**Diagnosis and management of upper gastrointestinal bleeding**

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**Abbreviations:**

Upper gastrointestinal bleeding (UGIB)

Nonsteroidal anti-inflammatory drug (NSAID)

Odds ratio (OR)

Peptic ulcer disease (PUD)

Peptic ulcer bleeding (PUB)

Helicobacter pylori (*H. Pylori*)

**Abstract**

Upper gastrointestinal bleeding (UGIB) causes significant morbidity and mortality in the United States. Bleeding due to peptic ulcer disease is the most common cause of UGIB and is associated with NSAID use and the relatively high prevalence of *H. Pylori* infection. Patients with portal hypertension and cirrhosis may hemorrhage from varices. Rapid assessment and resuscitation should precede diagnostic evaluation. Two large caliber peripheral catheters or a central venous line should be inserted for intravenous access and crystalloid intravenous fluids initiated. Initial laboratory tests should include: hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, INR, creatinine, BUN, type and cross match. Blood transfusion should be administered to patients with a hemoglobin level less than 7 g/dL. Patients can be risk stratified based on clinical assessment and endoscopic findings. Early endoscopy (within 24 hours of presentation) is recommended in most patients, allowing rapid diagnosis and application of endoscopic therapies including injection with epinephrine, thermal therapy, application of clips, and banding. Endoscopic therapy results in reduced morbidity, decreased hospital stay, decreased risk of recurrent bleeding, and the need for surgery. Although administration of proton pump inhibitors does not decrease mortality, risk for rebleeding, or surgery, they downstage the severity of the bleeding lesion and reduce the need for endoscopic therapy. Despite successful endoscopic therapy, rebleeding can occur in 10-20% of patients and a second attempt at endoscopic therapy is recommended. Arteriography or surgery may be needed if there is persistent and severe bleeding.

<LH>Background

In the US in 2004, non-variceal upper gastrointestinal bleeding (UGIB) resulted in 400,000 hospital admissions per year, costing more than $2 billion annually (1). UGIB is associated with increasing nonsteroidal anti-inflammatory drug (NSAID) usage and the high prevalence (64%) of *Helicobacter pylori* (*H. Pylori*) infections in patients with peptic ulcer bleeding (PUB) (2). UGIB is twice as common in men as in women and increases in prevalence with age (3). Despite advances in therapy, the in-hospital mortality from UGIB remains high (13%) and rebleeding is common (15%) (4, 5). This review article focuses on acute non-variceal UGIB in adults although we briefly review management of variceal bleeding.

<LH> Pathogenesis

UGIB includes hemorrhage originating from the esophagus to the ligament of Treitz. PUB is the main cause of UGIB (61%), and in the US, duodenal ulcers are more common than gastric ulcers (6). Hospitalizations for PUB decreased by 30% from 1996 to 2006, and in 2006 the inpatient mortality from PUB was 2.7% (6). Patients with gastric ulcers (55.1%) are hospitalized more commonly than patients with duodenal ulcers (38.5%), but the mortality rate for duodenal ulcers (3.7%) is higher than that of gastric ulcers (2.1%) (6). Duodenal ulcers are more likely to erode into large vessels causing more severe bleeding. Table 1 lists common causes of UGIB. In a meta-analysis of 16 studies of 1633 participants taking NSAIDs, both *H. Pylori* (odds ratio (OR) (1.7)) and NSAID use (OR 4.8) increase the risk of UGIB, and this risk increases when both factors are present (OR 6.1) (7). *H. Pylori* adheres to the gastric epithelium and renders the underlying mucosa more vulnerable to damage by producing enzymes and toxins (8), and affecting gastrin levels and acid output. The risk of UGIB varies based on the type of NSAID (9), (Table 2).

