Practice Guideline: the role of endoscopy in acute non-variceal upper-GI hemorrhage

INTRODUCTION

This guideline focuses on the role of GI endoscopy in patients with acute non-variceal upper-GI hemorrhage. This guideline does not address chronic GI blood loss or bleeding secondary to portal hypertension.

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical consideration may justify a course of action at variance to these recommendations.

Level of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Rating Scheme for the Strength of Recommendation

A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to target population; a body of evidence consisting principally of studies rated 1+, directly applicable to target population and with overall consistency of results

B A body of evidence including studies rated 2++ or extrapolated evidence from studies 1++ or 1+

C A body of evidence including studies rated 2+, directly applicable to target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated 2++

D Evidence level 3 or 4; or extrapolated evidence from studies rated 2+

Guideline Objectives

- To provide recommendations based on current evidence for best practice in the management of acute non-variceal upper gastrointestinal (GI) bleeding
- To reduce mortality and the need for major surgery in the management of bleeding patients
- To prevent unnecessary hospital admission for patients presenting with bleeding that is not life threatening

DEFINITION

Upper-GI bleeding refers to GI blood loss whose origin is proximal to the ligament of Treitz. Acute UGIB can manifest as hematemesis, ‘‘coffee ground’’ emesis, the return of red blood via a nasogastric tube, and/or melena with or without hemodynamic compromise. Hematochezia (bright red blood per rectum) may occur in patients with extremely brisk UGIB.

INITIAL ASSESSMENT AND TREATMENT

Patients with UGIB should undergo stabilization and resuscitation before the initiation of endoscopic therapy. The initial assessment should focus on the patient’s vital signs, the presence or the absence of hypovolemia and/or shock, and other medical co-morbidities. A thorough review of any medications the patient may be taking, with special attention to the use of anticoagulants, antiplatelet agents, or medications associated with GI hemorrhage (e.g., non-steroidal anti-inflammatory drugs [NSAID]) should be performed. In patients receiving anticoagulants, correction of coagulopathy is recommended but should not delay endoscopy. Initially, crystalloid fluids should be infused to maintain adequate blood pressure. Patients with evidence of severe hypovolemia, shock, or ongoing blood loss manifesting as hematemesis or frequent melena should be admitted to an intensive care setting. Blood products such as packed red blood cells should be transfused in patients with evidence of ongoing active blood loss or patients who have experienced significant blood loss or cardiac ischemia. Patients with ongoing, significant hematemesis or those who may not be able to protect their airway for any reason and are at risk for aspiration should be considered for endotracheal intubation before undergoing endoscopy.

The preendoscopic Rockall use only clinical and laboratory data (before endoscopy) to identify patients who require intervention, whereas the complete Rockall score also use endoscopic variables to predict rebleeding or mortality (Table 1). Use of the Rockall score has been shown to yield a more accurate diagnosis (significantly fewer undefined causes and increased identification of peptic ulcer) and shorter duration of hospitalization. A comparison of the Baylor College, Rockall, and Cedars–Sinai Medical Center predictive indexes found that the Rockall score best identified patients at low risk. This score has been validated in multiple countries but has better discriminative ability for mortality than for rebleeding.

The role of PPI use in patients with acute UGIB has been extensively studied. These focused on the use of intravenous (IV) omeprazole. Anti-secretory therapy with a proton pump inhibitor (PPI) is warranted, and this can be done intravenously or orally. A recent review of these studies found that PPI therapy was warranted in all patients with UGIB severe enough to

require endoscopic therapy and recommended considering PPI therapy in patients with suspected peptic ulcer bleeding associated with hemodynamic instability, patients in whom endoscopic evaluation is delayed or unavailable, and/or those who require blood transfusion. Furthermore, a recent study comparing IV omeprazole to IV omeprazole plus endoscopic therapy in patients with UGIB and non-bleeding visible vessel or adherent clot showed that patients in the combination therapy group experience fewer episodes of recurrent bleeding and had lower blood transfusion requirements. Oral omeprazole, 40mg administered every 12 hours for 5 days, was effective in reducing bleeding and the need for surgery in a randomized, placebo controlled study of patients with peptic ulcer disease (PUD).

