for stress ulcer bleeding, omeprazole (40 mg i.v. 12-hourly) was more effective than ranitidine (150 mg as a continuous i.v. infusion) or sucralfate (1 gm 6-hourly through a nasogastric tube) in preventing gastrointestinal bleeding (with no difference in the incidence of nosocomial pneumonia between groups).<sup>35</sup> Currently, we use omeprazole (40 mg i.v. 12-hourly or daily) to prevent acute gastric erosions in all at risk critically ill patients (e.g. patients with respiratory failure, coagulopathy, sepsis, shock, multiple trauma, renal failure, hepatic failure, severe burns or head injuries).

#### *Treatment of minor bleeding*

Treatment of minor bleeding from the gastrointestinal tract (e.g. blood or 'coffee grounds' appearing in the nasogastric aspirate or a blood loss less than 1 unit in 4 hr) includes measures to reduce stress ulceration by optimising gastric mucosal blood flow (i.e. correcting shock), correcting coagulation abnormalities, treating sepsis and early enteral feeding<sup>36</sup> (gastric enteral feeding also increases gastric pH<sup>37</sup>).

In clinical practice, when the patient has minor blood loss, the diagnosis of acute stress ulceration is often made without endoscopy and, for convenience and ease of administration, proton pump inhibitors or H<sub>2</sub>-blocker are commonly administered.

#### ***Proton-pump inhibitors (e.g. omeprazole, lansoprazole, pantoprazole)***

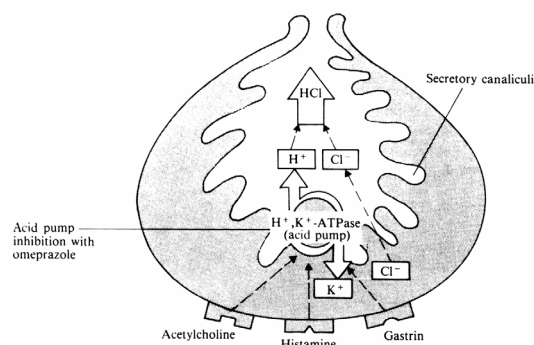
The three agents appear similar in their ability to suppress gastric acid secretion, with little to choose between them.<sup>38</sup>

*Omeprazole* is absorbed in the small intestine and reaches the parietal cells through the circulation. At a cytosolic pH of approximately 7.0, omeprazole (a weak base with a pKa = 4) is largely unionised, and crosses cell membranes. However, in the canalculus of actively secreting gastric parietal cells, omeprazole becomes ionised, trapped and converted into a sulfenamide (i.e. the active form) where it binds irreversibly to the cystine residues on the extracellular surface of the  $\alpha$  subunit the fundic parietal cell H<sup>+</sup>/K<sup>+</sup> ATPase (which normally functions by exchanging luminal K<sup>+</sup> ions for cellular H<sup>+</sup> ions) and selectively inhibits the enzyme (Figure 1).<sup>39,41</sup> The drug disappears rapidly from the plasma but its effect remains for approximately 18 - 24 hr (i.e. the half-life of the H<sup>+</sup>/K<sup>+</sup> ATPase<sup>41,42</sup>).

An oral dose of 20 mg of omeprazole results in 65% inhibition of H<sup>+</sup> secretion after 4 - 6 hr, and 25% after 24 hr.<sup>41</sup> After 4 days the degree of inhibition of the H<sup>+</sup>/K<sup>+</sup> ATPase plateaus.<sup>41</sup> The

pharmacokinetic characteristics of omeprazole are listed in Table 2.<sup>41,43</sup> While an oral dose of 40 mg of omeprazole inhibits the mean 24 hr gastric acid secretion by 100%,<sup>44,45</sup> it may take up to 5 days to achieve this effect.

