CLINICAL PRACTICE GUIDELINES

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MANAGEMENT OF NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN SOCIETY OF GASTROENTEROLOGY AND HEPATOLOGY

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Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in April 2003 and will be reviewed in April 2005 or sooner if new evidence becomes available

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1. INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common medical emergency associated with significant morbidity and mortality. Acute upper gastrointestinal haemorrhage accounts for about 2500 hospital admissions each year in the United Kingdom (2). The annual incidence varies from 47 to 116 (approximately 100) per 100 000 of the population and is higher in socioeconomically deprived areas (3) .The incidence is approximately 72 per 100000 in Malaysia (4,5) .Bleeding peptic ulcer remains the most common cause of acute non-variceal upper gastrointestinal bleeding.80% of such bleeds stop spontaneously. However, 20% of patients may have persistent or recurrent bleeding. Much of the morbidity and mortality of upper gastrointestinal bleeding occurs in patients with recurrent bleeding or significant co-morbid illnesses.

Hospital mortality has not improved over the past 50 years and remains at about 10%.This may in part be due to the fact that older patients, who have advanced cardiovascular, respiratory, or cerebrovascular disease that puts them at increased risk of death, now comprise a much higher proportion of cases. Therapeutic endoscopy is considered a safe and effective form of treatment today (6). Analysis of clinical and endoscopic factors permits accurate risk assessment, rational treatment planning and improved outcome.

2. AETIOLOGY

The commonest cause of Non-variceal UGIB is peptic ulcer disease. A history of proved ulcer or ulcer-like dyspepsia is absent in about 20% of cases. In these patients consumption of aspirin or non-steroidal antiinflammatory drugs (NSAIDS) is common. Infection with *Helicobacter pylori* is less prevalent in bleeding ulcers than in uncomplicated ulcers (7,8) .

2.1 Peptic Ulcers

Peptic ulcer bleeding occurs predominantly from duodenal ulcer or gastric ulcers. It occurs as a result of erosion of blood vessels and the severity of the bleed is dependent on the size of the vessel affected. Simple oozing is caused by damage to small submucosal vessels less than 0.1 mm in diameter. More severe arterial bleeding indicates a large vessel between 0.1 and 2 mm in diameter in the base of the ulcer has been eroded by the inflammatory process. Large ulcers arising from the posterior part of the duodenal cap can erode the gastroduodenal artery and provoke brisk bleeding.

2.2 Erosions

Acute erosive gastritis can cause persistent haemorrhage as a result of diffuse loss of mucosal epithelium and small ulcers. This condition is often associated with the use of non-steroidal anti inflammatory drugs, steroids and intake of alcohol. Haemorrhagic gastritis which probably occurs as a result of impaired mucosal blood flow is often caused by stressful stimuli including shock, hepatic failure and head injury.

2.3 Oesophagitis

Oesophagitis usually only causes minor acute bleeding. Occasionally a significant vessel may be involved with consequent massive arterial haemorrhage.

2.4 Mallory-Weiss Tear

This is an acute tear at the gastro-oesophageal junction as a result of severe vomiting or retching, often after excessive alcohol intake. Mallory-Weiss tear occurs mostly in the gastric mucosa, but may extend into the oesophagus resulting in profuse vomiting of bright red blood which usually settles spontaneously. Endoscopic haemostasis may sometimes be required. Occasionally repeated vomiting may result in a full thickness tear (Boerrhaave's syndrome) which is associated with sudden onset of severe pain in the upper abdomen or chest.

2.5 Malignancy

Carcinoma and lymphoma of the stomach commonly bleed at an advanced ulcerated stage, and occasionally present with acute haemorrhage.The prognosis is usually dictatated by the stage of the disease.

2.6 Miscellaneous

There are several other causes which may present as upper non-variceal gastrointestinal haemorrhage and these are listed in Table 1.

Table 1: Aetiology of Non-variceal Upper Gastrointestinal Bleeding (8)

Oesophagus

Mallory-Weiss tear, Reflux oesophagitis, Oesophageal ulcer, Barret's ulcer,Cameron ulcer within hiatus hernia*, Oesophageal neoplasm

Stomach

Gastric ulcer, Gastric erosions, Haemorrhagic gastritis,Gastric carcinoma, Gastric lymphoma, Leiomyoma, Gastric polyp, Hereditary haemorrhagic telangiectasia, Dieulafoy lesion*,Gastric Antral Vascular Ectasia(GAVE)*,Angiodysplasia*

Duodenum

Duodenal ulcer, Duodenal erosions, Vascular malformation, Aorta-duodenal fistula,Polyps (including Peutz-Jeghers syndrome and other polyposis syndromes), Carcinoma of ampulla, Carcinoma of pancrease, Haemobilia*

Small bowel

Stomal ulcer, Diverticulum (including Meckel's diverticulum),Vascular malformation, Tumor

*****Important causes of obscure UGIB

3. EPIDEMIOLOGY

UGIB is a common reason for emergency admission to hospitals. A recent large prospective study from the United Kingdom reported an overall incidence of 103 per 100000 adults per year, with an overall mortality of 14% but only 0.6% for those below 60 years of age without comorbidity. Most deaths were in elderly patients with considerable comorbidity (2). A retrospective study from USA also showed a similar incidence of 102 per 100000 adults (3) .Figures available from a small prospective study from Singapore more than a decade ago showed an overall mortality of 10% (9).