<LH> Diagnosis

Rapid assessment and resuscitation should precede the diagnostic evaluation in unstable patients with severe bleeding. Some patients may require intubation to decrease risk for aspiration. All patients with active bleeding resulting in hemodynamic instability should be admitted to an intensive care unit for resuscitation and close observation. Two large caliber peripheral catheters or a central venous line should be inserted for intravenous access and crystalloid fluids initiated. Other measures include monitoring urine output, obtaining electrocardiogram, and continuous telemetry monitoring. The physician should consider transferring a patient with significant UGIB to a tertiary medical center based on local expertise and the availability of facilities. Patients admitted primarily for UGIB have a lower mortality compared to patients admitted for other reasons who have a subsequent UGIB during their hospitalization (4, 10). See Figure 1 for an algorithmic approach to UGIB.

<SH> History and physical examination

Important historical information includes: presence of abdominal pain, vomiting, dysphagia, black tarry stools, bright red blood per rectum, hematemesis, and chest pain. Medication use should be elicited, especially prior use of clopidogrel, warfarin, NSAIDs, aspirin, selective serotonin reuptake inhibitors (SSRIs), or corticosteroids since treatment with these medications increase the risk for UGIB (11-13). SSRIs inhibit platelet aggregation and are associated with UGIB; the concurrent use of NSAIDs or aspirin with SSRIs further increases the risk of UGIB (13). The physician should ascertain prior history of peptic ulcer disease (PUD), prior episode of UGIB, history of cirrhosis, and alcohol or illicit drug use. The physician should also inquire about other comorbid conditions that may affect outcomes such as prior abdominal surgery, diabetes mellitus, coronary artery disease, chronic renal or liver disease, or chronic obstructive pulmonary disease.

Blood pressure and pulse rate may be normal. If bleeding is severe, patients may be hypotensive or tachycardic or may exhibit orthostatic hypotension. Physical examination should assess for tenderness, guarding, rebound, prior surgical scars, or sequela of chronic liver disease. Rectal examination should be performed and stool color assessed, e.g. for melena or bright red blood. Stool specimen should be collected for occult blood testing.

Initial laboratory tests should include: hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, INR, BUN, creatinine, and type and crossmatch. Patients with active bleeding and a coagulopathy or thrombocytopenia should be considered for transfusion with fresh frozen plasma and platelets, respectively (4). Blood transfusions should be administered to patients with hemoglobin of less than 7 g/dL and hemoglobin maintained at 9 g/dL (4, 14).

<SH> Nasogastric tube lavage

Evaluation should focus on determining whether the bleed is from an upper or a lower gastrointestinal source. Nasogastric lavage has a low sensitivity and poor negative likelihood ratio for UGIB in patients with melena or hematochezia (15, 16). However, a positive nasogastric tube lavage that yields blood or coffee-ground like material confirms the diagnosis of UGIB and predicts that bleeding is caused by a high-risk lesion (15, 16).

<SH>Risk stratification

Risk stratification is based on clinical assessment and endoscopic findings. Clinical assessment includes age, presence of shock, systolic blood pressure, heart rate, and comorbid conditions. Mortality increases with increasing co-morbid conditions and age (17). Endoscopic findings include the cause of the bleeding and stigmata of recent hemorrhage, see Table 3. The

Rockall risk scoring system uses a combination of clinical and endoscopic findings to predict the risk of rebleeding and mortality, (table 4) (18).

<LH> Treatment

Early upper endoscopy (within 24 hours of presentation) is recommended in most patients with UGIB as it confirms the diagnosis and allows for targeted endoscopic treatment, resulting in reduced morbidity, hospital stay, risk of recurrent bleeding, and need for surgery (4). Figures 2-6 show examples of endoscopic findings. Although prokinetic agents to evacuate the stomach are not recommended (19), gastric lavage should be considered. One of the benefits of gastric lavage is to clear the stomach of blood, increasing the success of endoscopic localization of the source of bleeding. Endoscopic therapies include injection with epinephrine, thermal application, application of clips, and banding. A Cochrane review of 18 studies of PUB including 1868 participants found that adding an additional endoscopic treatment after epinephrine injection significantly reduced rebleeding rates from 18.5% to 10% and reduced mortality from 4.7% to 2.5% (20). Low risk patients, e.g. clean ulcer base with PUB can be safely discharged on the same day as endoscopy (4). Most patients with high-risk PUB stigmata, e.g. active arterial bleeding, visible vessel, or adherent clot should be hospitalized for at least 72 hours with intravenous PPI therapy after endoscopic hemostasis since most rebleeding occurs in this time frame (4).