Somatostatin and its analogue octreotide reduce portal venous blood flow and arterial flow to the stomach and the duodenum, while preserving renal arterial flow. Fourteen studies in 1829 patients with non-variceal UGIB were summarized by a meta-analysis that concluded that somatostatin or octreotide reduced the risk of continued bleeding and the need for surgery, and that these agents are more effective in peptic ulcer bleeding than for non peptic ulcer bleeding (i.e., hemorrhagic gastritis). These agents may be considered as an adjunct treatment before endoscopy or when upper endoscopy is unsuccessful, contraindicated, or unavailable. Clinical features associated with a high risk of recurrent bleeding, need for surgery, and increased mortality are listed in Table 2.

Table 1. **Rockall risk scoring system**

Variable	**Score 0**	**Score 1**	**Score 2**	**Score 3**
age	<60	60- 79	>80	
Shock	No shock	Pulse >100	SBP <100	
Comorbidity	Nil major		CCF, IHD, major morbidity	Renal failure, liver failure, metastatic cancer
Diagnosis	Mallory-Weiss	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, spurting vessel	

***Pre-endoscopy**:*
Rockall Score 0 – no need to be admitted; early discharge with OPD follow-up
Rockall score >0- need endoscopy for full assessment of bleeding risk
***Post-endoscopy**:*
Rockall score <3 – low risk of rebleed and death; early discharge and OPD follow-up
For cases scoring 0, 1, or 2 rebleeding occurs in less than 5%/o of patients and mortality is virtually zero whether rebleeding occurs or not.
The Rockall score should be taken into account with other clinical factors in assigning patients to different levels of care. It should not be used in isolation to assign patients to high dependency care.

Table 2. Clinical risk factors for poor outcomes*
Older age (>60 y)
Severe comorbidity
Active bleeding (witnessed hematemesis, red blood per nasogastric tube, hematochezia)
Hypotension or shock
Red blood cell transfusion > 6 units
Inpatient status at time of bleed
Severe coagulopathy
*Recurrent bleeding, need for endoscopic hemostasis or surgery, or mortality.

ROLE AND EFFECTIVENESS OF ENDOSCOPY IN THE MANAGEMENT OF UGIB

Endoscopy in patients with UGIB is effective in diagnosing and treating most causes of UGIB and is associated with a reduction in blood transfusion requirements and length of intensive care unit and total hospital stay. Early endoscopy (within 24 hours of hospital admission) has a greater impact than later endoscopy on length of hospital stay and requirements for blood transfusion. In appropriate settings, endoscopy can be used to assess the need for inpatient admission. When evaluated in emergency room settings, up to 46% of hemodynamically stable patients who are evaluated for UGIB with upper endoscopy and subsequently are found to have low-risk stigmata for recurrent bleeding can be safely discharged and followed as outpatients.
Most patients who have undergone endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 hours thereafter.
Promotility agents were not warranted for routine use but may be useful in patients who are suspected to have substantial amounts of blood or clot in their upper gastrointestinal tract or those who have recently eaten.

ENDOSCOPIC PROGNOSTIC FEATURES

Several endoscopic findings most closely associated with PUD but sometimes seen with other causes of UGIB (e.g., severe esophagitis with ulceration), have been associated with specific recurrent bleeding rates and, thus, the need for endoscopic therapy (see Table 3). Endoscopic therapy is indicated for patients found to have actively bleeding or spurting arterial vessels and for those with a non-bleeding visible vessel (i.e., pigmented protuberances) in an ulcer. Adherent clot seen in an ulcer has been a source of controversy with regard to the need for endoscopic treatment, but recent data has shown benefit to endoscopic clot removal and treatment of an underlying lesion instead of observation alone. Flat, pigmented spots or

lesions with slow oozing of blood without other stigmata have not been definitively shown to benefit from endoscopic therapy. Clean-based ulcers have an extremely low recurrent bleeding rate and do not require endoscopic treatment. Other endoscopic predictors of increased risk for rebleeding and mortality include ulcer size (generally >2 cm), ulcer location (posterior lesser gastric curvature or posterior duodenal wall), and lesion type (for example, ulcer, varices, or cancer).

