Overview of the treatment of bleeding peptic ulcers

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INTRODUCTION

Upper gastrointestinal (UGI) bleeding secondary to peptic ulcer disease is a common medical condition that results in high patient morbidity and medical care costs. While the majority of patients with bleeding peptic ulcers will stop bleeding spontaneously and not rebleed during hospitalization, a subgroup of patients is at high risk for recurrent hemorrhage and requires endoscopic therapy to decrease this risk [1]. If endoscopic therapy fails, interventional angiography or surgery may be required.

Despite advances in pharmacologic and endoscopic therapy, mortality rates have not improved. In a Danish study of 13,498 patients with peptic ulcer bleeding studied between 2004 and 2011, rates for successful endoscopic therapy were higher in 2010 to 2011 than in 2004 to 2006 (94 versus 89 percent) [2]. In addition, rebleeding rates were lower (13 versus 18 percent). However, 30-day mortality did not improve (11 percent for both groups), though there was a trend toward decreased mortality after adjusting for potential confounders (adjusted relative risk 0.89, 95% CI 0.78-1.00).

The pharmacologic and endoscopic management of UGI bleeding due to peptic ulcer disease will be reviewed here. While there is variability among guidelines, the discussion that follows is generally consistent with a multidisciplinary international consensus statement updated in 2019, a 2012 guideline issued by the American Society for Gastrointestinal Endoscopy, and a 2021 guideline issued by the American College of Gastroenterology, a 2015 guideline issued by the European Society of Gastrointestinal Endoscopy, and a 2021 update issued by the European Society of Gastrointestinal Endoscopy [3-7].

A general approach to patients with UGI bleeding, general treatment of patients with peptic ulcer disease, an overview of the complications of peptic ulcer disease, a detailed discussion of the tools used for endoscopic hemostasis, and detailed discussions of angiographic and surgical management of patients with peptic ulcer disease are discussed separately. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Peptic ulcer disease: Treatment and secondary prevention" and "Overview of complications of peptic ulcer disease" and "Contact thermal therapy for the treatment of bleeding peptic ulcers" and "Angiographic control of nonvariceal gastrointestinal bleeding in adults" and "Surgical management of peptic ulcer disease".)

APPROACH TO THE PATIENT

The initial evaluation of a patient with upper gastrointestinal (UGI) bleeding starts with assessing hemodynamic stability and determining the need for fluid resuscitation and/or blood transfusion. This part of the evaluation is discussed in detail elsewhere. (See "Approach to acute upper gastrointestinal bleeding in adults".)

Patients with clinically significant UGI bleeding (ie, signs of active UGI bleeding including hematemesis, melena, or hematochezia, with or without hemodynamic instability or blood transfusion requirement) should be started on an intravenous proton pump inhibitor while undergoing their initial evaluation. Once the patient is stabilized, endoscopy is performed to diagnose high-risk lesions (table 1) [8]. Ulcers that are actively bleeding and most nonbleeding ulcers that are at high risk for recurrent bleeding based upon the presence of stigmata of recent hemorrhage require endoscopic therapy. Ulcers that lack high-risk stigmata can be managed acutely with acid suppression alone.

Stigmata of recent hemorrhage — Certain endoscopic findings, known as stigmata of recent hemorrhage, are associated with an increased risk of recurrent bleeding (up to 90 percent depending upon the finding) (table 2) [1].

The appearance of ulcers can be described using the Forrest classification [9]:

- Class Ia – Spurting hemorrhage (picture 1 and movie 1)
- Class Ib – Oozing hemorrhage
- Class IIa – Nonbleeding visible vessel (picture 2A-C)
- Class IIb – Adherent clot (picture 3)
- Class IIc – Flat pigmented spot (picture 4B)
- Class III – Clean ulcer base (picture 4A)

Stigmata of recent hemorrhage are present if anything other than a clean ulcer base is seen. However, only patients with active bleeding (spurting or oozing), a nonbleeding visible vessel, or an adherent clot are generally considered to be at high risk for recurrent bleeding. Most patients with high-risk stigmata require endoscopic therapy to decrease the risk of recurrent bleeding. On the other hand, patients without these high-risk stigmata are considered low risk and do not require endoscopic therapy. (See 'Endoscopic therapy' below and 'Inpatient versus outpatient management' below.)

INPATIENT VERSUS OUTPATIENT MANAGEMENT

Hospitalization is required for patients at high-risk for recurrent bleeding, patients with evidence of severe upper gastrointestinal (UGI) bleeding (hemodynamic instability, blood transfusion requirement), and patients at increased risk for complications should bleeding recur (eg, significant coronary artery or cerebrovascular disease, age over 65 years, patients taking antiplatelet or anticoagulant medications). Patients who are otherwise healthy and who are at low risk for recurrent UGI bleeding may be safely allowed to eat and be discharged from the hospital on oral antisecretory therapy once the effects of procedural sedation have worn off, provided that the patient is reliable and can promptly get medical care should bleeding recur. (See 'Stigmata of recent hemorrhage' above and "Gastrointestinal endoscopy in adults: Procedural sedation administered by endoscopists", section on 'Postprocedure care'.)

In addition to findings at the time of endoscopy, risk stratification scores can help differentiate patients who require hospitalization from those who are appropriate for outpatient management. It is recommended in the International Consensus Recommendations that all patients with upper gastrointestinal bleeding undergo risk stratification using the Blatchford score (calculator 1) [3]. (See "Approach to acute upper gastrointestinal bleeding in adults", section on 'Risk stratification'.)

Early discharge and return to work can significantly reduce both direct costs (eg, hospitalization cost) and indirect costs (eg, days lost from work) [10,11]. The safety of early discharge for low-risk patients was demonstrated in a retrospective study with 72 patients with a bleeding duodenal ulcer [10]. All of the patients were under the age of 60 years and presented with stable vital signs. On endoscopy, they had no stigmata of recent hemorrhage or only flat spots seen. The mean hospital stay was 1.4 days, and there were no episodes of recurrent bleeding or significant drops in hemoglobin concentration two weeks after discharge. The investigators then performed a prospective study with 75 similar patients and discharged them on the same day of endoscopy. There were no episodes of recurrent bleeding or significant drops in hemoglobin one week after discharge.

PHARMACOLOGIC THERAPY

All patients with bleeding peptic ulcers should receive acid suppressive treatment with a proton pump inhibitor (PPI). Our approach is to give a high-dose intervenous (IV) bolus of a PPI for patients with suspected clinically significant upper gastrointestinal bleeding prior to endoscopy as part of their initial management (eg, esomeprazole 80 mg). Typically, we try to perform endoscopy on these patients within 12 hours. However, if endoscopy is delayed, a second dose of an IV PPI should be given 12 hours later (eg, esomeprazole 40 mg). If the patient does not have an ulcer with high-risk stigmata at the time of endoscopy, we subsequently decrease the dose of the PPI. This differs from the International Consensus Group guideline in that we start an IV PPI prior to endoscopy, rather than starting a PPI after endoscopy (with the dose and route of administration determined by the endoscopic findings and treatment provided). (See "Approach to acute upper gastrointestinal bleeding in adults", section on 'Acid suppression'.)