The incidence of UGIB is twice as high in men as in women. The incidence increases markedly with age. Consequently, many patients presenting with UGIB have an active comorbid condition, a consistent risk factor for increased mortality. A recent local multicentre prospective study has provided new information on the epidemiology of UGIB in Malaysia (4) Recruiting 1830 patients from four government hospitals in East Malaysia over a period of two years, the study reported an incidence of UGIB of 72 per 10,0000 population and this peaked around the 4th to 6th decade. Mortality rate from UGIB was 10.2% but increased substantially with age and did not differ between the sexes. Inpatients that were admitted for other diagnosis but developed UGIB had the highest mortality; at almost 5 times higher than those with emergency admissions or transfers from other hospitals for UGIB. 64% of those admitted in this series had peptic ulcer disease as a cause of bleeding. The next most frequent cause is mucosal erosive diseases at 16.5%. Variceal bleed accounted for 6.4% and malignancies 3.6%. Almost 9% of patients had no discernable cause for UGIB after endoscopy. These results are comparable to other reported series. Interestingly, 1 in 7 patients with variceal bleed also had concomitant peptic ulcer disease.

Peptic ulcer disease has been documented as the main aetiological factor in UGIB in Malaysia. There are comparatively fewer cases of peptic ulcer disease in the Malay-majority east coast states of Terengganu and Kelantan, thought to be related to a low *Helicobacter pylori* infection rate (10-12). The Chinese patients predominate in the UGIB cases in urban centres such as Ipoh and Kuala Lumpur (13, 14). In Kota Kinabalu, comparing the distribution of the UGIB cases with that of the racial distribution in the state, the Chinese and the Kadazandusuns, one of the major indigenous groups, have a significantly higher rate of UGIB than expected and, reflecting the situation in West Malaysia, the Malay and Bajau ethnic groups have the lowest rate and relative risk of UGIB (5).

4. RISK FACTORS

4.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Some 15-30% of patients exposed to NSAIDs develop gastroduodenal ulcers, but the rate of serious gastrointestinal events such as bleeding, perforation and obstruction is

approximately ten times less (15) .The occurrence of injury may depend on clinical factors, type and dose of NSAID used.The use of NSAIDs has also been found to be a risk factor for peptic ulcer rebleeding in some studies.It may increase the risk of ulcer complications by a factor of four (16) .The risk of bleeding increases with older age, the use of conventional NSAIDs, co-morbid conditions, concomitant ingestion of steroids and anticoagulants and a prior history of gastrointestinal complications (17) .The advent of the selective COX-2 inhibitors holds promise in terms of reduced gastrointestinal toxicity (18) .

4.2 Aspirin

Exposure to aspirin carries a definite risk of gastroduodenal injury (19) .The risk of upper gastrointestinal bleeding is similar among users of non-coated low-dose aspirin and coated low-dose aspirin. Any dose of aspirin has the potential to cause gastrointestinal bleeding,the enteric-coated form carrying the same risk as plain aspirin (20) .The concomitant use of NSAIDs increases the risk of complications. A history of UGIB is a significant risk factor for recurrent bleeding in those taking low-dose aspirin or other NSAIDs (21).

4.3 Helicobacter Pylori

Helicobacter pylori is the main cause of uncomplicated peptic ulcer disease. The benefit of *H. pylori* eradication to decrease ulcer recurrence and bleeding after eradication of *H. pylori* infection at the index episode of bleeding is well established for those lesions that have *H. pylori* as the sole etiological factor (22-24). The protective effect afforded by *H. pylori* cure in this setting provides the same level of protection as that of continuous antisecretory therapy (25).The mode of *H. pylori* testing in the setting of UGIB may be of importance. In particular, biopsy-based urease tests may be false-negative (26).The interaction between NSAIDs and *H. pylori* remains controversial (27) .Eradication treatment may be appropriate for patients who had sustained UGIB secondary to low-dose aspirin, while treatment with omeprazole appears the best strategy for the prevention of recurrent-bleeding from NSAID-induced ulcers (28) .*H .pylori* contributes to an increased ulcer risk for patients starting NSAID treatment ,whereas NSAIDs probably account for the majority of ulcer disease in chronic NSAID users. The eradication of *H. pylori* substantially reduces the risk of ulcers for patients who are about to start long-term NSAIDs (29).

5. ASSESSMENT, RESUSCITATION AND RISK STRATIFICATION

5.1. Clinical Presentation

Acute upper gastrointestinal bleeding can present with either haemetemesis or melaena or both. Haemetemesis with bright red vomitus indicates acute bleeding while recent bleeding appears as “coffee grounds” vomitus due to gastric acid breaking down the

haemoglobin in red cells to haematin. Melaena consists of black, tarry, loose or sticky and malodorous stool due to degradation of blood in the intestine (30, 31).

Table 2: Upper Gastrointestinal Bleeding: Clinical Situations

Acute

1. Haemetemesis with or without melaena
2. Melaena with or without haemetemesis
3. Rarely Haematochezia indicating massive life threatening bleed

Chronic

4. Iron deficiency anaemia with or without evidence of visible blood loss
5. Blood loss detected by positive Occult Blood Test

5.2 Patient Assessment

Close monitoring of blood pressure, pulse and gross evidence of ongoing bleeding is mandatory. Agitation, pallor, hypotension and tachycardia may indicate shock requiring immediate volume replacement. Shock occurs when blood loss approaches 40% of the total blood volume. Postural hypotension of 10 mmHg or higher usually indicates at least 20% reduction in blood volume. Initial haematocrit obtained for a patient with acute bleeding poorly reflects the degree of blood loss due to haemoconcentration. The immediate goal is to resuscitate the patient to ensure a stable haemodynamic status prior to endoscopy.