An intravenous dose of 40 mg produces a maximum suppression of gastric acid secretion within 12 hr and is indicated in all critically ill patients with acute stress ulcer haemorrhage.<sup>46</sup> However, an intravenous bolus of 80 mg of omeprazole followed by 8 mg/hr for 72 hr then 20 mg orally for 8 weeks may be the preferred treatment in patients with acute severe haemorrhage.<sup>47</sup>



**Figure 1.** A diagrammatic representation of the parietal cell, the acetylcholine, histamine and gastrin receptors and the site of action of omeprazole (Modified from Wallmark B. *Scand J Gastroenterol Suppl* 1989;166:12-18).

The side-effects of omeprazole include nausea, diarrhoea, abdominal pain, constipation, flatulence, headache, lethargy, absent-mindedness, dizziness, vertigo, confusion, agitation, hallucinations, myalgia, arthralgia, urticaria, angio-oedema, vasculitic rash, thrombocytopenia, haemolytic anaemia, elevated serum CPK, impotence, gynaecomastia, gout and interstitial nephritis.<sup>46,48,49</sup> It also interacts with the cytochrome P<sub>450</sub> system and inhibits the metabolism of phenytoin, warfarin and diazepam (but not propranolol or aminophylline).<sup>41</sup> The

decrease in gastric acidity also increases the incidence of gastroenteritis caused by salmonella, campylobacter and giardiasis.<sup>50</sup> While the hypergastrinaemia associated with omeprazole therapy has produced carcinoid tumours and hypertrophy of enterochromaffin-like cells in animals,<sup>51</sup> the mean gastrin levels in humans treated with omeprazole is less than that found in patients who have pernicious anaemia.<sup>42</sup>

**H<sub>2</sub>-receptor antagonists.** Histamine H<sub>2</sub>-receptors are located on the basolateral membranes of the acid secreting parietal cells of the stomach, along with acetylcholine and gastrin receptors. The H<sub>2</sub>-receptors are activated by histamine (released largely in response to vagal and gastrin stimulation) derived from neighbouring mucosal (enterochromaffin-like or ECL) cells which are located in the lower part of gastric glands. These cells have surface gastrin receptors and neurotransmitter receptors (e.g. pituitary adenylate cyclase activating peptide receptor or PACAP receptor, vasoactive intestinal peptide or VIP).

Cimetidine,<sup>52,53</sup> ranitidine,<sup>54-56</sup> famotidine<sup>57</sup> and nizatidine are non competitive H<sub>2</sub>-receptor antagonists. The clinical pharmacokinetics of these agents are given in Table 2.<sup>57</sup> Because of the greater number of side-effects with cimetidine,<sup>58</sup> many prefer to use ranitidine or famotidine rather than cimetidine if a H<sub>2</sub>-receptor antagonist is to be used in the management of acute stress ulceration.<sup>57,59</sup> The intravenous doses of ranitidine and famotidine are half the oral doses and the dose of all agents should be halved with severe renal failure.<sup>55,57</sup> In the management of acute stress ulceration, continuous administration of ranitidine 50 mg as a bolus followed by 0.12 - 0.24 mg/kg/hr (i.e. 200 - 400 mg/70 kg/24 hr<sup>59</sup>) or famotidine 5 mg as a bolus followed by 0.01 - 0.02 mg/kg/hr (i.e. 20 - 40 mg/70 kg/24 hr<sup>60</sup>) is administered (often in the parenteral nutrition) and will provide a consistent maintenance of the pH above 3.5. Standard doses of H<sub>2</sub>-receptor antagonists usually elevate intragastric pH by about one unit, averaged over 24 hr, which is only a modest elevation compared with that

**Table 2. Clinical pharmacokinetics of drugs used to decrease gastric acid**

Drug	Dose (mg/24 hr)	Elimination half-life (hr)	Excretion (% in 24hr)	Plasma protein binding (%)	Duration of action (hr)	Bio- availability (% oral dose)
Cimetidine	400 - 1000	2	70 renal	15	3	70
Ranitidine	50 - 150	2	50 renal	15	3	50
Famotidine	5 - 40	3	70 renal	15	12	40
Omeprazole	20 - 40	1	95 hepatic	95	24	50

achieved with proton pump inhibitors, but often sufficient for successful treatment. Partial tolerance also develops after 3 - 5 days.