Acid suppression — Treatment with PPIs leads to elevation of gastric pH levels, which stabilizes blood clots and improves clinical outcomes [12-22]. As a result, PPIs are recommended for all patients with peptic ulcer bleeding. The optimal approach to PPI administration prior to endoscopy is unclear. Options include giving an IV PPI every 12 hours or starting a continuous infusion. Our approach is to give a high-dose bolus (eg, esomeprazole 80 mg) to patients with signs of active bleeding (eg, hematemesis, hemodynamic instability). Typically, we try to perform endoscopy on these patients within 12 hours. However, if endoscopy is delayed, a second dose of an IV PPI should be given 12 hours later (eg, esomeprazole 40 mg). For patients who may have stopped bleeding (eg, patients who are hemodynamically stable with melena), we give an IV PPI every 12 hours (eg, esomeprazole 40 mg). Subsequent dosing will then depend on the endoscopic findings. Oral formulations (eg, esomeprazole 40 mg orally twice daily) are a reasonable alternative if IV formulations are not available. Pantoprazole and esomeprazole are the only intravenous formulations available in the United States, and intravenous lansoprazole has been removed from the world market [3,5,23,24]. (See 'High-dose continuous infusions' below and 'Oral versus intravenous dosing' below.)

In patients with high-risk stigmata of recent hemorrhage, a high-dose continuous infusion of a PPI (eg, esomeprazole 8 mg per hour) should be started and continued for 72 hours. If the patient did not receive an IV PPI prior to endoscopy, the patient should receive a high-dose bolus of PPI (eg, esomeprazole 80 mg) prior to starting the continuous infusion. The high-dose IV PPI may be switched to a high-dose oral PPI (eg, omeprazole 40 mg twice daily) 72 hours after endoscopy, provided there is no evidence of recurrent bleeding (see 'Treatment of persistent and recurrent bleeding' below). A randomized trial suggested that twice-daily oral dosing may be preferable in patients at high risk of rebleeding. In the trial, patients with a

Rockall score ≥6 (calculator 2) who received a twice–daily oral PPI had a lower rebleeding rate than those who received a once-daily oral PPI (11 versus 29 percent at 28 days) [25].

It is unlikely that an IV PPI would be of significant benefit in patients who do not have active bleeding or other high-risk stigmata (such as a visible vessel or adherent clots) because their risk of recurrent bleeding is low. Such patients may be switched to a standard-dose oral PPI (eg, omeprazole or esomeprazole 20 mg once daily, pantoprazole 40 mg once daily) immediately following endoscopy. The goal of treatment in low-risk patients should be directed at healing the ulcers and eliminating precipitating factors (such as *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs). (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Initial management'.)

High-dose oral PPIs in patients with high-risk stigmata of recent hemorrhage are continued for a total of two weeks and then changed to a once daily dose. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Initial antisecretory therapy'.)

Studies of H2 receptor antagonists (H2RAs) in bleeding peptic ulcers have produced mixed but generally disappointing results and are not recommended for patients with acute upper gastrointestinal bleeding [14,26-29]. A meta-analysis concluded that there was a possible minor benefit with IV H2RAs in bleeding gastric ulcers but no benefit with duodenal ulcers [28]. The improved efficacy seen with PPIs may be due to their superior ability to maintain a gastric pH at a level above 6.0.

Efficacy of proton pump inhibitors — A meta-analysis of 21 randomized trials that compared PPIs with either placebo or an H2RA for bleeding ulcers (with or without endoscopic therapy) found a significant and consistent reduction in the risk of recurrent bleeding (odds ratio [OR] 0.46, 95% CI 0.33-0.64) and the need for surgery (OR 0.59, 95% CI 0.46-0.76) with PPIs [12]. However, there was no effect on mortality.

- An illustrative trial included 240 patients with ulcers that were actively bleeding or had a visible vessel. The patients were randomly assigned to IV omeprazole or placebo following endoscopic hemostasis [16]. Recurrent bleeding was observed significantly less often in patients receiving omeprazole (7 versus 23 percent), a finding that led to early termination of the trial. A separate analysis based upon these data suggested that the addition of IV omeprazole was cost-effective compared with placebo [30].

- A second randomized trial (published after the meta-analysis [12]) included 638 patients admitted with upper gastrointestinal bleeding [21]. Patients were assigned to either IV omeprazole or placebo at the time of admission. Patients then underwent endoscopy the following morning. Patients who received omeprazole were less likely than those who

received placebo to have endoscopic signs of active bleeding (6 versus 15 percent) or to require endoscopic hemostatic therapy (19 versus 28 percent).

High-dose continuous infusions — PPIs given for the treatment of bleeding peptic ulcers are often given as high-dose continuous infusions (eg, esomeprazole or pantoprazole 80 mg bolus followed by 8 mg per hour). High-dose continuous PPI infusions decrease rebleeding and mortality rates compared with H2RAs or placebo, whereas lower-dose PPI regimens (IV or oral) decrease rebleeding rates compared with H2RAs or placebo (but have not been proven to decrease mortality rates) [3,31]. While direct comparisons of high-dose continuous PPI infusions with lower-dose PPIs have not shown a difference in the risk of rebleeding or mortality, the International Consensus Group guideline favors high-dose continuous PPI infusions in patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, since indirect comparisons suggest that high-dose continuous PPI infusions may be superior to lower-dose PPIs when it comes to mortality.

Oral versus intravenous dosing — Oral dosing of PPIs is less expensive than IV dosing, and some studies suggest it may be an option for the treatment of patients with peptic ulcer bleeding [32,33]. However, where available, IV dosing is currently considered standard of care. If oral dosing is being considered, a high-dose of an oral PPI should probably be used (eg, omeprazole, pantoprazole, or esomeprazole 40 mg twice per day).

Studies comparing oral dosing with placebo or an H2RA have shown the following:

- A combined analysis of five trials evaluating oral dosing (with or without endoscopic therapy) found a significant reduction in the risk of recurrent bleeding and surgery compared with treatment with placebo or an H2RA [12]. However, oral dosing was not compared with high-dose IV dosing.

- A randomized trial conducted in 220 patients in a setting where therapeutic endoscopy was not available found that high-dose oral omeprazole (40 mg twice daily) was associated with a decreased risk of recurrent bleeding compared with placebo in patients who had ulcers with visible vessels or adherent clots who did **not** undergo endoscopic therapy (11 versus 36 percent) [15].

