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# Management of Acute Gastric Ulcer Bleeding

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## 1. Introduction

Acute gastric ulcer bleeding frequently presents as a gastrointestinal emergency. It has important implications for healthcare costs worldwide. Negative consequences include rebleeding and death usually caused by the functional worsening of concomitant medical conditions, precipitated by the acute bleeding incident. Advances in medical practice in recent decades have influenced the aetiology and management of upper gastrointestinal bleeding (UGIB), but their impact on the incidence and mortality is unclear.

## 2. Epidemiology

At one time peptic ulcer disease accounted for 50–70% of acute non-variceal UGIB (Barkun et al., 2004). Approximately 80% of these ulcers stop bleeding spontaneously. Gastric ulcer is more frequently the source of UGIB (55% versus 37%); compared to duodenal ulcer (Enestvedt et al., 2008). The current practice to use proton pump inhibitors as ulcer prophylaxis and eradication of *Helicobacter pylori*, has led to a worldwide decrease in the incidence of bleeding from peptic ulcer. However, this seems applicable only to patients younger than 70 years of age (Lanas et al., 2005; Loperfido et al., 2009; Targownik et al., 2006). Recent population-based estimates have suggested that the incidence is about 60 per 100,000 of the population (Lassen et al., 2006), with the incidences related to the use of aspirin and non-steroidal anti-inflammatory drugs on the increase (Ohmann et al., 2005). The mortality associated with peptic ulcer bleeding remains high at 5 to 10% (Lim et al., 2006). The estimated direct medical costs annually incurred in the United States for the in-hospital care of patients with peptic ulcer bleeding amounts to a total of more than \$2 billion (Viviane et al., 2008).

## 3. Pathophysiology

### 3.1 Risk factors

There are four major risk factors for bleeding peptic ulcers namely *Helicobacter pylori* infection, non-steroidal anti-inflammatory drugs (NSAIDs), stress and gastric acid (Hunt et al., 1995; Hallas et al., 1995). Reduction or elimination of these risk factors lessens ulcer recurrence and rebleeding rates (Graham et al., 1993; Tytgat 1995).

### 3.1.1 *Helicobacter pylori*

Compared to non-bleeding duodenal ulcers (70–90%), *Helicobacter pylori* plays a lesser role in the aetiology of bleeding and gastric ulcers (Maury et al., 2004). However, it is important to exclude *Helicobacter pylori* as a factor in the aetiology.

*Helicobacter pylori* eradication should be attempted in all peptic ulcer patients diagnosed with the infection to prevent ulcer recurrence and rebleeding (Hopkins et al., 1996). In Hopkin's report of 19 published studies, the recurrence rates in cured versus uncured *Helicobacter pylori* infection was 6% versus 67% for duodenal ulcer, and 4% versus 59% for gastric ulcer. Various regimens that usually combine one or two antibiotics plus an anti-secretory agent have eradication rates that vary between 80% and 90% (Walsh et al., 1995).

### 3.1.2 Non-steroidal anti-inflammatory drugs

NSAIDs, including aspirin, frequently cause gastrointestinal ulceration (Lanas et al., 2005; Scheiman 1994). NSAID-induced injury results from both local effects and systemic prostaglandin inhibition effected by blocking cyclooxygenase-1. The majority of these ulcers are asymptomatic and uncomplicated. However, elderly patients with a prior history of bleeding ulcer disease are at increased risk for recurrent ulcer and complications (Hansen et al., 1996; Smalley et al., 1995). NSAIDs are also implicated as critical in the non-healing of ulcers (Lanas et al., 1995). Aspirin in dosages as low as 75 mg daily transfer an increased risk of ulcers and bleeding (Lim et al., 2004).

Combining corticosteroids with NSAIDs doubles the risk of ulcer complications whilst the risk of gastrointestinal bleeding is increased ten fold (Piper et al., 1991). Cyclooxygenase-2 inhibitors reduce the risk of ulcer bleeding only when not combined with aspirin therapy. Of concern, is the increase in incidence of myocardial infarction and cerebrovascular accidents in patients taking selective cyclooxygenase-2 inhibitors. The combination of *Helicobacter pylori* infection and NSAID use may increase the risk of ulcer bleeding; however, the need for eradication of *Helicobacter pylori* in patients who are taking NSAIDs remains controversial. (al-Assi et al., 1996).

### 3.1.3 Stress-related ulcers

The incidence of stress-related ulcers in intensive care units (ICU) is approximately 0.67. This form of ulceration tends to occur in severely ill patients and is almost certainly triggered by ischaemia due to a combination of decreased mucosal protection and reduced mucosal blood flow (Cooper et al., 1999). It is a frequent cause of acute UGIB in patients who are hospitalized for life-threatening non-bleeding illnesses (Navab et al., 1995). The risk of stress ulcer-related bleeding is increased in patients with respiratory failure and those with a bleeding disorder (Cook et al., 1994). Also, the mortality is higher in patients that present with a UGIB after hospitalization compared to those primarily admitted with UGIB (Zimmerman et al. 1994).

Primary ulcer prophylaxis with anti-secretory agents such as H<sub>2</sub>-receptor antagonists or proton pumps inhibitors (PPIs) decreases the risk of stress-related mucosal damage and UGIB in high-risk patients (Cook et al., 1996). Achlorhydria associated with prophylactic acid inhibition effects bacterial growth in the stomach and possible ventilator-associated pneumonia in ICU patients. Furthermore, stress-related ulcers tend to have high rebleeding rates and are not as amenable to endoscopic therapy as patients that present to the hospital with bleeding peptic ulcer (Jensen et al., 1988).