5.3 Clear Airway

A drowsy or comatose patient is at high risk of aspiration if vomiting or haemetemesis continues. The patient is kept flat on his/her side. A cuffed endotracheal tube may be inserted to protect the airways if needed.

Table 3: Mental Status May Be Impaired Due To

1. Cerebral hypoperfusion due to severe acute blood loss
2. Encephalopathy due to concomitant chronic liver disease or renal failure
3. Alcohol or drug intoxication/overdose

5.4. Resuscitation

An immediate assessment of haemodynamic status and red cell transfusion requirements must be made.A confused, clammy and sweaty patient with cold peripheries and a fast thready pulse suggest hypovolaemia. The blood pressure may be low. Although no

controlled trials have examined each of the elements of resuscitation, the following are recommended (32) (*Grade C*).

Resuscitation must be commenced immediately with the insertion of at least two large bore intravenous cannulae, which should be inserted into large peripheral veins. Supplemental oxygen may help a confused, agitated elderly patient. Central venous pressure (CVP) monitoring is advisable in patients with profound shock or organ failure and in elderly patients with significant comorbidity. Given the lack of evidence for colloids, crystalloids are the choice for fluid resuscitation. Fluid resuscitation can be commenced with isotonic crystalloid solutions (0.9N saline, lactated Ringer's solution). Blood samples must be drawn for urgent full blood count, blood grouping and cross matching, coagulation screen, blood urea and electrolyte and liver function tests.

Table 4: Blood Tests On Admission To Hospital (1,7)

Haemoglobin-May be normal during the acute stages until haemodilution occurs

Urea and electrolytes-Elevated blood urea suggests severe bleeding

Cross match for transfusion-Two units of blood are sufficient unless bleeding is extreme. If the transfusion is not needed urgently, group the blood and save the serum

Liver function tests

Prothrombin time

The evidence to guide red cell transfusion is limited (*Grade C*). Packed cells are the preferred form of blood transfusion. The aim of transfusion is to restore blood volume and pressure and to correct anaemia to maintain the oxygen carrying capacity. This means maintaining a haemoglobin level of approximately 10 g/dl. Fresh frozen plasma may be given if the prothrombin time is at least 1.5 times higher than the control value. Platelet transfusion is indicated if the platelet count is below50 000/mm^3

Table 5: Indications For Blood Transfusion In Patients With Gastrointestinal Bleeding (7,8)

1.Systolic BP < 110 mmHg
2.Postural hypotension
3.Pulse > 110/min
4.Haemoglobin <8g/dl
5.Angina or cardiovascular disease with a Haemoglobin <10g/dl

5.5 Assessment of Ongoing Bleeding

Continuous haemetemesis or persistent hypovolaemia despite aggressive resuscitation suggest bleeding is still active. Passage of melaena does not imply continuous bleeding. However passage of "fresh" melaena, which is maroon coloured or passage of bright red visible clots suggest active bleeding. The insertion of a nasogastric tube may be helpful in demonstrating active bleeding.However,it may be poorly tolerated. The caveat is when there is a bleeding ulcer with the pylorus in spasm. Aspirate without evidence of blood or "coffeee-grounds" material is seen in about 15% of patients with UGIB (32).

5.6 Elucidating the Source of Bleeding

A good history from the patient or relatives and a quick examination help suggest the aetiology of the gastrointestinal bleeding. Ask for history of retching (Mallory Weiss tear), history of NSAIDS or aspirin, previous peptic ulcer disease, dyspepsia, ethanol ingestion, traditional medication and a history of hepatitis B or C. Examine for stigmata of chronic liver disease (e.g. palmar erythema, spider naevi ,etc), features of portal hypertension (eg ascites, splenomegaly. caput medusae), cutaneous and buccal telangiectasia (Osler-Weber-Rendu syndrome).

5.7 Risk Assessment

When a patient presents with gastrointestinal bleeding, risk assessment and resuscitation proceed simultaneously. Such assessment aids in rational decision making regarding treatment options. At the initial assessment it is important to define the factors that have prognostic importance (33) (Table 6). The main factors predicting death include increasing age, comorbidity and endoscopic findings. Mortality is low in patients below 40 years of age but increases steeply thereafter. Patients with severe comorbidity, particularly renal failure, liver failure and disseminated malignancy have a poor prognosis *(Grade A).* Death in these patients is more often due to disease progression rather than to the upper gastrointestinal bleeding. Patients who developed UGIB after hospitalisation for other serious illnesses have a much worse prognosis than those who are admitted because of bleeding, with a mortality of about 30%.

Endoscopic findings of active, spurting haemorrhage and a non-bleeding visible vessel within an ulcer are associated with a definite risk of rebleeding (Tables 7, 8) .The absence of these stigmata, varices or upper gastrointestinal cancer indicates a low risk of rebleeding (*Grade A)* .