- Another randomized trial included 160 patients who were at high risk for recurrent bleeding and had been treated with endoscopic injection therapy [34]. The patients who were assigned to receive oral omeprazole had a significantly lower rebleeding rate than those who received placebo (12 versus 26 percent).

Whether there is a difference in outcomes with oral and IV PPI dosing was examined in a meta-analysis of six randomized trials with 615 patients who underwent endoscopic treatment for peptic ulcer bleeding [33]. Four of the trials used high-dose IV PPIs (bolus followed by continuous infusion), and two used lower doses (40 mg of esomeprazole or omeprazole twice daily). There was no difference between those who received oral PPIs and those who received IV PPIs with regard to recurrent bleeding, mean volume of blood transfused, need for surgery, or all-cause mortality. Patients treated with oral PPIs had a shorter duration of hospital stay (-0.7 days). When the subset of studies that used high-dose IV PPIs was examined, the results were similar, though the trend toward decreased length of hospital stay with oral PPIs was no longer statistically significant.

In a subsequent randomized trial with 244 patients who received endoscopic therapy for bleeding peptic ulcers, patients were randomly assigned to IV esomeprazole (80 mg bolus followed by 8 mg/hour infusion) or oral esomeprazole (40 mg orally every 12 hours) [35]. Outcomes were similar between those who received IV esomeprazole and those who received oral esomeprazole with regard to recurrent bleeding within 30 days (8 versus 6 percent), blood transfusions (median 2 versus 1 units), need for repeat endoscopic therapy (1.7 versus 2.4 percent), and length of hospital stay (median 4.0 days for both).

High doses of PPIs given orally achieve adequate acid suppression more rapidly than standard doses (eg, omeprazole 20 mg daily), which may take several days to achieve adequate acid suppression [36]. In addition, high-dose IV PPIs achieve adequate acid suppression more rapidly than high-dose oral PPIs. This was demonstrated in a randomized trial that compared intravenous lansoprazole (90 mg bolus followed by a 9 mg/hour infusion) with oral lansoprazole (120 mg followed by 30 mg every three hours) in patients with bleeding ulcers [37]. Achievement of an intragastric pH >6 was similar for IV and oral lansoprazole (68 versus 64 percent), but the group that received IV lansoprazole achieved a more rapid increase in pH, reaching a mean pH of 6 approximately one hour sooner than the group that received an oral PPI (after two to three hours compared with three to four hours). Whether such frequent dosing of the oral PPI was necessary to achieve comparable clinical outcomes is unclear, and we suggest that if a high-dose oral PPI is going to be used, that it be given twice daily. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders".)

Somatostatin and octreotide — Somatostatin and its long-acting analogue octreotide (commonly used in the management of variceal bleeding) have a theoretical benefit in bleeding ulcer disease because they reduce splanchnic blood flow, inhibit gastric acid secretion, and may have gastric cytoprotective effects [38,39]. A clinical benefit has been described in ulcer

bleeding, but because of the effectiveness of PPI and endoscopic therapy, its role is generally limited to settings in which endoscopy is unavailable or as a means to help stabilize patients before definitive therapy can be performed.

Several studies have described the experience with these agents in patients with acute nonvariceal upper gastrointestinal bleeding. A meta-analysis of these trials suggested that somatostatin was associated with a reduced risk of continued bleeding (relative risk 0.53; 95% CI, 0.43 to 0.63) [40]. The risk also appeared to be reduced with octreotide, although there were fewer studies. Thus, somatostatin or octreotide can be used as adjunctive therapy before endoscopy, or when endoscopy is unsuccessful, contraindicated, or unavailable [41]. The doses used in the above studies were variable; a typical dose of somatostatin was 250 mcg given as a bolus followed by an infusion of 250 mcg per hour for three to seven days, while a typical dose of octreotide was 50 to 100 mcg given as a bolus followed by an infusion of 25 mcg per hour for up to three days. Of note, the dose of octreotide used is lower than that used for variceal bleeding (50 mcg bolus followed by an infusion of 50 mcg per hour), so if there is concern prior to the endoscopy that the bleed could be due to varices, the higher dose of octreotide should be used. (See "Methods to achieve hemostasis in patients with acute variceal hemorrhage", section on 'Somatostatin and its analogs'.)

Prokinetic agents — We suggest that erythromycin be used before endoscopy. A reasonable dose is 250 mg intravenously over 20 to 30 minutes. Endoscopy is performed 20 to 90 minutes after the infusion is complete. Patients receiving erythromycin need to be monitored for QTc prolongation. In addition, drug-drug interactions should be evaluated before giving erythromycin because it is a cytochrome P450 3A inhibitor (table 3). (See "Approach to acute upper gastrointestinal bleeding in adults", section on 'Prokinetics'.)

ENDOSCOPIC THERAPY

Endoscopic therapy is indicated for the treatment of most ulcers with stigmata of recent hemorrhage that increase the risk of recurrent bleeding. With appropriate treatment, high-risk lesions have recurrent bleeding rates of 5 to 20 percent, depending upon the endoscopic appearance of the ulcer. On the other hand, ulcers with a clean base or a flat pigmented spot are at low risk of recurrent bleeding (3 to 5 percent for clean-based ulcers and 7 to 10 percent for ulcers with a flat spot) and should not be treated endoscopically (picture 4A-B) [1]. (See "Contact thermal therapy for the treatment of bleeding peptic ulcers".)

Adherent clots that are not easily removed endoscopically (eg, with irrigation or gentle suctioning of the clot away from the ulcer crater to reveal the underlying stigmata) carry a 20 to

30 percent risk of recurrent bleeding. A traditional dictum has been to leave these clots in situ and manage patients medically. More recent experience suggests that removing the clot (eg, using a cold guillotine technique with a polypectomy snare) and then treating the underlying ulcer stigmata can significantly reduce the risk of recurrent bleeding [42,43]. However, meta-analyses have reached variable results. One meta-analysis of six studies with a total of 240 patients concluded that endoscopic therapy was associated with a significantly lower rate of recurrent hemorrhage in patients with bleeding peptic ulcers and adherent clots (8 versus 25 percent with medical therapy alone) [44]. On the other hand, a later meta-analysis found no clear evidence supporting specific endoscopic interventions in patients with an adherent clot [45].