### 3.1.4 Gastric acid

Gastric acid and pepsin are essential cofactors in the pathogenesis of peptic ulcer (Peterson et al., 1995). Factors such as *Helicobacter pylori*, NSAIDs, or physiologic stress impair the mucosal integrity leading to increased cell membrane permeability and back diffusion of hydrogen ions, resulting in intramural acidosis, cell death, and ulceration. Hyperacidity as is prevalent in patients with Zollinger-Ellison syndrome, is rarely the sole cause of peptic ulceration. However, control of gastric acidity is considered an essential therapeutic manoeuvre in patients with active UGIB.

## 4. Acute management (Figure 1)

Patients with acute gastric ulcer bleeding frequently present with haematemesis (vomiting of red blood that is suggestive of active bleeding or vomiting of coffee-ground material indicative of older non-active bleeding) and/or melaena (black tarry stools which suggests passage of old blood, usually from an upper gastrointestinal source). Haematochezia (the passage of red blood per rectum) can occasionally be due to massive UGIB as suggested by a hypotensive or shocked patient. Patients who presents with haematemesis and melaena generally have more severe bleeding than those who present with melaena only. Immediate evaluation and appropriate resuscitation are critical as these can reduce mortality in acute UGIB (Baradarian et al., 2004).

### 4.1 Resuscitation and stabilization

As first priority, the haemodynamic stability (pulse and blood pressure, including orthostatic changes) and the need for fluid replacement must initially be assessed at presentation of a patient with UGIB. A full blood count, urea, electrolytes, creatinine, international normalized ratio (INR), blood type and cross-match should be obtained. If indicated, volume resuscitation should be initiated with crystalloids and blood products in all patients with haemodynamic instability or active bleeding (manifested by haematemesis, bright red blood per nasogastric tube, or haematochezia). Patients with a resting tachycardia  $\geq 100$  beats per minute, a systolic blood pressure  $< 100$  mmHg, orthostatic hypotension (an increase in the pulse rate  $\geq 20$  beats per minute or drop in blood pressure of  $\geq 20$  mmHg on standing), a decrease in haematocrit of  $\leq 6\%$ , or transfusion requirement over two units of packed red blood cells) should be admitted to an intensive care unit for resuscitation. The haemoglobin in high-risk patients should be maintained above 10 g/dL, whereas a haemoglobin  $\geq 7$  g/dL is acceptable in young and otherwise healthy individuals. Patients with active bleeding and a bleeding disorder should be transfused with plasma and platelets if the INR  $\geq 1.5$  and the platelets  $\leq 50\,000/\mu\text{L}$  respectively.

The vital signs (blood pressure, ECG monitoring, and pulse oximetry), clotting profile and urinary output should be closely monitored. If indicated, elective endotracheal intubation in patients with respiratory failure and decreased consciousness may facilitate endoscopy and decrease the risk of aspiration. Patients older than 60 years, with chest pain or a history of heart disease should also be evaluated for myocardial infarction with electrocardiograms and serial troponin measurements. Nasogastric (NG) tube placement to aspirate and characterize gastric contents can be useful to determine if large amounts of red blood, coffee - grounds, or non-bloody fluid are present. Patients with definite haematemesis do not need an NG tube for diagnostic purposes, but may need one to clear gastric contents before

endoscopy and to minimize the risk of aspiration. Approximately 15% of patients without bloody or coffee-ground material in nasogastric aspirates are found to have high-risk lesions on endoscopy (Aljebreen et al., 2004).

Clinical and laboratory findings are useful to risk-stratify patients (Table 1). The Blatchford score or the clinical Rockall score have been validated as clinical tools in the risk assessment (Blatchford et al., 2000; Rockhall et al., 1996). Poor prognostic factors for bleeding peptic ulcers include the following: age >60 years, comorbid medical illness, orthostatic hypotension, bleeding disorder, bleeding onset in the hospital, multiple blood transfusions and red blood in the NG tube.