Table 6: Risk Factors For Death After Hospital Admission For Acute Upper Gastrointestinal Bleeding (33)

1. Advanced age
2. Shock on admission(pulse rate >100 beats/min; systolic blood pressure < 100mmHg)
3. Comorbidity (particularly hepatic or renal failure and disseminated malignancy)
4. Diagnosis (worst prognosis for advanced upper gastrointestinal malignancy)
5. Endoscopic findings (active, spurting haemorrhage from peptic ulcer; non-bleeding visible vessel)
6. Rebleeding (increases mortality 10 fold)

Table 7: Forrest Classification For Bleeding Peptic Ulcer (34)

Ia: Spurting Bleeding

Ib: Non spurting active bleeding

IIa: visible vessel (no active bleeding)

IIb: Non bleeding ulcer with overlying clot (no visible vessel)

IIc: Ulcer with hematin covered base

III: Clean ulcer ground (no clot, no vessel)

SRH=Stigmata of recent haemorrhage. Major SRH=Forrest 1a, 1b, 2a and 2b.

Minor SRH=Forrest 2c and 3.

5.7.1 Endoscopy For Risk Assessment

Early upper gastrointestinal endoscopy (within 12-24 hours) is the cornerstone of management of UGIB. Early endoscopy has 3 major roles viz. diagnosis, treatment and risk stratification. It is the most accurate method available for identifying the source of bleeding. Once the Forrest grade of ulcer is identified (Table7; Appendix 2), a risk assessment may be made and a decision made on whether ongoing hospitalisation is needed. Recently, a number of studies have indicated that systematic assessment of clinical and endoscopic risk factors (endoscopic triage) may obviate hospitalisation in some patients and may help in determining the appropriate length of stay in others (36-38) . Those determined to be at low-risk based on clinical and endoscopic criteria were discharged on the day of presentation and received out-patient care (39, 40). The aforementioned findings have led to the development of practice guidelines and clinical

care pathways for UGIB (41, 42) with some incorporating an initial phase of endoscopic triage (43).

Table 8: Risk of Rebleeding And Mortality In Patients With Peptic Ulcer Bleeding (35)

Endoscopic finding (SRH)*	Risk of Rebleeding (%)	Mortality (%)
Active bleeding	55	11
Visible Vessel	43	11
Adherent Clot	22	7
Flat Spot	10	3
Clean Base	5	2

*SRH=Stigmata of recent haemorrhage.

5.7.2 Use Of Risk Stratification Scoring Systems

A number of scoring systems have been designed to ascertain risk factors for poor outcome in patients with UGIB (33, 36, 38). One such system (Rockall risk assessment score), derived from the data of a national audit, is based on age, presence of shock, co-morbidity, diagnosis and endoscopic stigmata of recent haemorrhage (33) . In the Rockall risk assessment score, a series of independent risk factors were scored (Appendix 1) . Patients who score 2 or less have a mortality of 0.1% and a rebleeding rate of 4.3%, but a score in excess of 8 is associated with a 41% mortality and rebleeding rate of 42.1%.The score was more reliable in predicting mortality than it was in predicting rebleeding (*Grade A)* .Such risk assessment scores may be useful in triaging patients for either outpatient care or admission to an high dependency unit (37).

6. ENDOSCOPIC THERAPY

Endoscopic therapy has been shown to improve outcome in nonvariceal haemorrhage (*Grade A).* In a recent meta-analysis of 30 randomized trials involving more than 2000 patients, endoscopic therapy reduced rates of further bleeding (OR 0.38;95% confidence interval 0.32 to 0.45) , the need for urgent surgery (OR 0.36;95% CI 0.28 to 0.45) , and mortality (OR 0.55; 95% CI 0.40 to 0.76) (44) . Early gastroscopy is very valuable as a therapeutic and prognostic instrument , decreases rates of blood transfusions and significantly reduces hospital length of stay (45) (*Grade A*).

After resuscitation, endoscopy is undertaken. In most cases this is done electively on the next available routine list but within 24 hours of admission. Only a minority of profusely bleeding patients need "out of hours" emergency endoscopy. On-call endoscopists must be experienced and be able to apply a range of endoscopic treatments. Endoscopic therapy is indicated when there are major stigmata of recent haemorrhage (SRH). There is little doubt that Forrest 1a, 1b and 2a ulcers should have endoscopic haemostasis (5,35,46,51) (*Grade A).* Patients with an adherent clot may also constitute a high-risk group. Up to one-third of blood clots covering an ulcer can be removed to reveal major stigmata of recent haemorrhage. Current opinion favours the displacement of the clot by irrigation or mechanical removal, followed by endoscopic haemostasis of any underlying visible vessel (47-50) (*Grade A).* Minor SRH i.e. Forrest 2c and 3 ulcers, may be managed conservatively and discharged early.

The various modalities of endoscopic haemostasis are outlined in Table 9.

Table 9: Endoscopic Treatment For Non-variceal Upper Gastrointestinal Bleeding (7,8)

Thermal

- Heater probe
- Multipolar electrocoagulation (BICAP,Gold Probe)
- Argon plasma coagulation
- *Laser*

Injection

- Adrenaline (1:10000)
- Procoagulants(fibrin glue,human thrombin)
- *Sclerosants (ethanolamine, 1% polidoconal)*
- *Alcohol (98%)*

Mechanical

- Clips
- *Band Ligation*
- *Endoloops*
- *Staples*
- *Sutures*

Combination therapy

- Injection plus thermal therapy
- Injection plus mechanical therapy

Methods rarely used are depicted in italics.

6.1 Injection Therapy

6.1.1 Adrenaline

In experimental animal studies, mucosal injection of 1:10000 dilution adrenaline causes prolonged vasoconstriction for up to 2 hours. Adrenaline also causes platelet aggregation and a local tamponade effect on the vessel when injected in large volumes. A total volume of 4 -16ml (1:10000) may be injected safely (1) as most of the adrenaline will undergo first-pass metabolism in the liver. There are few systemic complications other than transient tachycardia. Adrenaline is the injection agent of choice, because it is non-tissue damaging. After bleeding has been controlled, a clear view of the vessel is then possible.