Given the significant risk of recurrent bleeding in patients with adherent clots, we suggest that gentle attempts be made to remove the clot so that endoscopic treatment can be applied if needed, provided the ulcer is in a location that is amenable to endoscopic therapy in the event that removing the clot precipitates bleeding, that additional surgical and/or interventional radiology support is available, and that the endoscopist performing the procedure is comfortable with the techniques involved with clot removal. If these conditions are not met and the patient is not actively bleeding, high dose IV PPI treatment alone is a reasonable alternative. (See "Contact thermal therapy for the treatment of bleeding peptic ulcers", section on 'Nonbleeding adherent clots'.)

Choice of endoscopic treatment — Although several types of endoscopic treatment for bleeding peptic ulcers have been described, including injection therapy, thermal coagulation, hemostatic clips, fibrin sealant (or glue), argon plasma coagulation, and combination therapy (typically injection of epinephrine combined with another treatment modality), relatively few prospective comparative trials have been performed. Currently, most patients are treated with either thermal coagulation therapy or hemostatic clips, with or without the addition of injection therapy. This approach is based upon results from meta-analyses of randomized trials comparing different forms of treatment to control bleeding [45-47].

One analysis included 74 randomized trials that compared endoscopic methods to control bleeding in patients considered to be at high risk for recurrent ulcer bleeding (ie, those with active bleeding, a nonbleeding visible vessel, or an adherent clot) [45]. The primary endpoint was persistent or recurrent bleeding. The following were the major conclusions:

- Compared with epinephrine monotherapy, the risk of further bleeding was significantly lower with other monotherapies, such as thermal coagulation (relative risk [RR] 0.6) or epinephrine followed by another modality (RR 0.3).

- Endoscopic clips were more effective than epinephrine alone for preventing recurrent bleeding (RR 0.2) but were not different than other endoscopic therapies.

- The efficacy of endoscopic therapies for adherent clots was uncertain.

The choice between endoscopic clips and thermal therapy will often depend upon factors such as the location of the ulcer and the preference of the endoscopist. Detailed discussions of the endoscopic techniques used for hemostasis are presented elsewhere. (See "Contact thermal therapy for the treatment of bleeding peptic ulcers" and "Endoscopic clip therapy in the gastrointestinal tract: Bleeding lesions and beyond".)

Standard approaches — Standard approaches to treatment include thermal coagulation and endoscopic clip placement. In addition, both of these modalities can be combined with injection therapy, an approach known as combination therapy (picture 5).

Injection therapy — Injection therapy should be used in conjunction with other forms of therapy, such as thermal coagulation or endoscopic clip placement. Injection therapy should not be used as monotherapy because it is associated with higher rates of recurrent bleeding than treatment with thermal coagulation, endoscopic clip placement, or combination therapy [45,48,49].

Injection therapy with dilute epinephrine results in local tamponade and vasospasm [50,51]. The technique is inexpensive and effective for temporary hemostasis [52-56]. Epinephrine diluted with saline to 1:10,000 to 1:20,000 is injected in 0.5 to 2.0 mL aliquots in four quadrants within 3 mm of the bleeding site. In patients who are at increased risk of having an adverse event with epinephrine injection, such as those with significant cardiac disease or those with lesions close to the esophagogastric junction (epinephrine injected into this area may enter the systemic circulation without a first pass through the liver), a dilution of 1:100,000 can be used.

A potential advantage of epinephrine injection is that it is easy to administer, can help slow or stop bleeding, and can reduce bleeding after attempts at mechanical hemostasis. During active bleeding, it can also produce a cleaner field, permitting targeted treatment of the bleeding site. Addition of a sclerosant (eg, ethanolamine) confers no advantage over injection with epinephrine alone and may cause tissue damage [54,56]. While no longer commonly performed, injection of absolute ethanol is another treatment option that is inexpensive and easy to perform [53,55,57,58].

Injection of saline also causes local tamponade, which can be effective in achieving temporary hemostasis. However, as was seen in studies comparing epinephrine monotherapy with other therapeutic modalities, saline injection alone is associated with higher recurrent bleeding rates

compared with other standard therapies. In a randomized trial with 100 patients with high-risk bleeding ulcers, recurrent bleeding occurred more often with saline monotherapy compared with thermal coagulation (29 versus 12 percent) [59].

Thermal coagulation — Thermal coagulation with contact probes achieves acute hemostasis and prevents recurrent bleeding by coaptive coagulation of the underlying artery in the ulcer base (picture 2B and picture 6) [52]. Coaptive coagulation involves applying pressure to the vessel with the probe to compress it while coagulation is performed. This results in sealing (coaptation) of vessel. A detailed discussion of thermal coagulation is presented elsewhere. (See "Contact thermal therapy for the treatment of bleeding peptic ulcers", section on 'Application of thermal coagulation'.)

An alternate form of thermal coagulation uses argon plasma coagulation (APC). This approach has a theoretical disadvantage for the treatment of bleeding ulcers since it is not coaptive. Nevertheless, at least two randomized trials suggested that APC can be effective. (See "Argon plasma coagulation in the management of gastrointestinal hemorrhage".)

Endoscopic clips — The endoscopic application of endoscopic clips is an alternative to thermal coagulation. Once applied, the clips achieve hemostasis in a manner similar to surgical ligation. Placement of an endoscopic clip can be of value even if an ulcer is not amenable to endoscopic therapy, since it may serve as a radiopaque marker for subsequent interventional angiographic or surgical intervention. The use of endoscopic clips in the treatment of upper gastrointestinal bleeding is discussed elsewhere. (See "Endoscopic clip therapy in the gastrointestinal tract: Bleeding lesions and beyond".)

Alternative approaches — Alternatives to standard endoscopic therapy that are being studied include the use of tissue adhesives and agents that promote hemostasis.

Fibrin sealant — One approach involves the use of endoscopically injected fibrin sealant to achieve initial hemostasis and decrease the rate of recurrent bleeding. An unblinded, multicenter, randomized trial of 854 patients with actively bleeding gastroduodenal ulcers compared the safety and efficacy of a single application of fibrin sealant, daily repeated doses of fibrin sealant until the visible vessel disappeared, or a single application of the sclerosant polidocanol [60]. While the safety profiles of all three treatment strategies were similar, the patients who received multiple applications of fibrin sealant had significantly less recurrent bleeding than the polidocanol group (15 versus 23 percent) and had fewer acute treatment failures (8 versus 13 percent). However, the resources necessary to perform repeated endoscopies are not inconsequential, and the precise role for fibrin sealant in this setting remains to be defined. (See "Fibrin sealants".)