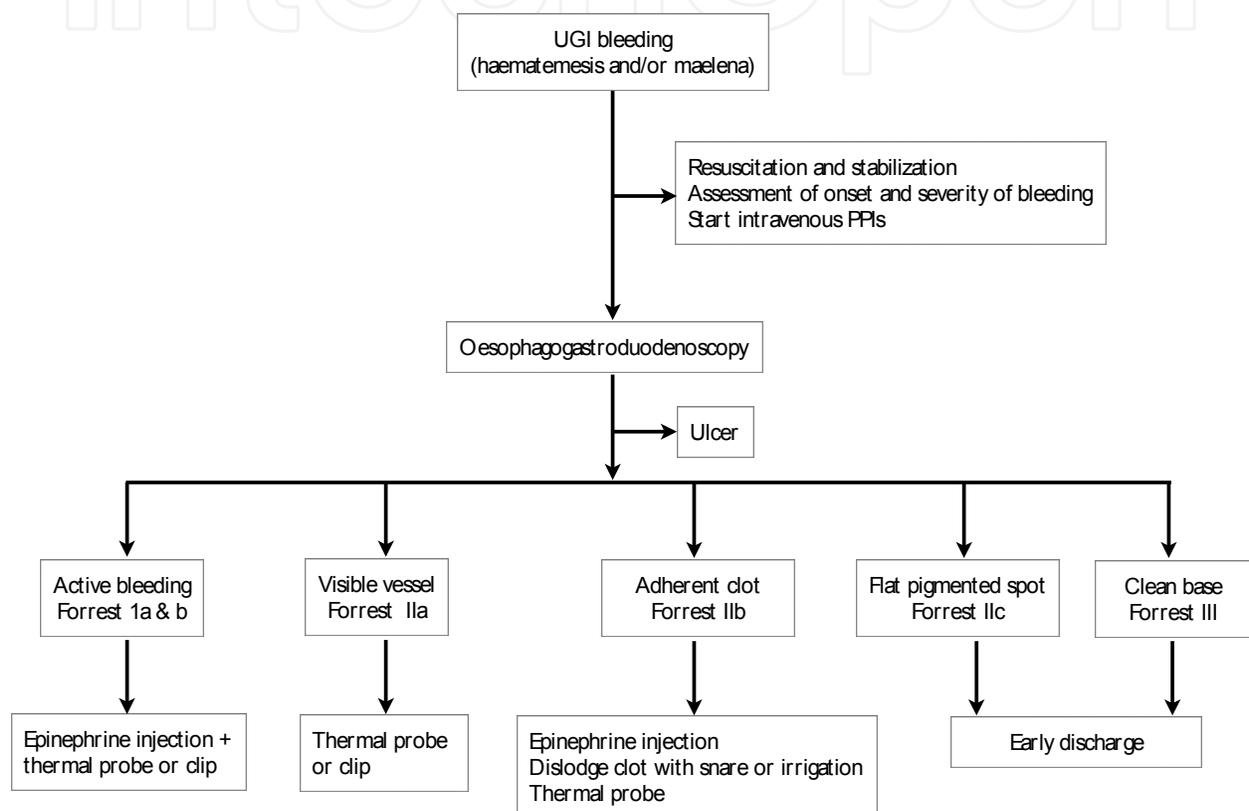


Fig. 1. Approach to upper gastrointestinal (UGI) bleeding. PPIs, proton pump inhibitors.

#### 4.2 Diagnostic endoscopy

Its high sensitivity and specificity in identifying and localizing bleeding lesions, makes upper endoscopy the diagnostic modality of choice for acute UGIB. Early endoscopy within 24 hours of presentation, aids risk stratification of patients and reduces the need for hospitalization. However, it may also expose additional cases of active bleeding and hence increases the use of therapeutic endoscopy. No evidence exists that very early endoscopy (within a few hours of presentation) can reduce risk of rebleeding or improve survival (Tsoi et al., 2009).

A large channel therapeutic upper endoscope should be used to allow for rapid removal of blood from the stomach and to utilize larger endoscopic hemostasis accessories. Well-trained assistants who are familiar with endoscopic hemostasis devices are critical to successful endoscopic hemostasis. At times it may be worth delaying a procedure in order to utilize assistants who are competent at using accessories in emergency situations. Forrest

described an endoscopic classification system that is commonly used (Figure 2). At index endoscopy the prevalence of ulcers with stigmata of recent haemorrhage, defined as Forrest I, IIa and IIb generally accounts for one third and Forrest IIc or III for the remainder (Lau et al., 1998) (Figure 2). An adherent clot is defined as a lesion that is red, maroon, or black and amorphous in texture which cannot be dislodged by suction or forceful water irrigation) (grade IIb). Low-risk lesions include flat, pigmented spots (grade IIc) and clean-base ulcers (grade III) (Figure 3). The inter-observer variation in diagnosing these endoscopic stigmata is low to moderate. At index endoscopy, high-risk lesions with rebleeding rates from 22% to 55% are seen in one-third to one-half of all patients.