The side-effects of ranitidine and famotidine include headache, anxiety, paraesthesia, depression, decreased libido, hallucinations, impotence and thrombocytopenia.

While the increase in gastric pH with H<sub>2</sub>-receptor antagonists (and proton pump inhibitors) increases the upper gastrointestinal tract bacterial colonisation with both Gram-negative and Gram-positive micro-organisms, many studies have found that the incidence of nosocomial pneumonia is not increased significantly when compared with placebo<sup>61</sup> (see later).

**Antacids.** On average, 1 - 2 hr of gastric pH control (i.e. pH > 3.5) may be expected from a single dose of antacid.<sup>62</sup> Antacids may contain magnesium hydroxide, aluminium hydroxide, calcium carbonate or sodium bicarbonate. All are able to neutralise gastric acid, but they have different side-effects. Calcium carbonate may cause hypercalcaemia and metabolic alkalosis, aluminium hydroxide can cause constipation and hypophosphataemia, and magnesium hydroxide may cause diarrhoea. In patients with chronic renal failure, magnesium hydroxide may cause hypermagnesaemia, and aluminium hydroxide may cause high aluminium levels with encephalopathy. Rarely, bowel impaction of magnesium or aluminium hydroxide, with obstruction and perforation, may also occur.<sup>63,64</sup> Mylanta II contains 400 mg aluminium hydroxide, 400 mg magnesium hydroxide and 30 mg simethicone in each 5 mL which is capable of neutralising 25.4 mmol of H<sup>+</sup>.

For acute stress ulceration, hourly antacid administration has been used for gastric bleeding although in contemporary practice due to convenience and ease of administration, proton pump inhibitors or H<sub>2</sub>-receptor antagonists rather than antacids are commonly used.

**Sucralfate.** This is a complex salt of sucrose sulphate and aluminium hydroxide.<sup>61,65</sup> It selectively adheres to damaged mucosal areas, particularly in an acid environment, having a mucosal protective role without altering the gastric pH. It also neutralises acid (13 mmol of H<sup>+</sup> per gram of sucralfate), inhibits the action of pepsin, binds to bile salts, stimulates local prostaglandin production (stimulating alkali and mucus secretion) and has an antibacterial effect.

Sucralfate 1 g, 4 to 6-hourly has been found to be as effective as H<sub>2</sub>-receptor antagonists in the management of established stress ulcer haemorrhage.<sup>26</sup> It has the advantage of not requiring pH estimations (as it reduces stress ulcer haemorrhage without reducing the gastric pH) and is not associated with an increased incidence of gastric Gram-negative bacterial colonisation.<sup>29</sup>

However, while the incidence of nosocomial pneumonia has been reported in some studies to be less with sucralfate than antacids or H<sub>2</sub>-receptor antagonists,<sup>66,67</sup> others have not found this and have concluded that that sucralfate has no particular advantages (when compared with H<sub>2</sub>-receptor antagonists) in the management of acute stress ulceration.<sup>61,68</sup>

The side-effects of sucralfate include constipation, dry mouth, urticaria, skin rash, headache, diarrhoea, nausea, vomiting, abdominal discomfort, hypophosphataemia, reduction in drug bioavailability and gastric or oesophageal bezoars (particularly when administered with enteral feedings<sup>61</sup>) as it forms insoluble salts with phosphate, precipitates dietary protein, and delays gastric emptying increasing the viscosity and gelling of the mixture, particularly in an acid environment.<sup>69</sup> With prolonged use in patients with chronic renal failure, aluminium toxicity (4 g provides 728 - 828 mg of aluminium which is comparable to that during treatment with aluminium hydroxide<sup>61</sup>) with encephalopathy (i.e. plasma aluminium levels greater than 2 µmol/L) may also occur.<sup>61,70,71</sup>

**Prostaglandins (PGE<sub>1</sub>, PGE<sub>2</sub> and PGE<sub>3</sub> analogues).** These agents have an antisecretory as well as a cytoprotective effect.<sup>72</sup> They have an efficacy similar to H<sub>2</sub>-receptor antagonists, although they may be more effective in treatment of erosive gastritis, particularly when induced by NSAIDs. The dose of misoprostil (a PGE<sub>1</sub> analogue) is 200 mg 6-hourly.