Although a systematic review of 6 randomized controlled trials of 2223 participants found no statistically significant differences in mortality, rebleeding, or surgery between patients receiving proton pump inhibitors (PPIs) and control treatment (placebo or $H_2$ receptor antagonists) (21). Patients treated with PPI therapy compared to control treatment had significantly reduced stigmata of recent hemorrhage, e.g. active arterial bleeding, visible vessel, or adherent clot (37.2% compared to 46.5%, OR 0.67) and reduced need for endoscopic

therapy (8.6% compared to 11.7%, OR 0.68) (21). In a randomized controlled trial of 767 patients with PUB randomly assigned to intravenous PPI therapy or placebo, fewer patients receiving intravenous PPI therapy (5.9%) had recurrent bleeding within 72 hours than those receiving placebo (10.3%) (*P*= 0.026) (22). The difference in bleeding recurrence remains significant at 7 days and 30 days (*P*= 0.010) (22). All patients admitted with significant UGIB should be started on intravenous PPI therapy until confirmation of the cause of bleeding at endoscopy (4). Use of $H_2$ receptor antagonists is not recommended for patients with UGIB.

<SH>Recurrent hemorrhage

Rebleeding after successful endoscopic therapy occurs in 10-20% of patients. The risk of rebleeding and mortality can be calculated with a clinical decision rule (18, 23). If rebleeding occurs, a second attempt at endoscopic therapy is recommended. In patients determined to be at high-risk for rebleeding, scheduled repeat endoscopy may reduce the rebleeding rate and be cost effective (4). However, a routine second-look endoscopy the next day is not recommended (4). Arteriography with embolization usually precedes surgical therapy since both are equally effective in treating patients with persistent bleeding (24). Surgical therapy is usually recommended if therapeutic methods including endoscopy and arteriography with embolization have failed to control the bleeding or if interventional radiology expertise is not available after failed endoscopic attempt. Surgical therapy is also indicated in patients with recurrent hemorrhage or hemodynamic instability despite fluid resuscitation and blood transfusion. In patients in whom no cause of UGIB was identified, small bowel evaluation with enteroscopy or video capsule endoscopy should be considered to evaluate for a small bowel source of the bleeding. Table 5 lists advantages and disadvantages of common tests used to diagnose UGIB.

<LH>Prevention

*H. Pylori* and NSAIDs are the major causes of PUB in the US and preventive strategies should focus on these etiologies. Smoking and alcohol use impairs ulcer healing and patients should be counseled about smoking cessation and moderation of alcohol use. A systematic review of 41 randomized controlled trials of patients on NSAIDs found that double dose $H_2$ receptor antagonist (RR 0.44) and PPIs (RR =0.40) significantly reduced the risk of PUB (25). In patients with a history of PUB, aspirin, clopidogrel, and NSAIDs should be avoided if possible. In patients on aspirin who develop PUB, aspirin therapy with PPI therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk of rebleeding (1). A Cochrane review of 7 studies of 578 patients concluded that eradication of *H. Pylori* infection in patients with PUB reduces the long-term rate of rebleeding (2.9%) compared with patients in the non-eradication group (20%) (NNT = 7) (26). In patients with PUB associated with *H. Pylori* eradication is essential and should be confirmed by urea breath test, stool antigen test, or the biopsy urease test. A repeat upper endoscopy in 8-12 weeks is recommended for patients with PUB secondary to gastric ulcers to assess for healing and to exclude malignancy and for patients with severe esophagitis to exclude Barrett's esophagus.