Adrenaline injection has reduced hospital stay, transfusion requirement and operative intervention (41% to 15%).The rebleeding rate in this randomized trial was 15% for adrenaline therapy versus 41% for controls in actively bleeding ulcers (51) (*Grade A*). It remains the gold standard (6, 52). It is cheap, easily available and achieves control in actively bleeding ulcers. It is an essential component of combination therapies.

6.1.2 Sclerosants

1% polidocanol, alcohol and ethanolamine are sclerosants used in ulcer haemostasis. In animal studies 1% polidocanol causes haemostasis by inducing bowel wall spasm and early oedema with subsequent inflammation and thrombosis of the vessel. Absolute alcohol stops bleeding by causing rapid dehydration and fixation of the tissue, thus obliterating the bleeding vessel. The amount of tissue damage is directly related to the volume of sclerosant injected. Alcohol, being more ulcerogenic, induces ulceration which lasts for a longer period. It may reduce rebleeding as well as emergency surgery rates (53) (*Grade B*).

In view of the risk of perforation, caution should be exercised when injecting large volumes of sclerosant. Fatal gastric necrosis has been reported (54). The addition of a sclerosant to the vessel after initial adrenaline injection has not conferred any advantage over adrenaline injection alone (55, 56) (*Grade A*).

6.1.3 Procoagulants (Thrombogenic Agents)

Human thrombin and fibrin sealant are procoagulants that have been investigated in ulcer haemostasis. Human thrombin after epinephrine injection has been compared with epinephrine injection alone. Significant reductions in recurrent bleeding, blood transfusion and deaths were observed in the combined treatment group (57). Fibrin glue is a formulation of fibrinogen and thrombin which when combined instantly forms a fibrin network. The two substances are injected via a double-lumen needle. The advantage of fibrin injection is that very little tissue damage occurs, therefore reducing the risk of tissue necrosis and perforation and allowing repeated injections In a European multicentre trial, patients with actively bleeding ulcers or ulcers with non-bleeding visible

vessels were randomized to receive a single injection of polidocanol, single fibrin sealant injection and daily fibrin injection until clean ulcers were seen. Fibrin sealant significantly reduced recurrent bleeding only if injected daily. A programme of daily scheduled endoscopy and repeated treatment has been advocated (58, 59). There is concern regarding viral transmission with the use of fibrin glue.

6.1.4 Technique of Injection Therapy

A therapeutic video-gastroscope (3.7 or 4.2mm working channel) with a disposable 23 or 25 gauge sclerotherapy needle is recommended. Between 4-16 ml of 1:10,000 adrenaline, in 0.5ml aliquots is injected into and around the bleeding point until the bleeding stops (1). Dehydrated ethanol (98%, Abbott Laboratories) is injected, using a 1-ml disposable plastic tuberculin syringe, with a total dose of no more than 1.5-2 ml. The ethanol is injected slowly, in amounts of 0.1 to 0.2 ml per injection, at three or four sites surrounding the bleeding vessel and 1 or 2 mm from the vessel (60). Polidocanol is less irritating and 10-15ml is used.

6.2 Thermal Modalities

This can be divided into contact and non-contact methods.A distinct advantage of contact over non-contact electrocoagulation is that mechanical pressure can be applied to the bleeding point using the electrode to compress the bleeding vessel prior to coagulation. The principle of coaptive coagulation is that a combination of mechanical compression and heat treatment produces a stronger sealing of the blood vessel compared to non-mechanical treatment.

6.2.1 Thermal Contact Methods

6.2.1.1 Monopolar electrocoagulation

In monopolar electrocoagulation the current flows through the patient and exits via a ground plate. Due to an unpredictable depth of coagulation, monopolar electrocoagulation is no longer recommended for endoscopic haemostasis (60).

6.2.1.2 Multipolar electrocoagulation

A multipolar electrocoagulation probe consists of 3 pairs of electrodes arranged in a linear array at the tip and connected to a power generator. The flow of the electrical current is limited between the electrodes on the probe thus avoiding problems with grounding and aberrant current. The depth of injury is shallower and more predictable compared to monopolar electrocoagulation. Small 7Fr and large 10Fr probes (BICAP,Gold Probe) are available for use with 2.8mm and 3.7mm channel endoscopes respectively. Optimal effect can be obtained by using a large 3.7mm probe with a low power setting of 3-5 on the generator and prolonged coagulation using 10-14 pulses of 2 seconds (60).The efficacy of BICAP is similar to that of the heater probe (61) (*Grade B)* .

6.2.1.3 Heater probe

The tip of the heater probe consists of a metal tip covered by Teflon which is heated by a computer-controlled coil to a temperature of 250℃. Practically this requires (i) forceful tamponade using a 3.2mm probe and (ii) sustained coagulation with 4 consecutive pulses at 30J for at least 8 seconds (62) .The heater probe is useful because it includes a water jet to wash away any blood. In general, heater probe and adrenaline injection are comparable in their efficacy (63) (*Grade A).* The rebleeding rates with the use of heater probe alone in comparison with laser or controls, and in comparison with laser or BICAP were not statistically significant (64).