#### **Other therapy.**

**Fibrinolytic inhibitor therapy.** Intravenous tranexamic acid 3 - 6 g/day for 3 days followed by 3 - 6 g orally for 3 - 5 days is associated with a 20 - 30% reduction in rate of rebleeding from upper gastrointestinal haemorrhage and a 40% reduction in mortality.<sup>73,74</sup>

**Vitamin A.** In some patients with stress ulceration, low levels of vitamin A have been demonstrated,<sup>75</sup> and in one report the incidence of stress ulcers decreased with vitamin A treatment.<sup>76</sup>

**Octreotide.** Intravenous octreotide (50 µg/hr) for 3 - 5 days followed by 50 - 100 µg subcutaneously 8-hourly has also been used to successfully control bleeding from acute gastric erosions.<sup>77</sup> However, one prospective randomised study found in patients with non-variceal upper gastrointestinal bleeding, the addition of octreotide to a H<sub>2</sub> receptor antagonist (ranitidine) compared with ranitidine alone was of no added benefit.<sup>78</sup>

**Vasoactive intestinal peptide.** While experimental studies have found that vasoactive intestinal peptide (VAP) reduces the incidence of acute stress ulceration,<sup>79</sup>

there have been no clinical studies in at risk patients showing significant benefits using VAP.

#### *Treatment of moderate or severe haemorrhage*

When moderate (i.e. 1 - 4 units in 4 hr) or severe (i.e. > 5 units in 4 hr or 10 units in 24 hr) haemorrhage occurs due to acute stress ulceration, correction of shock, sepsis and coagulation disorders and high dose proton pump inhibitor therapy (e.g. intravenous bolus of 80 mg of omeprazole followed by 8 mg/hr) with fibrinolytic inhibitor therapy may control the haemorrhage.

However, the additional use of gastric lavage with iced saline, vasopressin, DDAVP, octreotide, electrocoagulation or laser coagulation have not been effective in managing haemorrhage associated with acute stress ulceration.<sup>12</sup> Surgery with partial or total gastrectomy carries a mortality rate of 70% or greater and should only be considered when all conservative measures have failed.<sup>3,12</sup>

#### EXACERBATION OF A PREVIOUS PEPTIC ULCER

Peptic ulceration occurs largely in association with *Helicobacter pylori* infection and/or therapy with NSAIDs. *Helicobacter pylori* is a Gram-negative spiral bacterium that has a powerful urease that splits urea, producing ammonia which in turn neutralises H<sup>+</sup> and blocks the negative feedback of the low antral pH on gastrin secretion, raising acid production and impairing mucosal defence. NSAIDs inhibit cyclo-oxygenase with subsequent reduction in the cytoprotective prostaglandin concentrations in the mucosa.

#### **Duodenal ulcer**

Duodenal ulcer is usually a chronic and recurrent disease, 95% of which occur in the first part of the duodenum and is often found in patients who have approximately double the normal parietal cell mass, who are able to secrete H<sup>+</sup> up to a maximum of 40 mmol/hr. An increased frequency of duodenal ulceration is associated with smoking, NSAIDs, chronic renal failure, alcoholic cirrhosis, hyperparathyroidism, COPD and renal transplantation.

Gastric colonisation with *Helicobacter pylori* has been reported in more than 90% of patients with duodenal ulcer (and more than 80% of patients with gastric ulcers), and has been implicated in the delay of ulcer healing and ulcer recurrence,<sup>80</sup> although only a small proportion (perhaps 15% - 20%) of patients who are infected with *Helicobacter pylori* (prevalence of *Helicobacter pylori* in a normal population ranges from 20% in developed countries to 90% in underdeveloped countries<sup>81</sup>) will have a peptic ulcer during their lifetime.<sup>82,83</sup> Other diseases associated with *Helicobacter*

*pylori* include, gastritis, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>83</sup>

#### *Clinical features*

While many patients may be asymptomatic, characteristically the patient complains of a burning or boring epigastric pain occurring 1.5 - 3 hr after a meal, it may awaken the patient at night and is usually relieved immediately by antacids.