<LH> Variceal hemorrhage

Patients with cirrhosis should be screened with upper endoscopy to rule out varices (27). If patients have no varices on the initial endoscopy, it should be repeated in 3 years (27). Consider starting nonselective β-blockers, e.g. propranolol or nadolol in patients with varices to reduce portal pressure and decrease the risk of future hemorrhage (27). In patients with a history of varices who present with acute UGIB, upper endoscopy should be performed within 12 hours to confirm the diagnosis and to treat variceal hemorrhage (27). Endoscopic variceal ligation is the preferred endoscopic treatment for esophageal variceal hemorrhage and is superior to sclerotherapy (28). A review of 12 trials of 1241 patients found that broad-spectrum antibiotics, e.g. ceftriaxone, norfloxacin, ciprofloxacin in patients with variceal hemorrhage

reduced overall mortality (RR 0.79) and risk of rebleeding (RR 0.53) (29). A Cochrane review of 21 trials of 2588 patients found no difference in mortality or risk of rebleeding with somatostatin and its derivatives, e.g. octreotide in active variceal hemorrhage (30). Octreotide is often administered to patients with variceal hemorrhage however its use is controversial. If octreotide is used it should be initiated promptly in patients with variceal bleeding and continued for 3-5 days in conjunction with endoscopic therapy since this improves the immediate and 5 day rebleeding rates (27). Salvage treatment with transjugular intrahepatic portosystemic stent-shunt procedure or surgery should be considered especially for patients with gastric varices when medical and endoscopic treatment fail to control bleeding (31). The Model for End-Stage Liver Disease score should be calculated for prognosis and as a guide to decision-making regarding liver transplant (32).

Key recommendations for practice.

| **Key Clinical Recommendation** | **Evidence Rating** | **References** |
|---|---|---|
| Immediately evaluate and initiate appropriate resuscitation | **C** | (4) |
| Transfuse patients with hemoglobin level < 7.0 mg/L | **C** | (4, 14) |
| Perform upper endoscopy for the evaluation of upper gastrointestinal bleeding within 24 hours of presentation | **C** | (4) |
| Low-risk patients with acute peptic ulcer bleeding based on clinical and endoscopic criteria may be discharged promptly after | **C** | (4) |

| | | |
|---|---|---|
| endoscopy | | |
| High-risk patients based on clinical and endoscopic criteria should remain hospitalized for at least 72 hours | **C** | (4) |
| Start intravenous proton pump inhibitors at presentation until confirmation of a cause of bleeding at endoscopy | **B** | (33) |
| Routine second-look endoscopy is not recommended | **C** | (34) |

Table 1. Causes of upper gastrointestinal bleeding.

| Diagnosis | Distinguishing features | Frequency (%) |
|---|---|---|
| Peptic ulcer disease | Prior history of aspirin or NSAID use associated with abdominal pain, food reduces pain, nocturnal symptoms, past history of peptic ulcer disease or *Helicobacter pylori* | 62 |
| Esophagogastric varices | History of cirrhosis and portal hypertension | 6 |
| Gastritis and duodenitis | Same as peptic ulcer disease above | 8 |
| Mallory-Weiss tears | History of repeated retching or vomiting | 4 |
| Gastrointestinal malignancy | History of weight loss, smoking, or alcohol consumption, more common in Asians | 2 |
| Arteriovenous malformations | Painless bleeding in older patients (>70 years old), history of iron deficiency anemia | 10 |
| Esophagitis or esophageal ulcer | Heartburn, indigestion, or dysphagia | |
| Dieulafoy's lesion | More common in men, painless bleeding | |
| Other | Variable | |
| No identifiable source | | 8 |

Adapted from (3)

Table 2. The relative risk of upper gastrointestinal bleeding associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs)

| NSAID | Relative risk of upper gastrointestinal bleeding |
|---|---|
| Ibuprofen | 2.7 |
| Diclofenac | 4.0 |
| Meloxicam | 4.0 |
| Naproxen | 5.2 |
| Indomethacin | 5.3 |
| Ketoprofen | 5.7 |
| Piroxicam | 9.3 |
| Ketorolac | 14.0 |