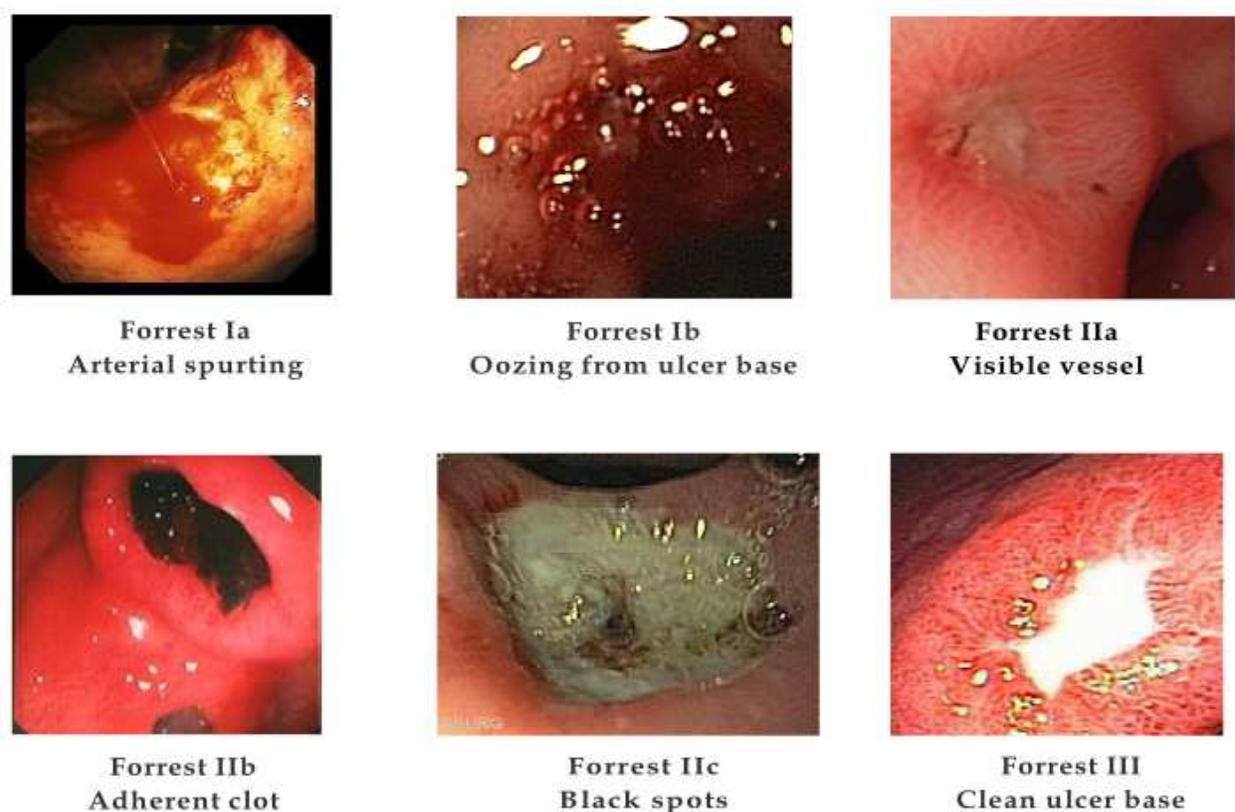


Fig. 2. Endoscopic grading according to Forrest classification

#### 4.2.1 Preparation for emergency esophagogastroduodenoscopy

A large-bore orogastric or NG tube with gastric lavage (use tap water at room temperature) is useful to improve visualization of the gastric fundus on endoscopy; however, this practice has not predictably improved the outcome (Lee et al., 2004). Intravenous erythromycin, as a motilin receptor agonist, promotes gastric motility and substantially improves visualization of the gastric mucosa at index endoscopy. However, erythromycin does not substantially improve the diagnostic yield of endoscopy or the outcome of acute peptic ulcer bleeding. A single 250-mg dose of erythromycin 30–60 minutes before endoscopy should be considered (Carbonell et al., 2006).

Empiric intravenous PPI treatment can be initiated prior to endoscopy in patients that presents with severe UGIB. Several studies and meta-analyses have shown that this practice significantly reduces the proportion of patients with stigmata of recent bleeding at index

endoscopy and therefore the need for endoscopic therapy. However, there is no evidence that PPI treatment affects clinically important consequences, namely mortality, rebleeding or need for surgery (Sreedharan et al., 2010).

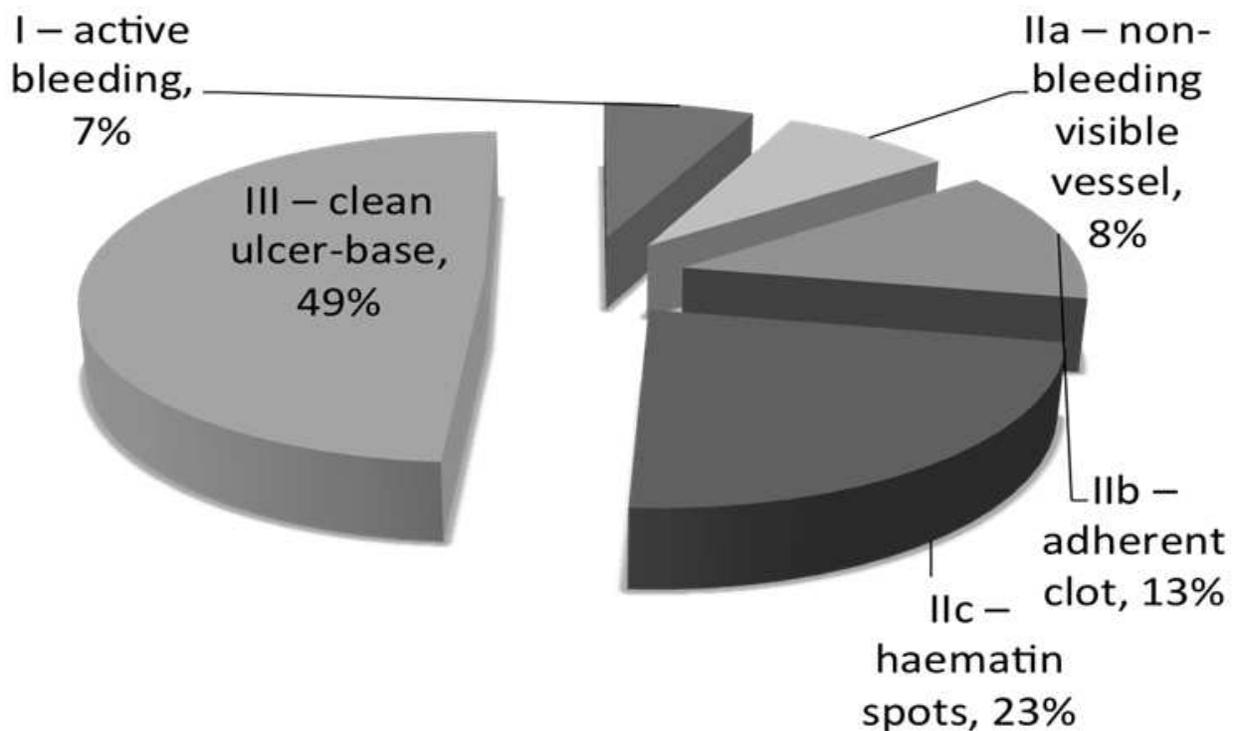


Fig. 2. Stigmata of bleeding prevalence according to the Forrest classification

#### 4.2.2 Stratification of the rebleeding risk

Rebleeding the vital risk factor for mortality increases the rate 5 times compared to patients in whom the bleeding has spontaneously stopped (Church et al., 1999; Forrest et al., 1974). Predictive models evolved to identify high-risk patients for rebleeding and those for early hospital discharge or outpatient care.