Table 3. Stigmata of ulcer hemorrhage and risk of recurrent bleeding without endoscopic therapy

Stigmata-	***Risk of recurrent bleeding without therapy***
Active arterial (spurting) bleeding-	Approaches 100%
Non-bleeding visible vessel ("pigmented protuberance")	Up to 50%
Non-bleeding adherent clot -	30%-35%
Ulcer oozing (without other stigmata) -	10%-27%
Flat spots	<8%
Clean-based ulcers	<3%

Endoscopic treatment modalities for GI hemorrhage

Injection methods. The method of action of injection therapy is primary tamponade because of volume effect, with some agents having a secondary pharmacologic effect. Agents available for injection to produce tamponade include normal saline solution and epinephrine (adrenaline). Sclerosants such as ethanol, ethanolamine, and polidocanol are not used to produce tamponade but instead cause direct tissue injury and thrombosis. Agents also can be used in combination (such as epinephrine followed by ethanolamine). Limited data suggest that higher volumes of epinephrine injected at endoscopy bleeding site have a superior effect in achieving hemostasis compared with lower volumes.

Cautery. Cautery devices include heat probes, neodymium-yttrium aluminum garnet lasers, argon plasma coagulation (APC), and electrocautery probes. Laser therapy is not widely used in many centers because of cost, training, and support issues. Electrocautery refers to the use of monopolar electrocautery or bipolar (multipolar) electrocautery. Heat probes and electrocautery probes also use local tamponade (mechanical pressure of the probe tip at/ on the bleeding site) combined with heat or electrical current to coagulate (and thus close) the vessel in question, a process known as coaptation. Argon plasma coagulation uses a stream of ionized gas to conduct electricity resulting in coagulation of superficial tissues. Argon plasma coagulation is primarily used for the treatment of superficial lesions, such as vascular abnormalities, but may have a role in some patients with bleeding from other causes.

Mechanical therapy. Mechanical therapy refers to the implantation of a device that causes physical tamponade of a bleeding site. Currently, the only mechanical therapies widely available are endoscopically placed clips and band ligation devices. Endoscopic clips usually are placed over a bleeding site (e.g., visible vessel) and left in place. Clips currently are available in

two or three pronged configurations, can be affixed to bleeding sites, and typically slough off days to weeks after placement. A meta-analysis compared the efficacy of endoscopic clipping versus injection and thermocoagulation in the control of non-variceal GI bleeding. Definitive hemostasis was higher with hemoclipping (86%) than by injection (75%). Use of clips significantly reduced rebleeding and need for surgery compared with injection. Clipping and thermocoagulation had comparable efficacy. No differences in mortality were reported between any interventions.
Endoscopic band ligation devices, commonly used in variceal bleeding, also have been used to treat non-variceal causes of bleeding and involve the placement of elastic bands over tissue to produce mechanical compression and tamponade.

Combination therapy. Although monotherapy with epinephrine injection is more effective than medical therapy in patients with high-risk stigmata, it is inferior to other monotherapies or to combination therapy that uses 2 or more methods. Numerous meta-analyses indicate that adding a second procedure, such as a second injectate (for example, alcohol, thrombin, or fibrin glue), thermal contact, or clips, is superior to epinephrine injection alone. Epinephrine plus a second method for treating high-risk stigmata significantly reduced rebleeding, surgery, and mortality compared with epinephrine monotherapy.

OVERVIEW OF ENDOSCOPIC APPROACHES TO COMMON CAUSES OF ACUTE UGIB
In patients with UGIB, the most common etiologies are as follows: PUD, gastroduodenal erosions, esophagitis, varices, Mallory-Weiss tear, vascular malformations, with other conditions (e.g., malignancy) making up the remaining cases.