Source: (9)

Table 3. The prevalence and risk of rebleeding based on the endoscopic stigmata of hemorrhage in peptic ulcer bleeding

| **Endoscopic appearance** | **Prevalence (%)** | **Rebleeding rate without endoscopic treatment (%)** | **Rebleeding rate with successful endoscopic treatment (%)** |
|---|---|---|---|
| Active arterial bleeding | 12 | 90 | 15-30 |
| Visible vessel | 22 | 50 | 15-30 |
| Adherent clot | 10 | 33 | 5 |
| Oozing without stigmata | 14 | 10 | Data not available |
| Flat spot | 10 | 7 | Data not available |
| Clean ulcer base | 32 | 3 | Data not available |

Source: (17, 35)

Table 4. Rockall risk scoring system for risk assessment after acute upper gastrointestinal bleeding

| Variable * | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| **Age** | Less than 60 years old | 60-79 years old | Greater than 80 years old | |
| **Shock** | Absent | Tachycardia | Hypotension | |
| **Systolic blood pressure (mm Hg)** | >100 | >100 | <100 | |
| **Heart rate** | <100 | >100 | >100 | |
| **Comorbidities** | None | None | Heart failure, coronary artery disease | Renal failure, liver failure, disseminated malignancy |
| **Endoscopic diagnosis** | Mallory-Weiss tear or no lesion identified, and no stigmata of recent hemorrhage | All other diagnoses | Malignancy of upper gastrointestinal tract | |
| **Stigmata of recent hemorrhage** | None or dark spot only | | Blood in upper gastrointestinal tract, adherent clot, visible or spurting vessel | |

* Score the patient on each variable and calculate the total score. The total score is used below to calculate risk of rebleeding and mortality.

Risk of rebleeding and mortality based on Rockall risk score

| **Score** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **>8** |
|---|---|---|---|---|---|---|---|---|---|
| Rebleeding (%) | 4.9 | 3.4 | 5.3 | 11.2 | 14.1 | 24.1 | 32.9 | 43.8 | 41.8 |
| Mortality (%) | 0 | 0 | 0.2 | 2.9 | 5.3 | 10.8 | 17.3 | 27.0 | 41.1 |

Source: (18)

Table 5. Advantages and disadvantages of various tests to assess for upper gastrointestinal bleeding.

| Test | Advantages | Disadvantages |
|---|---|---|
| Esophagogastroduodenoscopy with endoscopic therapy | Confirms diagnosis and initiates endoscopic therapy, decreases risk for rebleeding, transfusion requirements, and length of hospital stay | Costs, risk of sedation, risk of aspiration, invasive test, risk of perforation |
| Arteriography | Targeted therapy for ongoing hemorrhage, may prevent need for surgery | Invasive, expensive, requires special expertise, exposure to radiation, risk of contrast-induced nephropathy, risk of bleeding from arterial puncture site |
| Small bowel enteroscopy | Allows for precise identification of lesion in small bowel and application of endoscopic therapy, localization of lesion with tattooing if surgery is planned | Operator-dependent, requires special equipment and expertise, may not visualize all of small bowel, expensive, risk of sedation, risk of perforation, expensive |

| | | |
|---|---|---|
| Capsule endoscopy | No sedation required, noninvasive test, allows visualization of the entire small bowel | Capsule retention may occur, can miss lesions because images are not continuous, cannot perform therapeutic maneuvers |

Figure 1. An algorithm for management of acute upper gastrointestinal hemorrhage.