The signs include epigastric tenderness (which may be severe with ulcer penetration), haematemesis and melaena, pallor due to chronic anaemia, an acute abdomen due to perforation and vomiting due to chronic duodenal scarring with gastric outlet obstruction.

#### *Diagnosis*

The diagnosis of the duodenal ulcer is confirmed by endoscopy. Radiocontrast studies (e.g. gastrograffin meal) may also confirm the presence of a duodenal abnormality and is useful in determining the presence of a perforation.

Infection with *Helicobacter pylori* is diagnosed by serological tests for IgG antibodies to *Helicobacter pylori* antigens, tissue *Helicobacter pylori* IgA antibody or by the detection of carbon-13 or carbon-14 in the breath after oral administration of isotopically labelled urea (the urea is split by *Helicobacter pylori* urease, liberating ammonia and carbon dioxide). The test should be performed no sooner than four weeks after the patient has discontinued antibiotics, proton inhibitors or bismuth compounds.<sup>80</sup> *Helicobacter pylori* infection may also be diagnosed by gastric biopsy and direct histological examination, culture or dye test for bacterial urease of the specimen.<sup>82</sup>

#### *Treatment*

The management of duodenal ulceration includes:

##### ***Advice to cease smoking and NSAID therapy***

***Antacids.*** These are often used for symptomatic management of ulcer pain only, although in one study 5 - 6 mL of Mylanta II before and after each meal and at bedtime (i.e. 200 mmol of H<sup>+</sup> neutralising capacity) recorded a similar incidence in duodenal ulcer healing after 4 weeks as H<sub>2</sub>-receptor antagonists.<sup>84</sup>

***H<sub>2</sub>-receptor antagonists.*** These facilitate peptic ulcer healing by decreasing gastric acid output, and should be initiated as soon as the diagnosis is made (e.g. ranitidine 300 mg or famotidine 40 mg at night for 4 to 8 weeks followed by 150 mg of ranitidine or 20 mg of famotidine at night). Endoscopic confirmation of healing should be made at the end of the 4 to 8 week period. Slow healing indicates non compliance or gastrinoma.

All H<sub>2</sub>-receptor antagonists have equal effectiveness and heal duodenal ulcers in 75% of patients at the end of 4 weeks increasing to 90% by the end of 8 weeks.<sup>85</sup> If therapy is discontinued, the ulcer recurrence rate is high over the next 12 months, with 33% being symptomless and appearing as haemorrhage or perforation. Thus a night time dose (e.g. 50 mg of ranitidine) is often administered for at least 1 year.

**Omeprazole.** In the 5 - 10% of patients who have duodenal ulcers that are resistant to H<sub>2</sub> antagonists by the end of 8 weeks, a 2 - 4 week trial of omeprazole 40 mg daily is indicated.<sup>85</sup> In one prospective randomised controlled study of patients who required continuous treatment with NSAIDs and who had peptic ulcers, omeprazole (20 mg orally daily) healed and prevented ulcers more effectively than did ranitidine (150 mg 12-hourly).<sup>86</sup> In another randomised study of patients with a history of upper gastrointestinal bleeding who were infected with *Helicobacter pylori* and who were taking aspirin or other NSAIDs, omeprazole 20 mg daily was as effective as eradication therapy in preventing recurrent bleeding in patients taking aspirin, and was better than eradication therapy in preventing recurrent bleeding in patients taking other NSAIDs (e.g. naproxen).<sup>87</sup>

**Pirenzepine.** The selective muscarinic M<sub>1</sub> antagonist pirenzepine can inhibit gastric acid secretion by 50 - 60%, with minimal (but not absent) anticholinergic side-effects (e.g. urinary retention, visual disturbances, drowsiness and constipation).<sup>88</sup> It has a 25% bio-availability, and an elimination half-life of 12 hr. While pirenzepine 100 - 150 mg/day has a similar success rate in healing a duodenal ulcer as cimetidine 1000 mg/day,<sup>53</sup> it does so with slower relief of ulcer pain and more side-effects, and so is unlikely to supplant H<sub>2</sub>-receptor antagonists or proton pump inhibitors in management of peptic ulcer disease.