PUD
Peptic ulcer disease represents the most common cause of UGIB, accounting for a third to a half of all episodes. The most frequent causes of PUD are NSAIDs and Helicobacter pylori infection, although a variety of other clinical settings can predispose patients to PUD. Endoscopic therapy for patients with UGIB caused by PUD has been studied in randomized, controlled trials. Laser therapy; monopolar electrocautery ; bipolar electrocautery; heat probe; epinephrine injection; and epinephrine injection with additives, such as the sclerosants ethanolamine and polidocanol, are all effective when compared with no therapy or sham therapy. Numerous prospective randomized studies of endoscopic treatment methods have been performed. No single modality has been shown to be superior for treating UGIB caused by PUD. For epinephrine injection, the addition of a second modality (combination therapy) reduces further bleeding, the need for surgery, and mortality. Operator experience plays a significant role in modality choice and in achieving hemostasis. All patients with PUD should undergo diagnostic testing for H pylori infection. In the setting of active bleeding, rapid urease tests have reduced sensitivity and cannot be relied upon to rule out infection. *Negative* H. pylori *diagnostic tests obtained in the acute setting should be repeated.* All patients with positive test results should be treated to eradicate infection. Patients with PUD and H pylori infection who undergo treatment for infection have a significantly lower risk of recurrent bleeding than those who only receive antisecretory therapy.

Esophageal lesions

Esophagitis can be caused by gastroesophageal reflux, infection, medications, caustic ingestion, or radiation. In the majority of patients, no endoscopic therapy is required. A Mallory-Weiss tear is a laceration of the mucosa at the gastroesophageal junction, gastric cardia, or distal esophagus. Bleeding is most commonly self limited. Patients with ongoing or severe bleeding require endoscopic therapy. Multipolar electrocautery appears to be the most effective therapy, but epinephrine injection, clips, or band ligation also appear to be effective. Uncontrolled bleeding may require angiographic therapy or surgery.

Vascular abnormalities

Vascular malformations typically cause microscopic chronic blood loss and, occasionally, acute GI hemorrhage. These lesions can occur sporadically or in association with other disorders: cirrhosis, renal failure, radiation injury, various collagen vascular diseases, and hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Endoscopic ligation, laser, APC, contact cautery, and sclerotherapy have been reported to be effective. There are no prospective trials comparing treatment methods for acute UGIB caused by vascular malformations. Dieulafoy's lesion typically presents with intermittent, recurrent UGIB. The lesion occurs when an abnormally large-caliber submucosal artery becomes exposed at the surface of the mucosa and then ruptures, usually in the stomach, but also in the small bowel. Endoscopic methods to treat Dieulafoy's lesion include banding, clipping, electrocautery, cyanoacrylate glue, sclerosant injection, epinephrine injection, heat probe, and laser therapy. Large single-center experiences have not identified one modality as being superior to others, and no prospective randomized trials have been published. Epinephrine injection monotherapy is associated with a higher rate of recurrent bleeding. Tattooing of the lesion should be considered to facilitate future treatment should recurrent bleeding occur. If endoscopic treatment is successful, recurrence of bleeding at the same site is rare. If endoscopic therapy fails, interventional radiology or surgical approaches may be required.

Aortoenteric fistulas

Aortoenteric fistulas may be primary (caused by arteriosclerosis, aortic aneurysms, aortic infections or secondary (aortic repair with implantation of a synthetic graft). Most aortoenteric fistulas occur at the level of the distal duodenum or the jejunum, which may be beyond the reach of a standard upper endoscope. Aortic graft material may be seen protruding into the bowel lumen. CT scans and angiography sometimes demonstrate the fistula if contrast can be seen extravasating into the bowel. There is no endoscopic therapy for aortoenteric fistula. Surgery is the only definitive treatment.