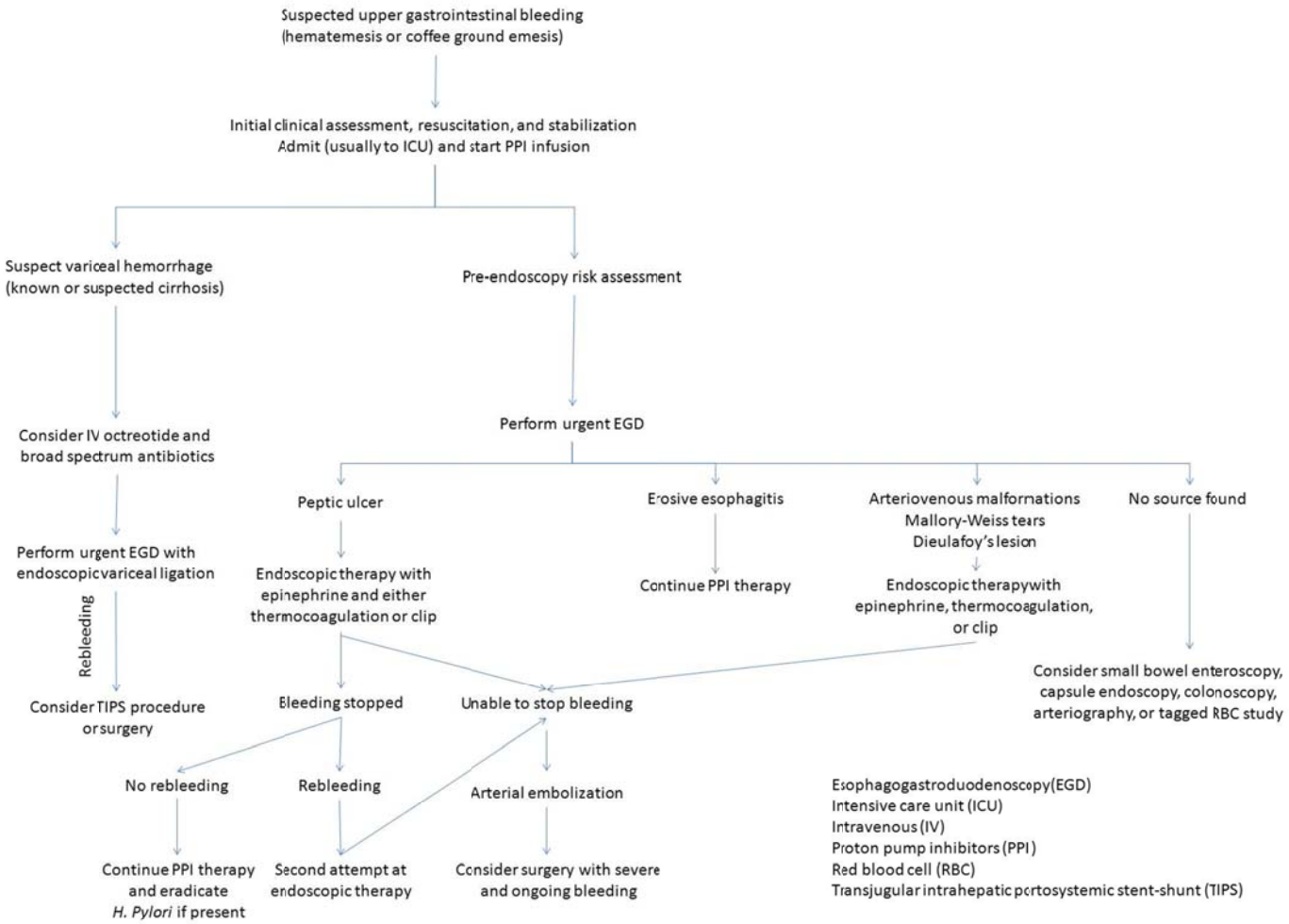


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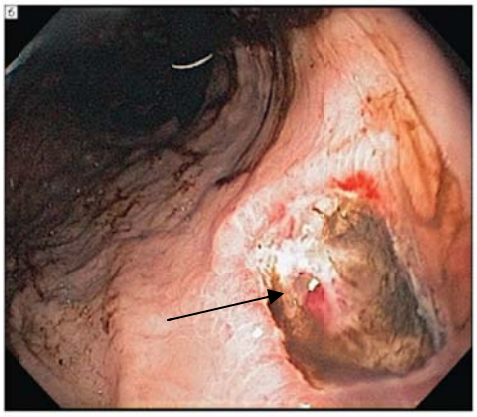
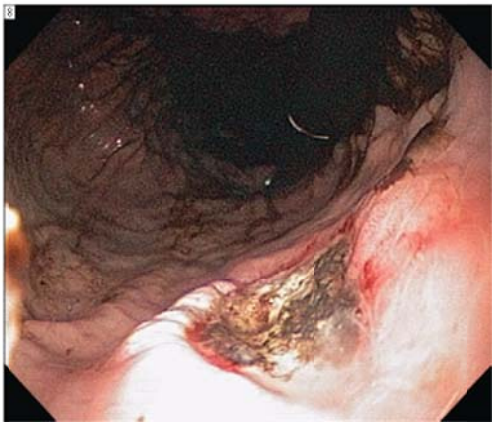
Figure 2. Gastric ulcer with protuberant vessel treated with heater probe. Followup endoscopy to assess healing at 4 weeks.