Hemostatic sprays — Hemostatic sprays can be used to control active GI bleeding in a variety of contexts, particularly when traditional endoscopic techniques fail to control massive GI bleeding. The 2019 consensus guidelines recommend hemostatic sprays as a temporizing measure to stop bleeding when conventional modalities to control bleeding fail or are not available [3]. Hemostatic spray may be deployed in patients with bleeding from a GI malignancy, which may be from multiple sites and can be difficult to control with standard techniques [61-63]. In one randomized trial, 106 patients with bleeding gastrointestinal malignancies in the upper or lower GI tract received treatment with hemostatic spray or standard endoscopic techniques [63]. Patients treated with hemostatic spray were more likely to have immediate hemostasis (100 versus 68.6 percent, $p<0.001$) and less likely to experience rebleeding within 30 days (2.1 versus 21.3 percent, $p = 0.003$) than those treated with standard endoscopic techniques.

Hemostatic spray may be delivered by physicians with endoscopic skills, but who lack training in hemostasis, as a temporizing measure to stabilize the patient until additional expertise is available or the patient is transported to a different facility. Lesions at high-risk of rebleeding such as actively bleeding peptic ulcers should undergo additional endoscopic treatment, such as endoscopic clips to prevent rebleeding.

Hemostatic sprays include a nanopowder that promotes hemostasis (Hemospray) and a starch-derived spray composed of absorbable hemostatic polysaccharides (EndoClot PHS [Polysaccharide Hemostatic System]).

- Hemostatic nanopowder – Hemostatic nanopowder becomes cohesive and adhesive when it comes into contact with moisture, forming a stable mechanical barrier at the site of bleeding. It also has been shown to enhance clot formation and shorten coagulation time [64]. The powder is delivered through a catheter and sprayed onto the bleeding site under endoscopic guidance, without the need for direct tissue contact. Potential advantages of this hemostatic approach are that it is easy to apply, does not require an en face view of the ulcer, and does not require direct tissue contact. Hemostatic nanopowder has been used to treat a wide spectrum of gastrointestinal bleeding sources, including ulcers, tumors, iatrogenic lesions (eg, postpolypectomy bleeding), and varices [65-70]. Reported success rates for achieving initial hemostasis in patients with nonvariceal upper gastrointestinal bleeding are 75 to 100 percent, with rebleeding rates of 9 to 49 percent [65-68,71-76].

  This treatment modality is available in Canada and Europe and was FDA approved in the United States in 2018 [77]. In the data submitted to the FDA, there were 750 patients treated with hemostatic nanopowder. Hemostasis on index endoscopy was reported as

being achieved in 97.8 percent. There was an overall rebleeding rate of 10.2 percent [78]. In a subsequent prospective multicenter international registry study that looked at outcomes in 202 patients with bleeding peptic ulcers, the primary hemostasis rate with hemostatic nanopowder was 88 percent and rebleeding occurred in 17 percent [75]. Primary hemostasis and rebleeding outcomes were similar among those who received hemostatic nanopowder as monotherapy, as part of combination therapy, or as rescue therapy. However, 30-day all-cause mortality was lower in those who received combination therapy compared with those who received monotherapy (adjusted RR 0.51, 95% CI 0.28-0.93, p <0.001).

- Starch-derived hemostatic spray – A starch-derived hemostatic spray composed of absorbable hemostatic polysaccharides (EndoClot PHS [Polysaccharide Hemostatic System]) was FDA approved in January 2021 for use in the United States. The adhesive hemostatic polymer forms a gel adhesive matrix that adheres to a bleeding site and promotes the clotting cascade. Application of the powder through the endoscope requires a delivery system that consists of a delivery catheter, a powder/air mixing chamber connected to a powder dispenser and an air compressor. This hemostatic spray is FDA approved for hemostasis of nonvariceal gastrointestinal bleeding, excluding Forrest Ia (spurting) classification of bleeding.

Data on the starch-derived hemostatic spray are more limited than for the nanopowder spray but suggest it is effective [79-82]. In a randomized trial, 216 patients with peptic ulcer bleeding were assigned to epinephrine injection followed by either hemostatic spray or conventional therapy (thermocoagulation or placement of hemostatic clips) [82]. Initial hemostasis rates with the hemostatic spray were similar to those in the conventional therapy group (88 versus 87 percent), as were 30-day rebleeding rates (7.8 versus 9.3 percent).

Second-look endoscopy — Second-look endoscopy refers to the practice of performing a planned follow-up endoscopy, generally within 24 hours of the initial endoscopy. If there is active bleeding or a nonbleeding visible vessel, endoscopic therapy is performed (see 'Treatment of persistent and recurrent bleeding' below). Data are conflicting regarding the benefits of second-look endoscopy, and in general, guidelines and reviews do not recommend it [23,83-85].

One problem with the available studies is that many were performed without optimal hemostatic approaches (eg, treatment with epinephrine monotherapy rather than combination therapy) and did not include the use of proton pump inhibitors. A meta-analysis that included five randomized trials with 998 patients found that second-look endoscopy with thermal coagulation was associated with a decreased risk of rebleeding (relative risk [RR] 0.29; 95% CI

0.11-0.73), but second-look endoscopy with injection therapy was not (RR 0.85; 95% CI 0.63-1.14). [86]. In addition, second-look endoscopy was not associated with a decreased risk of surgery or mortality.

A subsequent meta-analysis with eight randomized trials with 938 patients found that compared with standard medical care, routine second-look endoscopy was associated with a decreased risk of rebleeding (odds ratio [OR] 0.55; 95% CI 0.37-0.81) and surgery (OR 0.43; 95% CI 0.19-0.96), but not mortality (OR 0.65; 95% CI 0.26-1.62) [87]. However, only one of the included studies treated patients with a high-dose proton pump inhibitor, and three of the studies did not use cautery or endoscopic clipping as part of the endoscopic treatment. Finally, when two trials that included patients at high risk for rebleeding were removed, the benefit with second-look endoscopy was no longer seen.

The 2010 International Consensus Recommendations for the management of patients with nonvariceal upper gastrointestinal bleeding do not recommend routine use of second-look endoscopy [23]. However, the guidelines also suggest that patients at particularly high risk for recurrent bleeding may benefit from second-look endoscopy.

Situations that might warrant a second-look endoscopy include:

- If visualization during the initial endoscopy was limited by blood or debris
- If there is concern on the part of the endoscopist that the prior endoscopic therapy was suboptimal

In addition, repeat endoscopy is indicated if there is recurrent bleeding in order to exclude previously missed lesions and/or to retreat the bleeding ulcer. (See 'Treatment of persistent and recurrent bleeding' below.)

Treatment-related complications — Complications can arise prior to, during, or after emergency endoscopy [88]. Complications that may occur before endoscopy include aspiration (especially in a sedated, combative, or encephalopathic patient), hypoventilation (related to oversedation), or hypotension (due to inadequate volume replacement or transfusions, in addition to sedation with opiates). (See "Overview of upper gastrointestinal endoscopy (esophagogastroduodenoscopy)", section on 'Complications'.)