GI tumors

Benign or malignant GI tumors, whether primary or metastatic, cause approximately 5% of cases of UGIB. Case series of endoscopic therapy have reported initial hemostasis rates similar to or lower than that seen in PUD, but recurrent bleeding rates were high, between 16% and 80%. Procedure related complications also were more frequent. The optimal treatment modality has not been defined. Surgery or angiography may be better approaches to ensuring

long-term hemostasis. Any lesion appearing malignant when seen in the context of an episode of UGIB should be biopsied.

RECURRENT BLEEDING AFTER ENDOSCOPIC TREATMENT

Despite adequate initial endoscopic therapy, recurrent bleeding in patients with UGIB can occur in up to 24% of high-risk patients, although more recent studies that emphasize the use of PPI therapy in addition to combination endoscopic therapy show recurrent bleeding rates of approximately 10%. Patients with recurrent bleeding respond favorably to repeat endoscopic therapy. *Routine second-look endoscopy is not recommended in the advent of endoscopic therapy with high dose PPI combination.* Endoscopy and endoscopic treatment may be repeated within 24 hrs when initial endotherapy was considered sub-optimal (e.g. difficult access, poor visualization, technical difficulties) or pts where rebleeding is likely to be life-threatening. (B)

Bleeding not controlled by endoscopy should be treated with repeat endoscopic treatment, selective arterial embolization or surgery. (D)

For patient with massive GI Bleeding from the outset, consultation with a surgeon and/or interventional radiologist is recommended.

Pharmacologic Treatment

An intravenous bolus 80 mg/iv followed by continuous-infusion 8mg/hr PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy. Pre-endoscopic PPI therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.

In patients with previous ulcer bleeding who require an NSAID, it should be recognized that treatment with a traditional NSAID plus PPI or a cyclooxygenase-2 (COX-2) inhibitor alone is still associated with a clinically important risk for recurrent ulcer bleeding. In patients with previous ulcer bleeding who require an NSAID, the combination of a PPI and a COX-2 inhibitor is recommended to reduce the risk for recurrent bleeding from that of COX-2 inhibitors alone.

Patients with UGIB who require secondary cardiovascular prophylaxis should start receiving acetylsalicylic acid (ASA) again as soon as cardiovascular risks outweigh gastrointestinal risks (usually within 7 days); In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI.

SUMMARY

For the following points: (A), prospective controlled trials; (B), observational studies; (C), expert opinion.

__The initial management of UGIB is patient assessment and stabilization with volume resuscitation. (C)

__High-risk patients are those with hematemesis, hemodynamic instability, coagulopathy, renal failure, older age, and multiple comorbidities; these patients require more intensive monitoring. (B)

__Antisecretory therapy with PPIs is recommended for patients with bleeding caused by peptic ulcers or in those with suspected peptic ulcer bleeding in whom endoscopy is delayed or unavailable. (A)

__While not part of the routine management of nonvariceal UGIB, somatostatin or octreotide can reduce the risk of continued bleeding and the need for surgery but should be viewed as an adjunct to endoscopic and PPI therapy. (A)

__Endoscopy is effective in the diagnosis and the treatment of UGIB. (A)

__Endoscopic stigmata that predict a high risk of recurrent bleeding in PUD are active spurting, a visible vessel, and an adherent clot; these lesions should be treated. (A)

__Available endoscopic treatment modalities include injection, cautery, and mechanical therapies. (A)

_ Studies have not demonstrated clear superiority of any modality. Epinephrine injection alone is inferior to combination therapy for peptic ulcer bleeding. (A)

_ Patients with PUD should be tested and treated for Helicobacter pylori. (A)

References:

1. American Society For Gastrointestinal Endoscopy (ASGE) guideline 2004
2. Scottish Intercollegiate Guidelines Network. A national clinical guideline 2008
3. Clinical Guidelines : International Consensus Recommendations on the Management of Patients With Non-variceal Upper Gastrointestinal Bleeding- Ann Intern Med January 2010