The Rockall scoring system is probably the most widely known risk-stratification tool for UGIB. This represents an accurate and validated predictor of rebleeding and death, achieving better results in the prediction of mortality (Rockall et al., 1996). The clinical Rockall score (i.e. the score before endoscopy) is calculated solely on the basis of clinical variables at the time of presentation. For the complete Rockall score the clinical and endoscopic stigmata to predict the risks of rebleeding and death are added; the scale ranges from 0 to 11 points, with higher scores indicating greater risk.

The clinical Rockall and Blatchford scores share mutual features that include the patient's hemodynamic status and comorbid illnesses. These might reduce the need for urgent endoscopic evaluation in patients deemed at low risk. In addition to clinical and laboratory features, endoscopic stigmata can be used to risk-stratify patients that present with acute gastric ulcer bleeding (Table 1).

The endoscopic stigmata of bleeding gastric ulcers provide excellent predictability of the likelihood of rebleeding based on the Forrest classification, which ranges from Ia to III. The risk for rebleeding varies from 55 - 22% in gastric ulcers if left endoscopically untreated

(Laine & Peterson, 1994; Lau et al., 1998). The highest risk is in those with active arterial bleeding (grade I), a non-bleeding visible vessel (grade IIa) and an adherent clot (grade IIb). Additional data are needed to confirm the possible improvement in risk stratification provided by the use of endoscopic Doppler ultrasonography applied directly to the ulcer stigmata.

A. Blatchford Score - At Presentation	Score	B. Rockall Initial Score /7 - Criteria (before gastroscopy)	Score
Systolic Blood Pressure		Age (years)	
• 100 - 109 mmHg	1	• < 60	0
• 90 - 99 mmHg	2	• 60 - 79	1
• <90 mmHg	3	• ≥ 80	2
Blood urea nitrogen		Shock	
• 6.5 - 7.9 mmol/L	2	• "No shock" = (SBP ≥100 mmHg, Pulse <100 /min)	0
• 8.0 - 9.9 mmol/L	3	• "Tachycardia" = (SBP ≥100 mmHg, Pulse ≥100 /min)	1
• 10.0 - 24.9 mmol/L	4	• "Hypotension" = (SBP <100 mmHg)	2
• ≥25 mmol/L	6	Co-morbidity	
Haemoglobin for men		• No major co-morbidity	0
• 12.0 - 12.9 g/dL	1	• Cardiac failure, IHD or any major co-morbidity	2
• 10.0 - 11.9 g/dL	3	• Renal or liver failure, disseminated malignancy	3
• <10.0 g/dL	6	Rockall Full Score /11 - Additional Criteria (after gastroscopy)	
Haemoglobin for women		Diagnosis	
• 10.0 - 11.9 g/dL	1	• Mallory-Weiss tear, no lesion seen, no SRH	0
• <10.0 g/dL	6	• All other diagnosis	1
Other presentation variables		• Malignancy of upper GI tract	2
• Pulse >100/minute	1	Major stigmata of recent haemorrhage	
• Maelena	1	• None - clean ulcer base, flat pigmented spot	0
• Syncope	2	• Blood in upper GI tract, active bleeding, visible vessel, clot	2
• Hepatic disease	2		
• Cardiac failure	2		

Table 1. Risk-stratification tools for UGIB

### 4.3 Therapeutic endoscopy

Gastric ulcers with a high risk of rebleeding should be treated endoscopically at the initial endoscopy. Since the late 1980s, endoscopic haemostatic therapy has been widely accepted as the first-line therapy for UGIB. Many well-conducted, randomized controlled trials, meta-analyses, and consensus conferences have confirmed the efficacy of endoscopic therapy in this setting (Sacks HS et al. 1990; Cook DJ et al., 1992). These data supported a reduction in recurrent bleeding, the need for urgent surgery, and mortality in patients with high-risk stigmata (Barkun et al., 2003; Adler et al., 2004). However, most of these studies were conducted before the widespread use of PPIs, and predominantly used injection therapy, bipolar-probe coagulation therapy, or a combination of injection and coagulation therapy.

In general, for the highest-risk lesions of active bleeding or non-bleeding visible vessels, endoscopic haemostasis alone will decrease the rebleeding rate to approximately 20-25%. The adjunctive use of PPIs decreases this rate even further. Endoscopic therapy can be broadly categorized into injection therapy, thermal coagulation, and mechanical haemostasis. As no single method of endoscopic thermal coagulation therapy is necessarily superior. Therefore, a familiar haemostatic technique applicable to the identified ulcer stigmata should be used.

#### 4.3.1 Injection therapy

Injection therapy is the most commonly used treatment worldwide, mainly because it is widely available, easy to perform, safe and inexpensive. A disposable needle is used to inject a solution (1:10,000) of diluted adrenaline in normal saline. This mainly has a tamponade-

effect induced by the volume of solution injected (15–25 ml being a standard dose). Although solutions of agents other than adrenaline (such as polidocanol, saline and even dextrose) may have a similar effect, none proved superior in achieving haemostasis. The injection of sclerosant (including absolute alcohol) should be avoided as extensive and uncontrolled tissue necrosis of the ulcer base can lead to perforation and related complications. Adrenaline injection as definite haemostatic therapy is not recommended for the risk of rebleeding, but it should be followed either by contact thermal therapy or a second injectable agent (e.g. fibrin glue) to avoid further bleeding, the need for surgery and mortality in bleeding peptic ulcer (Vergara et al., 2007). This practice reduces the risk of perforation and subsequent thermal burn damage that might complicate endoscopic therapy.