A. Gastric ulcer with protuberant vessel



B. Gastric ulcer following treatment with heater probe



C, Healing gastric ulcer (after 4 weeks)

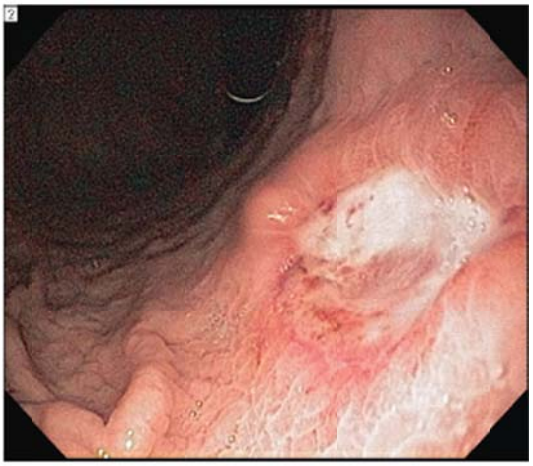


Figure 3.  Duodenal ulcer with adherent clot

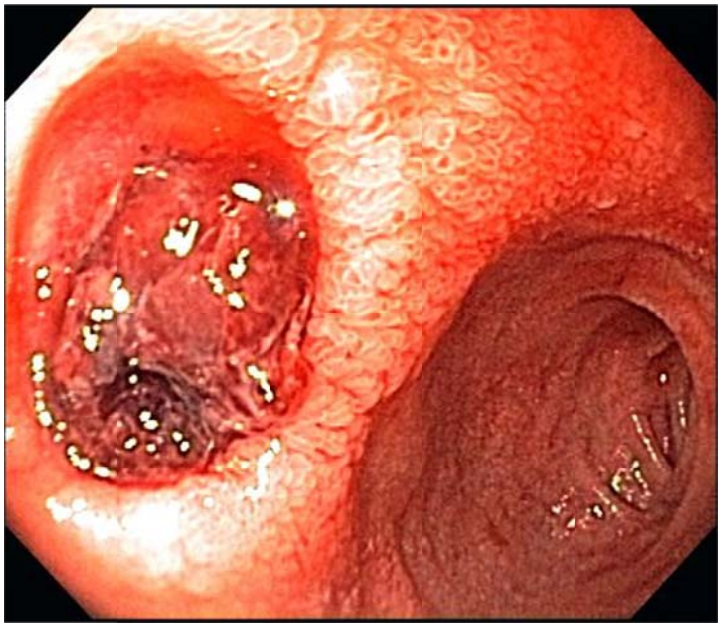
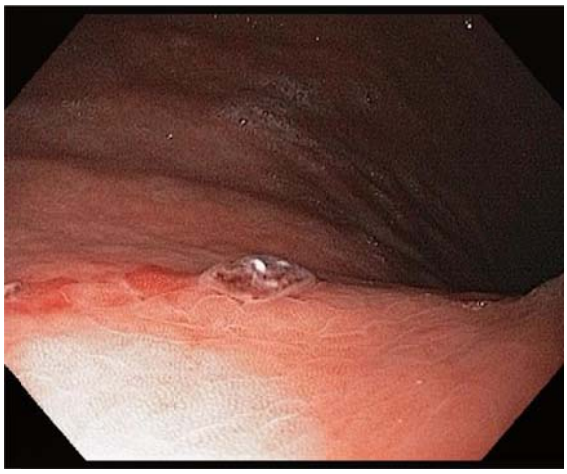