6.3 Combination Therapy

The addition of heater probe therapy to epinephrine injection in the subgroup of patients with a spurter significantly reduced the need for surgery when compared to epinephrine injection alone (65) (*Grade B).* Most studies, however, have not demonstrated any added benefit in combining injection therapy with thermal coagulation. The latter not withstanding, the current trend favours combination therapy using injection as well as thermal or mechanical therapy (8).

6.4 Thermal non-contact methods

6.4.1 Argon Plasma Coagulation

Argon plasma coagulation (APC) is a special electrosurgical modality in which high-frequency electric current is conducted ‘contact-free’ through ionized and thus electrically conductive argon (argon plasma) into the tissue to be treated. The aim of this technique is to create therapeutically effective temperatures for thermal haemostasis and/or the ablation of pathologic tissue.

In haemostasis, APC is especially useful for diffuse bleeding arising from a large area, bleeding owing to coagulation disorders or tumour bleeding. It has been used successfully to treat gastric antral vascular ectasia (GAVE) (69), angiodysplasia and haemorrhagic telangiectasia.. Reported complications (< 1%) include bowel wall emphysema, pneumomediastinum and perforation.

Treatment of bleeding ulcers with APC does not appear to confer any advantage over the heater probe for endoscopic haemostasis (70) (*Grade B).*

6.4.2 Laser

Several trials comparing the methods of monopolar, multipolar, and heater-probe electrocoagulation with Nd:YAG and argon laser, as well as the injection modalities of adrenaline, ethanol and polidocanol revealed that all methods were effective in lowering the incidence of rebleeding and the need for emergency surgery (64,66-68).

Complications of laser therapy include perforation, bleeding, fistula formation and stenosis. Laser therapy is currently not recommended (1) (*Grade B).*

6.5. Other Endoscopic Modalities

6.5.1 Mechanical Methods

Endoscopic placement of metal clips has recently been advocated for haemostasis (*Grade B).* One prospective randomised trial compared haemoclips with a thermal modality. Acute rebleeding occurred in 1.8% of the haemoclip patients compared with 21% of heater probe patients ($p<0.05$). The median number of blood units transfused and hospital days was also significantly lower for haemoclips. There was no difference in emergency surgery rate or 30-day mortality (71). Haemoclips may be particularly useful for actively bleeding large vessels but may be difficult to apply in awkwardly placed ulcers (e.g. high lesser curve or posterior duodenal ulcers) (1, 72).

7. PHARMACOLOGICAL THERAPY

In vitro, platelet aggregation and disaggregation, coagulation and fibrinolysis are strongly dependent on intragastric pH. Platelet aggregation and blood coagulation are optimal at pH 7.4 (73) .Peptic digestion of the thrombus is maximal in the pH range of 1-3.5 and pepsin 1 may continue to function up to pH of 5 (74). Platelet aggregation is also severely impaired at low pH in-vitro. As blood coagulation and platelet aggregation are abolished at pH lower than 5.4, the perceived failure of traditional antisecretory drugs to promote haemostasis in bleeding peptic ulcers may reflect inadequate pH control. Acid suppressive therapy also decreases the increased fibrinolytic activity noted in bleeding ulcers (75) .This has provided the rationale use of more potent acid reducing agents such as proton pump inhibitors in the management of peptic ulcer bleeding.

7.1 H2-Receptor Antagonists

A meta-analysis examining 27 randomised trials of cimetidine or ranitidine in the treatment of UGIB involving more than 2500 patients showed no significant difference between H2 antagonist therapy (21%) and placebo (23%) (76). In fact, only one of the 27 individual trials reported a significant decrease in rebleeding with a H2 antagonist therapy .A large, prospective, randomized, double-blind, placebo-controlled trial evaluating the use of famotidine in acute bleeding peptic ulcer found that recurrent bleeding rates, need for surgery and the number of deaths were no different between the two groups (77) . A recent meta-analysis concluded that there was no evidence to support the use of H2- receptor antagonists in the treatment of bleeding duodenal ulcers but there is evidence of a moderate benefit in gastric ulcers (78). The use of H2 antagonists in upper gastrointestinal bleeding is not recommended (*Grade A).*

7.2 Proton Pump Inhibitors (PPIs)

The use of intravenous boluses of omeprazole in comparison with placebo revealed less endoscopic evidence of persistent bleeding in the omeprazole treated patients but other end points, including mortality, were similar in both groups (79) .A single centre study revealed that high dose oral omeprazole resulted in less rebleeding and lower transfusion requirements when compared to placebo (80) . Endoscopic therapy was not used in this trial. Various trials have compared the use of high dose intravenous omeprazole with placebo following primary endoscopic haemostasis (81-84). The most convincing study (84) revealed a significant reduction in rebleeding within 30 days in the omeprazole group (6.7%) in comparison with placebo (22.5%). Although the mortality rate and the number requiring surgery were also lower in the omeprazole group, these differences were not significant.

Intravenous pantoprazole has also been used in peptic ulcer bleeding. Pantoprazole infusion was compared with ranitidine in patients with Forrest Ia, Ib, IIa and IIb after undergoing endoscopic haemostasis with adrenaline or adrenaline with polidocanol. There was a tendency for lower rebleeding rate in the pantoprazole group as opposed to ranitidine (85).