#### **4.3.2 Thermal devices**

Thermal devices are the mainstay of endoscopic haemostasis and can be divided into contact (heater probe, monopolar and bipolar electrocoagulation) and noncontact types (laser treatment, argon plasma coagulation [APC]). Although no single method of endoscopic thermal coagulation therapy is superior, electrocoagulation with bipolar contact probes is more commonly used. Haemostasis of the underlying vessel is achieved when heat is generated during contact of these probes with the bleeding lesion. Thermal contact probes can seal arteries up to 2 mm. The risks of thermal probes include perforation and inducing more bleeding. While the haemostatic effects of contact probes are well established by clinical trials, the use of APC in the treatment of peptic ulcer bleeding has only recently been reported. In a randomised, controlled study comparing APC with heater probe coagulation, the former proved equally safe and effective (Chau et al., 2003). No significant differences were detected in terms of initial haemostasis at index endoscopy, frequency of recurrent bleeding, requirement for emergency surgery, number of units of blood transfused, length of hospital stay, and mortality rate.

#### **4.3.3 Mechanical devices**

Mechanical devices in the form of haemoclips for endoscopic haemostasis in bleeding gastric ulcer disease have gained popularity in recent years. In a landmark study by Cipolletta and colleagues, they compared haemoclips with heater probe thermocoagulation (Cipolletta et al., 2001). The successful application of haemoclips led to a significantly decline in recurrent bleeding (1.8% versus 21%). Deployment of haemoclips on fibrotic ulcer floors may prove problematic, especially when used tangentially, or with the endoscope retroflexed. The difficulty of successful application in these situations may limit the efficacy of haemoclips. These technical problems might be overcome with improvements in future design.

#### **4.4 Control of active bleeding or high-risk lesions**

Despite many endoscopists favouring dual endoscopic therapy in patients with severe peptic ulcer bleeding, there is currently no definite recommendation in this regard. In actively bleeding ulcers, an injection can diminish or even stop bleeding; allowing a clear view of the bleeding vessel that in turn facilitates accurate thermal coagulation. Theoretically, the cessation of blood flow prevents dissipation of thermal energy, thereby minimizing tissue injury.

In a systematic review and meta-analysis dual endoscopic therapy proved significantly superior to injection therapy alone. However, it had no advantage over thermal or mechanical monotherapy to improve the outcome of patients with high-risk peptic ulcer bleeding (Marmo et al. 2007). When combining injected substances with thermal coagulation in bleeding peptic ulcer disease, there is a significant risk of complications such as perforation and gastric wall necrosis. Successful application of haemoclips is comparable to thermocoagulation (Sung et al. 2007).

#### **4.5 Managing an ulcer with an adherent clot**

In the event of an ulcer with an overlying clot, attempting to remove the clot by targeted washing is critical. Endoscopic removal of the clot by washing or cold snare has been demonstrated to be effective in reducing the recurrence of bleeding (Bini et al., 2003). The findings under the clot (e.g. bleeding vessel, visible vessel, flat spot, clean base) help determine the therapy needed and improve efficacy by allowing treatment to be applied directly to the vessel. A combination of injection with heater probe or bipolar coaptive coagulation is often used and has been shown to be more effective in patients with active bleeding. Vigorous washing of the clot formed after therapy is useful to determine the adequacy of coagulation.

#### **4.6 Treatment of persistent or recurrent bleeding after initial haemostasis**

Despite the effectiveness of endoscopic haemostasis, rebleeding occurs in 10–25% of cases, irrespective of the method of treatment. A second attempt at endoscopic control is warranted. Some experts have concerns about the perils of a second endoscopy, which may result in delayed surgery, perforation, and increased morbidity and mortality. Combining techniques is sensible when re-treating the ulcer site as the first attempt at endoscopic therapy might have produced necrosis and weakening of the intestinal wall. By using injection as the first step the thickness of the submucosal layer is increased, thus providing some margin of safety.

#### **4.7 Second-look endoscopy**

A planned, second-look endoscopy within 24 hours after initial endoscopic therapy is not recommended on the basis of existing evidence (Barkun et al. 2003; Adler et al. 2004). Even though it proved to be efficacious in two meta-analyses that second-look endoscopy with heater probe coagulation reduces the risk of recurrent bleeding, it had no overall effect on mortality or the need for surgery (Marmo et al. 2003; Tsoi et al. 2009). Also, this approach may not be cost-effective when profound acid inhibition is achieved by high-dose intravenous PPIs (Spiegel et al. 2003). Second-look endoscopy may be considered in patients who are categorized as high risk for rebleeding (shock at presentation, fresh blood in the stomach, endoscopic stigmata of active bleeding, large ulcers and high lesser curvature gastric ulcers) if adjunctive high-dose intravenous PPI was not commenced. Similarly, if at the time of index endoscopy clots obscured the endoscopic view or the efficacy of the primary endoscopic haemostasis is doubtful, second-look endoscopy may be indicated (Chiu & Sung, 2010).