Complications of endoscopic therapy include perforation and precipitation (or worsening) of bleeding. In addition, epinephrine can cause tachycardia and arrhythmias. Aggressive initial treatment or repeated applications of thermal or injection therapy may improve hemostasis, but also increase the risk of treatment-induced complications. Thus, predetermined limits (volume of injection solution, total treatment pulses, and total energy delivered) should be set

and not exceeded for each technique, in order to minimize the risk of complications. We usually do not exceed 20 mL of epinephrine (1:10,000 dilution) injection or more than six pulses of thermal coagulation. In addition, in patients at increased risk for cardiac complications from epinephrine, one option is to further dilute the epinephrine to 1:100,000.

TREATMENT OF PERSISTENT AND RECURRENT BLEEDING

Although the majority of bleeding ulcers can be controlled endoscopically, some patients have persistent or recurrent bleeding [89,90]. Persistent bleeding refers to active bleeding that does not stop despite endoscopic therapy or bleeding that develops during endoscopic therapy of a nonbleeding lesion that cannot be controlled endoscopically. Recurrent bleeding refers to bleeding that occurs following spontaneous hemostasis or after successful endoscopic hemostasis.

The following criteria have been proposed for defining recurrent bleeding in studies [91]:

- Hematemesis or bloody nasogastric aspirate more than six hours after endoscopy
- Melena after normalization of stool color
- Hematochezia after normalization of stool color or after melena
- Development of tachycardia (heart rate ≥110 beats per minute) or hypotension (systolic blood pressure ≤90 mmHg) after at least one hour of hemodynamic stability (ie, no tachycardia or hypotension) in the absence of an alternative explanation for hemodynamic instability, such as sepsis, cardiogenic shock, or medications (of note, many endoscopists, ourselves included, consider tachycardia to be present if the heart rate is greater than 100 beats per minute)
- Hemoglobin drop of 2 g/dL or more after two consecutive stable hemoglobin values (less than a 0.5 g/dL decrease) obtained at least three hours apart
- Tachycardia or hypotension that does not resolve within eight hours after index endoscopy despite appropriate resuscitation (in the absence of an alternative explanation), associated with persistent melena or hematochezia
- Persistently dropping hemoglobin of more than 3 g/dL in 24 hours, associated with persistent melena or hematochezia

Patients with one episode of recurrent bleeding following initially successful endoscopic therapy are typically treated with a second attempt at endoscopic therapy. Therapy may consist of the same therapy initially used or a different endoscopic modality (eg, if thermocoagulation therapy was used initially it may either be repeated or treatment with a hemostatic clip employed). If the bleeding was initially controlled with endoscopic clips, treating with thermal coagulation is an option, even if it is needed next to a clip or if there might be contact with the clip during treatment (however, thermal coagulation should not be applied to the clip intentionally with the goal of heating it up). Surgery or angiography-guided intervention may be indicated for patients who fail endoscopic therapy (persistent bleeding or recurrent bleeding after two therapeutic endoscopies).

This approach was supported by a randomized trial that included 92 patients with recurrent bleeding after endoscopic therapy who were randomly assigned to repeat endoscopic therapy or surgery [92]. Long-term control of bleeding was achieved in 35 of 48 patients (73 percent) treated with repeated endoscopic therapy. Salvage surgery was performed in the 13 patients who failed endoscopic therapy (11 because of continued bleeding and 2 because of perforation resulting from thermocoagulation). Mortality was similar between the two groups, though complications were less frequent in the endoscopy group (15 versus 36 percent).

Another treatment option in patients with rebleeding is the use of an over-the-scope clip (OTSC). In a multicenter randomized trial, 66 patients with recurrent peptic ulcer bleeding were randomized to treatment with an OTSC or standard therapy [93]. Persistent bleeding was seen in 19 patients (58 percent) who had standard therapy versus 5 patients (15 percent) treated with an OTSC ($p=0.001$). In 14 patients randomized to the conventional therapy arm, crossover to OTSC occurred because of persistent bleeding (10 patients) or recurrent bleeding (four patients) and was successful in all patients. The use of an OTSC to treat recurrent peptic ulcer bleeding is a promising therapeutic option. (See "Endoscopic clip therapy in the gastrointestinal tract: Bleeding lesions and beyond".)

Risk factors for persistent or recurrent bleeding — Factors associated with persistent or recurrent bleeding include, ulcer location, the patient's presentation, the appearance of the ulcer at the time of endoscopy, size of the ulcer, and presence of comorbid illnesses.

In one report, gastric ulcers along the lesser curvature and duodenal ulcers along the posterior wall of the duodenal bulb were at greater risk for severe or recurrent bleeding compared with ulcers in other locations because of their proximity to large underlying arteries (left gastric and posterior gastroduodenal arteries, respectively) [89]. In addition, patients who presented with active hemorrhage, shock, and the lowest hemoglobin concentrations did less well than those without these risk factors. Factors that did **not** predict the outcome of endoscopic therapy were

a history of nonsteroidal anti-inflammatory drug or aspirin use, coagulopathy, previous peptic ulceration, and concomitant cardiorespiratory disease. In another report, severe bleeding, active bleeding, fresh blood in the stomach, and large ulcers (2 cm in diameter or larger) were independent risk factors for therapeutic failure after injection of epinephrine plus heater probe treatment [90]. Large ulcers tend to have larger blood vessels (>2 to 3 mm), and ulcers in the posterior duodenal bulb also may have a large vessel (gastroduodenal artery). These large vessels may be difficult or not possible to control with endoscopic therapies, and we advise the use of endoscopic combination therapies as well as a low threshold to advance to other therapies, including angiography and surgery.

A meta-analysis of 10 studies found that predictors of recurrent bleeding included active bleeding at endoscopy, large ulcers (>1 to 2 cm), posterior duodenal ulcers, and gastric ulcers on the lesser curvature [94].

End-stage kidney disease may also increase the risk of recurrent bleeding. A case-control study of 150 patients found that patients with end-stage kidney disease requiring dialysis were more likely to experience recurrent bleeding than were patients with chronic kidney disease who were not on dialysis (OR 3.8) or normal controls (OR 3.8) [95].

Surgery — Traditionally, surgery was required for patients who failed endoscopic therapy, though depending upon local resources and expertise, many patients now undergo an attempt at interventional angiography prior to surgery. Surgical treatments for peptic ulcer disease include oversewing of the artery with truncal vagotomy and pyloroplasty, antrectomy with gastrojejunostomy (Billroth II procedure), and highly selective vagotomy. Emergency surgery for bleeding peptic ulcer disease involves oversewing of the ulcer (to ligate the bleeding artery) plus truncal vagotomy (to decrease acid secretion) and pyloroplasty (for gastric drainage). More time consuming procedures, such as highly selective vagotomy, can be performed either at standard laparotomy or laparoscopically for non-emergency ulcer surgery [96]. (See "Surgical management of peptic ulcer disease", section on 'Bleeding duodenal ulcer' and "Surgical management of peptic ulcer disease", section on 'Bleeding gastric ulcer'.)