**Ocreotide.** Intravenous ocreotide (50 µg/hr) for 3 - 5 days followed by 50 - 100 µg subcutaneously 8-hourly has also been used to control bleeding from peptic ulcer disease.<sup>89</sup> although the addition of ocreotide to a H<sub>2</sub> receptor antagonist (ranitidine) is of no added benefit.<sup>78</sup>

#### **Cytoprotective agents**

**Prostaglandins (PGE<sub>1</sub>, PGE<sub>2</sub> and PGE<sub>3</sub> analogues).** Misoprostil is a PGE<sub>1</sub> analogue, and enprostil and arbabrostitil are PGE<sub>2</sub> analogues. These agents have an efficacy similar to H<sub>2</sub>-receptor antagonists, although they may be more effective in treatment of erosive gastritis particularly if they are induced by NSAIDs. The dose of misoprostil is 200 mg 6-hourly. The side-effects include diarrhoea, uterine bleeding and abortion.

**Sucralfate.** Sucralfate 1 g 4-hourly and H<sub>2</sub>-antagonists have a similar rate of healing for duodenal ulceration.<sup>61</sup>

**Colloidal bismuth subcitrate (CBS).** This agent promotes healing in peptic ulceration largely by inhibiting *Helicobacter pylori*.<sup>90</sup> While it also binds to protein and necrotic debris at the ulcer base to form a coating impermeable to acid, stimulates prostaglandin E<sub>2</sub> production and stimulates secretion of alkali into the mucus layer, colloidal bismuth subcitrate has no antipeptic ulcer effect independent of its anti-*Helicobacter pylori* action.<sup>91</sup> Colloidal bismuth subcitrate causes healing rates comparable to that of cimetidine and has a slower ulcer relapse rate in comparison to the H<sub>2</sub>-receptor antagonists.<sup>90</sup> The dose for peptic ulceration is 480 mg daily for 4 - 8 weeks given in 2 - 4 divided doses. The side-effects include a blackening of the tongue and stool and (rarely, particularly with prolonged administration) encephalopathy.<sup>90</sup>

**Antibiotics.** For patients infected with *Helicobacter pylori*, tripple therapy eradication regimens (Table 3) are currently recommended as therapy of choice.<sup>46,83,92-94</sup> Once cure has been achieved, reinfection rates are low (0.5% per year).<sup>95</sup> As serum IgG antibodies to *Helicobacter pylori* antigens take 6-12 months to disappear after eradication of the infection, the efficacy of antibiotic treatment is usually assessed by urea breath tests performed four weeks after the completion of antibiotic therapy.<sup>82</sup> Positive to negative seroconversion of tissue *Helicobacter pylori* IgA antibody may also occur within 4 weeks of eradication of the infection.<sup>96</sup>

**Endoscopic haemostasis.** Electrocoagulation,<sup>97</sup> laser photocoagulation<sup>96</sup> or an injection of adrenaline<sup>98</sup> or alcohol<sup>99</sup> sclerosants directly into the base of an ulcer are simple safe and initially control bleeding in greater than 90% cases,<sup>100</sup> although with acute bleeding lesions, the inability to see, or to approach the bleeding point or the presence of massive bleeding may preclude endoscopic therapy or may render it ineffective.<sup>101</sup> However, recurrence of bleeding is high particularly in patients with deep ulcers, severe coagulopathies, severe coexisting disease and hypotension.<sup>102</sup> In one study, repeated endoscopic injection of fibrin-glue into an actively bleeding peptic ulcer was found to be significantly more effective than a single injection of a sclerosant (polidocanol) in controlling bleeding from gastroduodenal ulcers.<sup>103</sup> In a prospective randomised controlled study in patients with recurrent bleeding from peptic ulcers, comparing surgery with endoscopic adrenaline injection followed by thermocoagulation, a 73% long term control of bleeding was reported with fewer complications and a lower mortality.<sup>104</sup> In another