#### **4.8 *Helicobacter pylori* testing**

As one of the main etiological risk factors, all patients with acute bleeding gastric ulcers should be tested for *Helicobacter pylori* infection. Confirmatory testing for *Helicobacter pylori*

in the setting of acute ulcer bleeding may be false negative. Biopsy-based methods, such as rapid urease test, histology, and culture, have a low sensitivity, but a high specificity, in patients with UGIB. The accuracy of  $^{13}\text{C}$ -urea breath test remains very high under these circumstances. Stool antigen test is less accurate in UGIB. Although serology seems not to be influenced by UGIB, it cannot be recommended as the initial diagnostic test for *Helicobacter pylori* infection in this setting (Gisbert et al., 2006). Treatment of *Helicobacter pylori* infection is more effective than anti-secretory non-eradicating therapy (with or without long-term maintenance anti-secretory therapy) in preventing recurrent bleeding from peptic ulcer (Gisbert et al., 2004). Therefore, if this infection is not initially detected, it is important to repeat the evaluation subsequently to confirm the initial result. The economic impact of this strategy, especially in young ulcer patients, must be emphasized.

## 5. Pharmacotherapy

Proton pump inhibitors initiated after endoscopic haemostasis of bleeding peptic ulcer significantly reduced rebleeding compared with placebo or  $\text{H}_2$ -receptor antagonists (Sung et al., 2009; van Rensburg et al., 2009). The initiation of PPIs before endoscopy significantly decreases the proportion of patients with stigmata of a recent bleed (e.g. visible vessel) and a need for endoscopic haemostasis, but does not reduce mortality, rebleeding, or surgery risks compared with  $\text{H}_2$ -receptor antagonists or placebo (Dorward et al 2006; Lau et al., 2007). The effects of PPIs are more pronounced in Asian compared with non-Asian populations. There is no role for  $\text{H}_2$ -receptor antagonist, somatostatin, or octreotide in the treatment of acute bleeding gastric ulcer.

The rationale for using acid inhibition in peptic ulcer disease is based on the observation that the stability of a blood clot is reduced in an acidic environment. Acid impairs platelet aggregation and causes disaggregation. Clot lysis is accelerated predominately by acid-stimulated pepsin. Furthermore, it may impair the integrity of the mucus-bicarbonate-barrier. Thus a pH greater than 6 is necessary for platelet aggregation while clot lysis occurs when the pH drops below 6.

### 5.1 Role of $\text{H}_2$ -receptor antagonists and somatostatin (octreotide)

There are no convincing data to support the use of  $\text{H}_2$ -receptor antagonists as these drugs do not reliably or consistently increase gastric pH to 6 irrespective of the route of administration (Julapalli & Graham, 2005). These drugs had minimal efficacy in clinical trials and the development of tolerance is a problem.

Somatostatin and its analogue, octreotide, inhibit both acid and pepsin secretion and reduce gastroduodenal mucosal blood flow. However, these drugs are not routinely recommended in patients with peptic ulcer bleeding, since contemporary randomized, controlled trials have shown little or no benefit attributable to them, either alone or in combination with an  $\text{H}_2$ -receptor antagonist. Furthermore, there are no strong data to support the adjunctive use of these drugs after endoscopic therapy for ulcer bleeding. (Arabi et al., 2006).

### 5.2 Role of proton pump inhibitors

Proton pump inhibitors can increase the intra-gastric pH > 6.0 for 84 – 99% of the day (Lin et al., 1998). Tolerance has not been reported and continuous infusion is superior to intermittent bolus administration (Brunner et al., 1996). Pantoprazole given as an initial 80-

mg bolus injection, followed by 8 mg/h continuous infusion, seems to be the adequate treatment in patients with a high risk of rebleeding. Compared to an initial 80 mg-bolus injection, followed by 6-mg/h continuous infusion, it demonstrated a lower inter-individual variability of intra-gastric pH and the pH was  $\geq 6$  for a greater percentage of time (van Rensburg et al. 2003). About five percent of patients with peptic ulcer bleeding responded poorly to intravenous omeprazole with rebleeding rates higher in patients with a mean intra-gastric pH of less than 6 (Hsieh et al., 2004).

PPIs in bleeding peptic ulcer have shown to reduce the rebleeding rate and the need for surgery, but not mortality whether the patients had an attempt at endoscopic haemostasis or not. PPI therapy for ulcer bleeding proved more efficacious in Asia than elsewhere. This may be due to an enhanced pharmacodynamic effect of PPIs in Asian patients (Leontiadis et al., 2005). The use of high-dose PPIs (80-mg bolus, followed by 8-mg/h as continuous infusion for 72 hours) has been widely studied and used. However, the most effective schedule of proton pump PPI administration following endoscopic haemostasis of bleeding ulcers remains uncertain. It has been shown in a systemic review and meta-analysis that compared with low-dose PPIs, high-dose PPIs do not further reduce the 30-day rates of rebleeding, surgical intervention, or mortality after endoscopic treatment in patients with bleeding peptic ulcer (Wang et al., 2010).

### 5.2.1 Proton pump inhibitors – clinical effectiveness and cost-effectiveness

Potent acid-suppressing PPIs do not induce tachyphylaxis and have had favorable clinical results. Recent meta-analyses showed that the use of proton-pump inhibitors significantly decreased the risk of ulcer rebleeding (odds ratio, 0.40; 95% confidence interval [CI], 0.24 to 0.67), the need for urgent surgery (odds ratio, 0.50; 95% CI, 0.33 to 0.76), and the risk of death (odds ratio, 0.53; 95% CI, 0.31 to 0.91), (Bardou et al., 2005; Leontiadis et al., 2006) findings that have also been confirmed in a “real-world” setting (Barkun et al., 2004). In ulcer bleeding, PPIs reduce rebleeding and the need for surgery and repeated endoscopic treatment. PPIs improve mortality among patients at highest risk i.e. patients with active bleeding or a non-bleeding visible vessel (Leontiadis et al., 2007) compared with placebo or H<sub>2</sub>-receptor antagonists. PPI treatment initiated prior to endoscopy in UGIB significantly reduces the proportion of patients with stigmata of recent bleeding at index endoscopy but does not reduce mortality, re-bleeding or the need for surgery. The strategy of giving oral PPI before and after endoscopy, with endoscopic haemostatic treatment for those with major stigmata of recent haemorrhage, is likely to be the most cost-effective.