Figure 4. Dieulafoy's lesion causing upper GI bleeding

A. Dieulafoy's lesion causing upper GI bleeding



B. Dieulafoy's lesion after application of clip

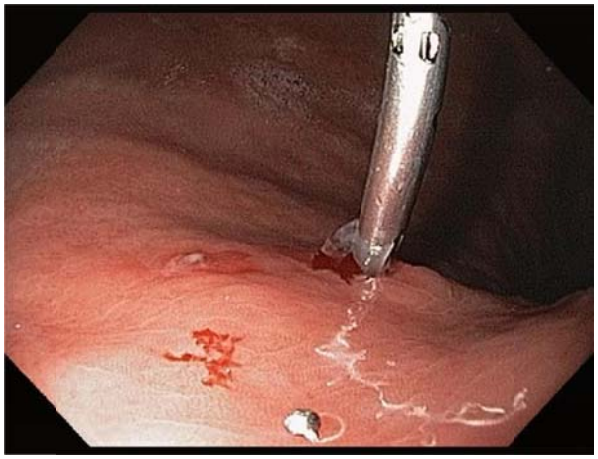


Figure 5. Mallory-Weis tear

A. Mallory-Weiss tear

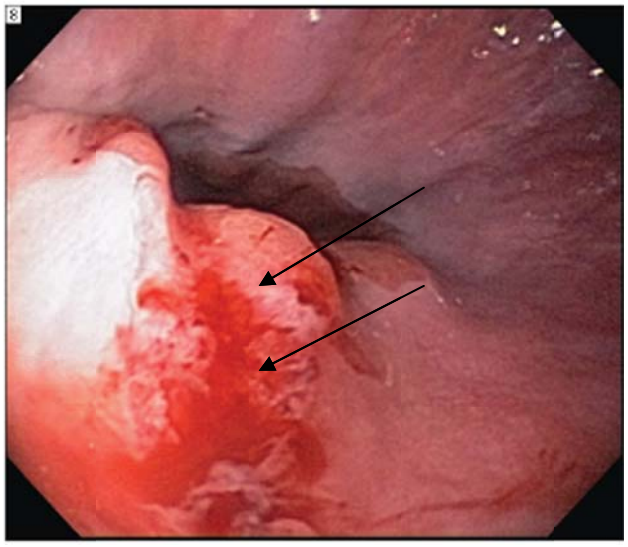
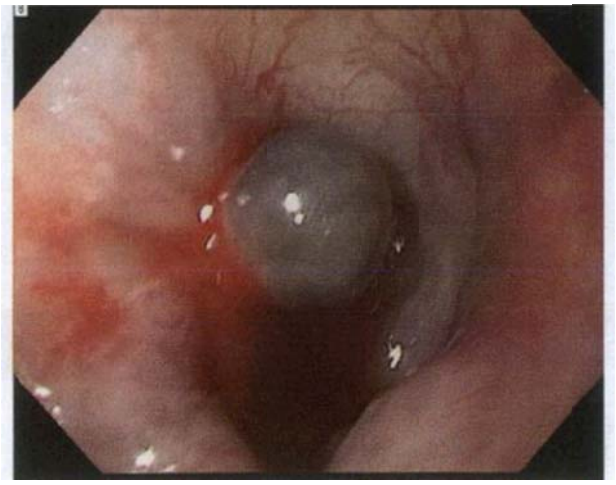


Figure 6. Esophageal varix causing upper GI bleeding after endoscopic ligation



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