In a meta-analysis comparing proton pump inhibitors with H2 antagonists, it was observed that persistent or recurrent bleeding was less frequent with proton pump inhibitors (6.7%) than with H2 antagonists (13.4%) (OR 0.4; 95%CI: 0.27-0.59%). The need for surgery and mortality rates did not reach statistical significance but showed a favourable trend towards PPIs. When the analysis was stratified according to endoscopic therapy, only the subgroup of patients who were not treated endoscopically showed a significant reduction in persistent or recurrent bleeding (OR 0.24; 95% CI 0.13 to 0.14) (86).

It is recommended that following endoscopic therapy in major peptic ulcer bleeding, high dose intravenous PPI (eg IV Omeprazole 80mg stat followed by an infusion of 8mg hourly for 72 hours) be commenced (*Grade B).*

8. MANAGEMENT of OTHER CAUSES of UGIB

8.1 Mallory-Weiss Tears

Occasionally, endoscopic therapy is required to arrest severe bleeding. Adrenaline (87), thermal methods or mechanical clips (88) have been used (*Grade C).*

.

8.2 Vascular Malformations (Including Telangiectasia and GAVE)

Multiple sessions of Argon plasma coagulation (APC) or heater probe therapy (89) may be required to achieve haemostasis (*Grade B)*

8.3. Dieulafoy Lesion

Uncontrolled series report success with band ligation injection and thermal methods (90) (*Grade C)*.

9. AFTER CARE

After the initial endoscopy and the institution of endoscopic therapeutic measures where necessary, the key point in the aftercare is the recognition of patients at high risk of rebleeding and death who would require careful monitoring in an intensive care or high dependency setting. Predictors of an increased risk of rebleeding and death (as well as failure of endoscopic therapy) include (i) clinical factors such as shock at the time of presentation, advanced age, co-existing illnesses, (ii) endoscopic features such as ulcer location (posterior duodenal ulcer) , size of the ulcer (>2cm) , stigmata of recent haemorrhage and the presence of blood at the time of endoscopy as well as (iii) laboratory features such as haemoglobin (<10g/dl) and elevated blood urea levels (91-95) .While there is some controversy as to which of these factors are more important in predicting rebleeding and death, an overall picture emerges that having a severe initial bleed ,being elderly and having coexisting severe illnesses increases the risk of an adverse outcome. While rebleeding is an important cause of death, mortality could occur in the absence of rebleeding especially in patients with coexisting illnesses.

The role of second-look endoscopy is unclear. Published studies on the routine use of second-look endoscopy consist of inadequate numbers (96-98) .The difference is probably marginal.

10. MANAGEMENT of REBLEEDING

Recurrent bleeding remains the single most important adverse prognostic factor. Morbidity and mortality are higher in those with rebleeding and 95% of rebleeding occurs within the first 72 hours of hospitalisation (99).

10.1 Rebleeding After Initial Endoscopic Control of Bleeding Ulcers

The major challenge in applying endoscopic therapy for bleeding peptic ulcers is that haemostasis is not permanent and re-bleeding occurs in about 15-20% of the cases. Endoscopic treatment would avoid the surgical risk. However, delay in establishing haemostasis may result in hypotension and adversely affect the survival.

In patients with peptic ulcers and recurrent bleeding after initial endoscopic control of bleeding, endoscopic retreatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than is surgery (100) (*Grade A)* .

Surgery if decided upon should be performed early rather than late to avoid an unfavorable outcome especially in the hypotensive elderly patient. In some patients, endoscopic appearances (eg, a giant posterior duodenal ulcer) may suggest that surgery be the preferred option (1) (*Grade C).*

11. ROLE OF SURGERY.

The role of surgery has changed with wider use of endoscopic hemostasis in bleeding ulcers, no longer aiming to cure the disease but primarily to stop the hemorrhage. Mortality after urgent surgery correlates with the preoperative Apache 2 score (101) .

11.1 Indications for Surgery as the Primary Mode of Treatment

11.1.1. Massive bleeding

There is still no proven alternative to emergency operation for massive bleeding uncontrolled by endoscopic procedures. This may be due to bleeding that is unresponsive to endoscopic hemostasis or failure of endoscopic visualization of the bleeder due to profuse hemorrhage. A continued attempt with endoscopic treatment is futile and dangerous.

11.1.2. Ulcer inaccessible to endoscopic control

There are situations where the bleeding ulcer is inaccessible to endoscopic control. This can occur in duodenums that are often deformed and narrowed. Primary surgery is indicated in such circumstances.The rate of primary-emergency surgery varies depending on the case mix and the expertise of endoscopic management.

Thus the surgeon should be involved from the outset in the team caring for the patient early and close cooperation between endoscopists/gastroenterologists and surgeons is vital.

11.2 Type of Surgery for Bleeding Peptic Ulcer

There appears to be no difference between local (under-running/ over-sewing or excision of ulcer) and radical surgery (gastric resection or vagotomy) with respect to mortality although rebleeding rate may be higher in the local group (102).

While under-running or over-sewing for bleeding ulcers is advisable in a large proportion of cases, ulcer excision or even more radical surgery (e.g. gastric resection for large, chronic, penetrating gastric ulcers) may be performed in selected cases. There is only one trial of different surgical procedures for bleeding duodenal ulcers (103). The rebleeding rate was lowest in patients having a gastrectomy to include the ulcer either with Billroth I or Billroth II reconstruction when compared with more conservative surgery. However, the bile leak was following gastrectomy was much higher and the overall mortality was similar in the two randomized groups. The same study suggested that when a bleeding duodenal ulcer is under-run, ligation of the gastroduodenal and right gastroepiploic

arteries reduced the rebleeding rate to a similar level as gastrectomy (*Grade B).* Currently it is not possible to make definite recommendations in the absence of any good prospective randomized trials. The magnitude of surgery should be tailored to the type of ulcer, severity of illness in the patient and experience of the surgeon.