**Table 4. Regimens for eradication of *Helicobacter pylori***

	<i>Dose</i>	<i>Duration</i>	<i>Eradication rate</i>
Proton-pump inhibitor			
Omeprazole	20 mg 12-hourly	2 weeks	80%-90%
or Lansoprazole	30 mg 12-hourly		
or Pantoprazole	40 mg 12 hourly		
Metronidazole	400 mg 8-hourly		
Amoxicillin	500 mg 6-hourly		
Colloidal bismuth (subcitrate)	108 mg 6-hourly	1 week	80%-90%
Metronidazole	400 mg 8-hourly		
Tetracycline	250 mg 6-hourly		
Proton-pump inhibitor	(dose as above)	1 week	> 90%
Metronidazole <b>or</b>	400 mg 12-hourly		
Amoxicillin	1000 mg 12-hourly		
Clarithromycin	500 mg 12-hourly		
Ranitidine bismuth citrate	400 mg 12-hourly	2 weeks	> 90%
Clarithromycin	500 mg 12-hourly		

study, endoscopic adrenaline injection and thermo-coagulation followed by omeprazole (80 mg i.v. followed by 8 mg/hr for 72 hours then 20 mg orally for 8 weeks) reduced the recurrence of bleeding in patients with bleeding peptic ulceration from 22% to 6.7%.<sup>47</sup>

**Surgery.** This is reserved for patients who are greater than 60 years of age, with a chronic duodenal ulcer that bleeds continuously (i.e. greater than 5 u of blood in 24 hr) and is uncontrolled by medical therapy.<sup>84</sup> Operative measures include oversewing of the bleeding point, truncal vagotomy and pyloroplasty.

### Gastric ulcer

The peak incidence of gastric ulceration occurs at 60 years of age (approximately 10 years later than duodenal ulceration). The diagnosis is confirmed by endoscopy with biopsy of the ulcer edge to exclude carcinoma. Treatment involves an H<sub>2</sub>-blocker (e.g. ranitidine 300 mg or famotidine 40 mg at night for 4 - 8 weeks followed by maintenance therapy with 150 mg of ranitidine or 20 mg of famotidine at night). Omeprazole is superior to H<sub>2</sub>-receptor antagonists for healing and maintaining remission in patients with benign gastric ulcers.<sup>105</sup> While antibiotics to eradicate *Helicobacter pylori* infection (Table 4) may reduce the incidence of ulcer recurrence,<sup>80</sup> treatment of gastric ulcers with antibiotics to eradicate *Helicobacter pylori* has no additional effect to omeprazole (and may even impair ulcer healing in patients with NSAID-induced gastric ulcers<sup>106</sup>).

Cytoprotective agents (i.e. sucralfate) or surgery (i.e. partial or total gastric resection with biopsy to exclude malignancy) may be considered in those without complete healing after 12 weeks of medical therapy, or in those patients who have a carcinomatous ulcer change, perforation or recurrent haemorrhage.

The management of bleeding gastric ulceration includes a number of measures which are similar to that of a bleeding duodenal ulcer.

### CUSHING'S ULCER

Acute ulcerative lesions in the oesophagus, stomach or duodenum were initially described by Cushing in association with coma from any cause.<sup>107</sup> The Cushing ulcer is now described to be an acute peptic ulceration associated with severe head injury and increased intracranial pressure.<sup>12</sup> The ulcer is caused by increased secretion of gastric acid resulting from stimulation of vagal nuclei in the floor of the fourth ventricle.<sup>108,109</sup> While prophylaxis with H<sub>2</sub>-receptor antagonists has been reported to decrease bleeding associated with head injuries,<sup>110</sup> in contemporary practice, omeprazole (40 mg i.v. 12-hourly or daily) is often used.

### CURLING'S ULCER

The characteristic Curling's ulcer is circumscribed, up to 2 cm in diameter and occurs after 3 days in the first or second part of the duodenum, in patients with greater than 35% burns.<sup>12</sup> It is also caused by increased gastric acid secretion and should be treated initially with proton-pump inhibitors or H<sub>2</sub>-receptor antagonists.

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