Treatment of *Helicobacter pylori* infection was found to be more effective than anti-secretory therapy in preventing recurrent bleeding from peptic ulcer. *Helicobacter pylori* eradication alone or eradication followed by misoprostol (with switch to PPI, if misoprostol is not tolerated) are the two most cost-effective strategies for preventing bleeding ulcers among *Helicobacter pylori*-infected NSAID users, although the data cannot exclude PPIs also being cost-effective. Further large randomised controlled trials are needed to address areas such as PPI administration prior to endoscopic diagnosis, different doses and administration of PPIs, as well as the primary and secondary prevention of UGIB (Leontiadis et al., 2007).

## 6. Interventional radiology

Angiography with transcatheter embolization provides a non-operative method to identify and control bleeding when the endoscopic approach fails. Although the technical success

rate can be as high as 90–100%, the clinical success rate varies from 50–83% (Cheung et al., 2009). Embolization might not stop the bleeding permanently.

## 7. Surgery

The role of surgery in acute peptic ulcer bleeding has markedly changed over the past two decades. The widespread use of endoscopic treatment has reduced the number of patients requiring surgery. Therefore, the need for routine early surgical consultation in all patients presenting with acute UGIB is now obviated (Gralnek et al., 2008).

Emergency surgery should not be delayed, even if the patient is in haemodynamic shock, as this may lead to mortality (Schoenberg, 2001). Failure to stop bleeding with endoscopic haemostasis and/or interventional radiology is the most important and definite indication. The surgical procedures under these circumstances should be limited to achieve haemostasis. The widespread use of PPIs obviated further surgical procedures to reduce acid secretion. Rebleeding tends to necessitate emergency surgery in approximately 60% of cases with an increase in morbidity and mortality (Schoenberg et al.; 2001). The reported mortality rates after emergency surgery range from 2 – 36%.

Whether to consider endoscopic retreatment or surgery for bleeding after initial endoscopic control is controversial (Cheung et al., 2009). A second attempt at endoscopic haemostasis is often effective (Cheung et al., 2009), with fewer complications avoiding some surgery without increasing mortality (Lau et al., 1999). Therefore, most patients with evidence of rebleeding can be offered a second attempt at endoscopic haemostasis. This is often effective, may result in fewer complications than surgery, and is the current recommended management approach.

Available data suggest that early elective surgery for selected high-risk patients with bleeding peptic ulcer might decrease the overall mortality rate. It is a reasonable approach in ulcers measuring  $\geq 2$  cm or patients with hypotension at rebleeding that independently predicts endoscopic retreatment failure (Lau et al., 1999). Early elective surgery in patients presenting with arterial bleeding or a visible vessel of  $\geq 2$  mm is superior to endoscopic retreatment and has a relatively low overall mortality rate of 5% (Imhof et al., 1998 & 2003). Additional indications for early elective surgery include age  $>65$  years, previous admission for ulcer plication, blood transfusion of more than 6 units in the first 24 hours and rebleeding within 48 hours (Bender et al., 1994; Mueller et al., 1994). This approach is associated with a low 30-day mortality rate as low as 7%.

## 8. Conclusion and recommendations

Peptic ulcer bleeding, the most common cause for UGIB, is best managed using a multidisciplinary approach. The initial clinical evaluation involves an assessment of haemodynamic stability and the necessity for fluid replacement. Combined with early endoscopic findings (within the first 24 hours), patients can effectively be risk-stratified for recurrent ulcer bleeding and managed accordingly. Those patients with active arterial bleeding or a visible vessel in the ulcer base should receive combined endoscopic therapy (that is, injection and thermal coagulation) as standard of care.

Despite a lack of concrete evidence of high-dose PPIs being more effective than non-high-dose PPIs, an 80-mg bolus followed by 8-mg/h as continuous infusion for 72 hours should be commenced as this is the only method of administration that reliably achieves the desired

high intra-gastric target-pH. Optimal management of bleeding peptic ulcer with an adherent clot should probably include an attempt at endoscopic removal, where after the same treatment to reduce the risk of recurrent bleeding should be affected. In the event of rebleeding after initial successful endoscopic haemostasis repeat-endoscopic therapy should be performed rather than surgery with generally a similar outcome with fewer complications.

For refractory bleeding, transcatheter angiography is equally effective as surgery and should be considered particularly in patients at high surgical risk. Second-look endoscopy should not routinely be performed considering the limited reduction in rebleeding rate and the questionable cost-effectiveness as profound acid inhibition is achieved with current medical treatment. Critical issues are detecting and eradicating *Helicobacter pylori* infection and the resuming NSAIDs or anti-platelet agents when clinically indicated with co-administration of gastro protective agents.

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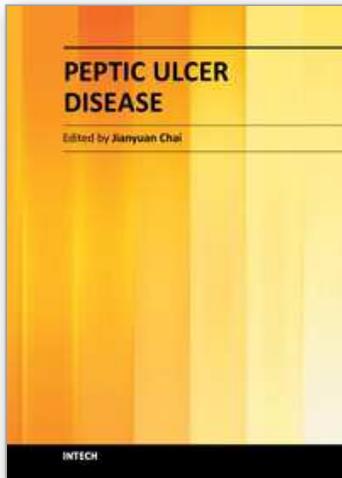
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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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