In addition to failure of endoscopic therapy, other indications for surgery for peptic ulcer hemorrhage include:

- Hemodynamic instability despite vigorous resuscitation (more than a three unit transfusion)
- Shock associated with recurrent hemorrhage
- Perforation

Secondary or relative indications include rare blood type, difficult crossmatch, refusal of transfusion, shock on presentation, advanced age, severe comorbid disease, and chronic gastric ulcer as the origin of hemorrhage. In addition, surgery may be appropriate for older adult patients who are unlikely to tolerate prolonged attempts at resuscitation, large volume transfusions, or periods of hypotension [97]. (See "Surgical management of peptic ulcer disease", section on 'Indications for peptic ulcer surgery'.)

If performed emergently, surgery is associated with high mortality rates (up to 36 percent) [98]. On the other hand, early elective surgery is associated with a much lower mortality rate (0 to 7 percent). Recurrent bleeding rates following surgery vary from 3 to 23 percent [98,99].

Interventional angiography — Angiography with transarterial embolization (TAE) for persistent or recurrent peptic ulcer bleeding is a less invasive alternative to surgery. Initial success rates for patients with acute peptic ulcer bleeding are between 52 and 98 percent, with recurrent bleeding rates of 10 to 20 percent [100]. (See "Angiographic control of nonvariceal gastrointestinal bleeding in adults".)

Indications for interventional angiography for acute nonvariceal upper gastrointestinal bleeding have been suggested in a consensus statement from the American College of Radiology [101]:

- Endoscopy is the best initial diagnostic and therapeutic procedure.
- Surgery and transcatheter arteriography/intervention are equally effective following failed therapeutic endoscopy, but transcatheter arteriography/intervention should be considered, particularly in patients at high risk for surgery.
- Transcatheter arteriography/intervention is less likely to be successful in patients with impaired coagulation.
- Transcatheter arteriography/intervention is the best technique for treatment of bleeding into the biliary tree or pancreatic duct.

TAE has been compared with surgical therapy for patients with peptic ulcer bleeding that could not be controlled endoscopically. In a metaanalysis of 13 observational studies with 1077 patients, 427 underwent TAE and 650 underwent surgery. There was a trend toward reduced mortality rates with TAE (22 versus 25 percent, odds ratio [OR] 0.77; 95% CI 0.50-1.18) and complication rates were lower (31 versus 50 percent, OR 0.45; 95% CI 0.30-0.47). Rebleeding was more common with TAE (35 versus 18 percent, OR 2.44; 95% CI 1.77-3.36), as was the need for further intervention (33 versus 18 percent, OR 2.13; 95% CI 1.21-3.77). A subsequent study with

282 patients found a decreased risk of death with TAE (hazard ration [HR] 0.66; 95% CI 0.46-0.96), an increased risk of rebleeding (HR 2.48; 95% CI 1.33-4.62), and a lower risk of complications (8.3 versus 32.2 percent, p <0.0001).

Given the less invasive nature of angiography, we suggest that patients who have failed endoscopic therapy first undergo attempted angiography with TAE, and that surgery be reserved for those who fail angiographic therapy. However, surgery is a reasonable alternative if an interventional radiologist with expertise in TAE is not available, if the lesion is deemed unlikely to respond to angiographic therapy or if the patient has underlying conditions that may complicate the ability to perform angiography or TAE (eg, renal insufficiency). (See "Angiographic control of nonvariceal gastrointestinal bleeding in adults".)

RESUMPTION OF ANTICOAGULANTS AND ANTIPLATELET AGENTS

Data are limited with regard to the appropriate timing for resuming anticoagulation or antiplatelet agents following endoscopic hemostasis. The timing will depend on the patient's risk of suffering a thromboembolic event while off of the medication(s). When to resume these agents after hemostasis has been achieved is discussed elsewhere. (See "Management of anticoagulants in patients undergoing endoscopic procedures", section on 'Resuming anticoagulants after hemostasis' and "Management of antiplatelet agents in patients undergoing endoscopic procedures".)

DIET ADVANCEMENT

Patients with lesions that are low risk for recurrent bleeding (eg, an ulcer with clean base or flat pigmented spot) may resume oral intake with a normal diet within 24 hours [3]. Our approach is to start liquids once the patient has recovered from sedation and to advance the diet as tolerated. For patients with lesions that are high risk for rebleeding, we typically wait 24 hours before resuming oral intake, starting with clear liquids.

DURATION OF ACID SUPRESSION

For patients with bleeding peptic ulcers, the duration of proton pump inhibitor therapy will depend on factors such as the location of the ulcer, the underlying etiology, and whether the patient is taking medications that may predispose to ulcer recurrence. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Duration' and "Peptic ulcer disease: Treatment and secondary prevention", section on 'Maintenance antisecretory therapy'.)

FOLLOW-UP

All patients with bleeding peptic ulcers need to be evaluated for factors that predispose to ulcer formation (eg, *H. pylori*) and treated as appropriate. This issue and issues related to maintenance proton pump inhibitor use/discontinuation are discussed in detail elsewhere. (See "Peptic ulcer disease: Treatment and secondary prevention" and "Peptic ulcer disease: Epidemiology, etiology, and pathogenesis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastrointestinal bleeding in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Peptic ulcers (The Basics)")
- Beyond the Basics topics (see "Patient education: Peptic ulcer disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Initial evaluation**

- The initial evaluation of the patient with upper gastrointestinal (UGI) bleeding involves an assessment of hemodynamic stability and the necessity for fluid resuscitation (table 1). (See "Approach to acute upper gastrointestinal bleeding in adults".)

- We calculate a bleeding risk score such as the Blatchford score (calculator 1) as part of the initial assessment of patients with UGI bleeding. Patients with a Blatchford score of 0 to 1 may be considered for out-patient management.

- **Endoscopy**

  - We recommend endoscopy within 24 hours of presentation for the diagnosis and treatment of active UGI bleeding and for the prevention of recurrent bleeding rather than waiting more than 24 hours (**Grade 1B**). (See "Approach to acute upper gastrointestinal bleeding in adults".)

  - We recommend that patients with active bleeding (oozing or spurting) or a visible vessel receive endoscopic therapy and acid suppressive therapy rather than acid suppressive therapy alone (**Grade 1B**). Endoscopic therapy decreases the risk of recurrent bleeding in patients with these high-risk stigmata.