12. INTERVENTIONAL RADIOLOGY

In the critical or unstable patient who is not amenable to immediate surgical intervention radiological intervention appears increasingly as a very effective option. In a recent retrospective evaluation of interventional embolization therapy over an 8 year period, bleeding was stopped in 83% of cases. The rate of complications was 14%.Sodium diatrizoate, metal coils, tissue adhesives and Gelfoam particles were used (104).

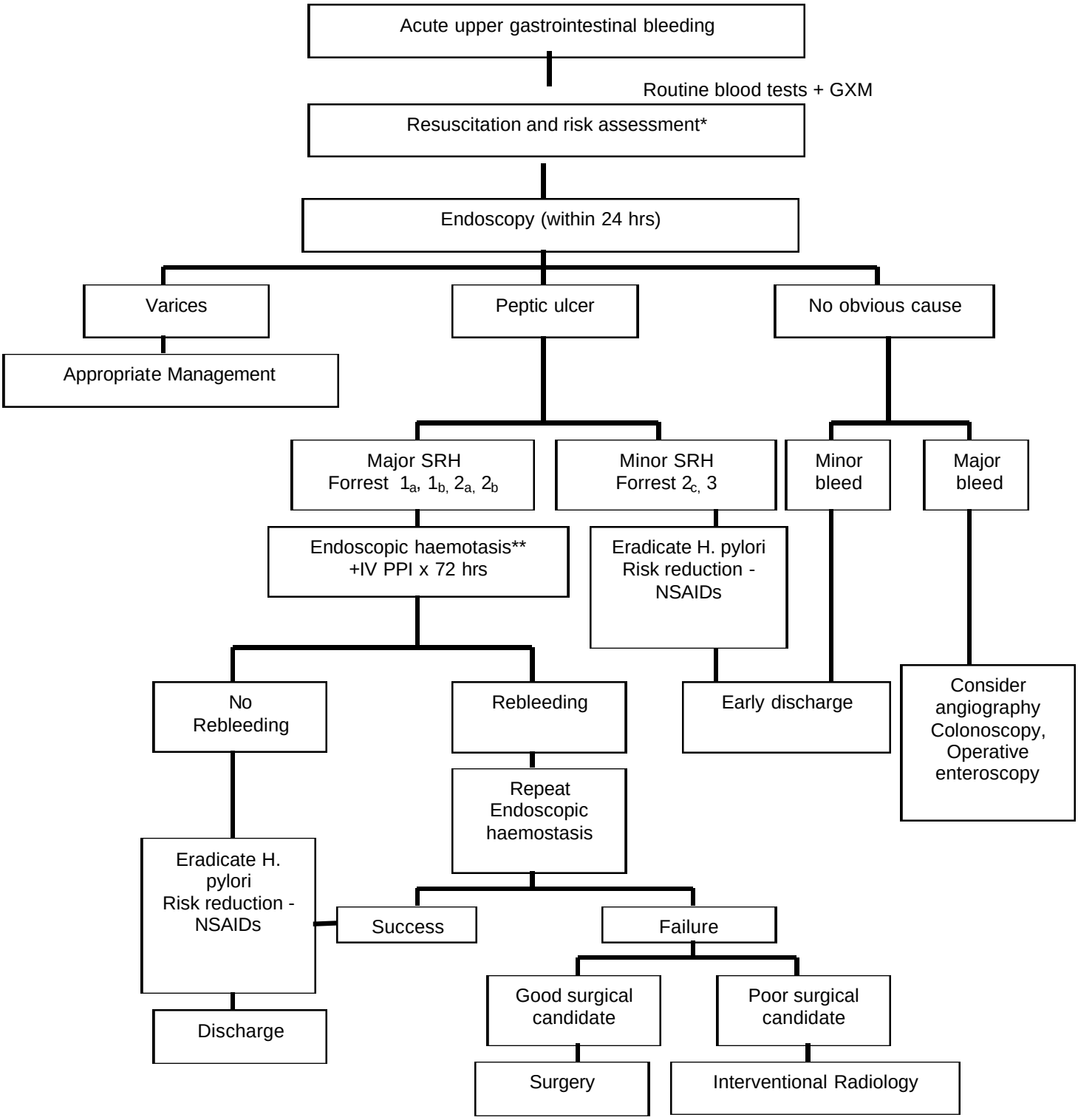
13. FOLLOW UP

Patients admitted for bleeding peptic ulcer should be discharged with oral proton pump inhibitors .Those with gastric ulcers should be re-endoscoped in 6 weeks to assess healing and rule out malignancy. Attention should be paid to *Helicobacter pylori* eradication for all *H. pylori* positive ulcers. The latter is also recommended for those on long-term aspirin. Those who need to continue on NSAIDs should consider COX-2 inhibitors, or the least damaging NSAID with a proton pump inhibitor (Section 4.3) .

14. ALGORITHM: MANAGEMENT OF NON-VARICEAL UPPER GASTEROINTESTINAL BLEEDING [1,7,8]

* The Rockall Risk Assessment score is recommended. Patients with a score of ≤ 2 may be considered for early discharge[33].

** Adrenaline injection with heater probe is recommended.



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APPENDIX 1

The Rockall Risk Assessment Score

APPENDIX 2

Forrest Classification