    Patients may be treated with thermal coagulation or endoscopic clips (with or without epinephrine injection) but should not be treated with epinephrine monotherapy due to an increased risk of recurrent bleeding. Application of hemostatic sprays can be used if traditional techniques fail to achieve hemostasis and over-the-scope clips may be an option for patients with recurrent bleeding. (See 'Stigmata of recent hemorrhage' above and 'Endoscopic therapy' above.)

    Whether to treat patients with adherent clots will depend upon the location of the ulcer, the availability of surgical or interventional radiologic backup should bleeding start, and the experience of the endoscopist. Our approach is to make gentle attempts to remove the clot so that endoscopic treatment can be applied if needed, provided the ulcer is in a location that is amenable to endoscopic therapy should bleeding start.

- **Proton pump inhibitors**

  - **Prior to endoscopy** – We recommend that patients with actively bleeding peptic ulcers or ulcers with high-risk stigmata (such as a visible vessel or adherent clot) receive an intravenous (IV) proton pump inhibitor (PPI) rather than no acid suppression or an H2 receptor antagonist (**Grade 1A**). The optimal approach to PPI administration prior to endoscopy is unclear. Our approach is to give a high-dose bolus (eg, esomeprazole 80

mg) to patients with signs of active bleeding (eg, hematemesis, hemodynamic instability). If endoscopy is delayed beyond 12 hours, a second dose of an IV PPI should be given (eg, esomeprazole 40 mg). For patients who may have stopped bleeding (eg, patients who are hemodynamically stable with melena), we give an IV PPI every 12 hours (eg, esomeprazole 40 mg). Subsequent dosing will then depend on the endoscopic findings. (See 'Acid suppression' above and "Approach to acute upper gastrointestinal bleeding in adults", section on 'Acid suppression'.)

- **Following endoscopy** – Patients with active bleeding, a visible vessel, or an adherent clot should be started on a high-dose continuous infusion of a PPI (eg, esomeprazole 8 mg per hour) following endoscopy. The infusion should be continued for 72 hours. If the patient did not receive a high-dose bolus of a PPI (eg, esomeprazole 80 mg) prior to endoscopy, the patient should receive the high-dose bolus prior to starting the continuous infusion. If there are no signs of recurrent bleeding, the patient may then be switched to a high-dose oral PPI (eg, omeprazole 40 mg twice daily for 14 days followed by a once-daily PPI). Patients with low-risk ulcers can be switched to a standard-dose oral PPI following endoscopy (eg, omeprazole or esomeprazole 20 mg once daily, pantoprazole 40 mg once daily).

- **If IV PPIs are not available** – We recommend that an oral PPI be given when IV formulations are not available (**Grade 1A**). When used for acute GI bleeding, oral PPIs should be given twice daily at high doses. (See 'Acid suppression' above.)

- **Persistent or recurrent bleeding**

  - We suggest that most patients who fail endoscopic therapy first undergo attempted transarterial angiographic embolization (TAE) rather than surgery (**Grade 2C**). We suggest angiography rather than surgery because it is less invasive and because surgery is still an option in patients who fail angiographic therapy. However, surgery is a reasonable alternative if an interventional radiologist with expertise in TAE is not available, if the lesion is deemed unlikely to respond to angiographic therapy, or if the patient has underlying conditions that may complicate the ability to perform angiography or TAE (eg, renal insufficiency). (See 'Treatment of persistent and recurrent bleeding' above.)

  - The majority of patients with UGI bleeding due to peptic ulcer disease will stop bleeding spontaneously, and most will not rebleed during hospitalization. However, a subgroup of patients is at high risk for recurrent hemorrhage. The major endoscopic predictors of persistent or recurrent bleeding include active bleeding at endoscopy, a

nonbleeding visible vessel, and an adherent clot (table 2). (See 'Stigmata of recent hemorrhage' above.)

- **Discharge and follow-up**
  - We suggest that otherwise healthy patients without severe bleeding or high-risk stigmata be discharged following endoscopy on a standard-dose PPI rather than being admitted to the hospital for observation (**Grade 2C**). Such patients are at low risk for recurrent bleeding. (See 'Inpatient versus outpatient management' above.)
  - All patients with bleeding peptic ulcers need to be evaluated for factors that predispose to ulcer formation (eg, *H. pylori*) and treated as appropriate. (See "Peptic ulcer disease: Treatment and secondary prevention" and "Peptic ulcer disease: Epidemiology, etiology, and pathogenesis".)

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Topic 2573 Version 69.0

GRAPHICS

Acute management of severe upper gastrointestinal bleeding

1. Resuscitation and stabilization, initiation of medical therapy with an intravenous proton pump inhibito
2. Assessment of onset and severity of bleeding
3. Risk stratification using validated prognostic scale
4. Diagnostic endoscopy
▪ Preparation for emergent upper endoscopy
▪ Localization and identification of the bleeding site
▪ Identification of stigmata of recent hemorrhage
▪ Stratification of the risk for rebleeding
5. Therapeutic endoscopy
▪ Control of active bleeding or high-risk lesions
▪ Minimization of treatment-related complications
▪ Treatment of persistent or recurrent bleeding

Graphic 52860 Version 5.0

Endoscopic predictors of recurrent peptic ulcer hemorrhage[1,2]

Endoscopic stigmata of recent hemorrhage	Prevalence, percent	Risk of rebleeding on medical management, percent
Active arterial bleeding (Forrest Ia)	12% (arterial bleeding + oozing)	55 (arterial bleeding + oozing)
Oozing without visible vessel (Forrest Ib)		
Non-bleeding visible vessel (Forrest IIa)	8	43
Adherent clot (Forrest IIb)	8	22
Flat spot (Forrest IIc)	16	10
Clean ulcer base (Forrest III)	55	5

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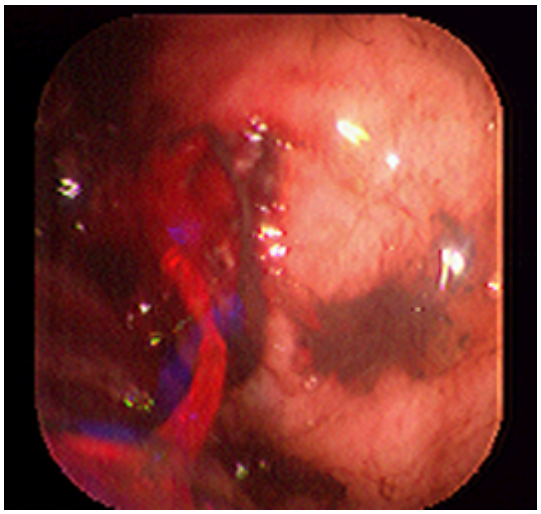
Graphic 78607 Version 8.0

Bleeding gastric ulcer

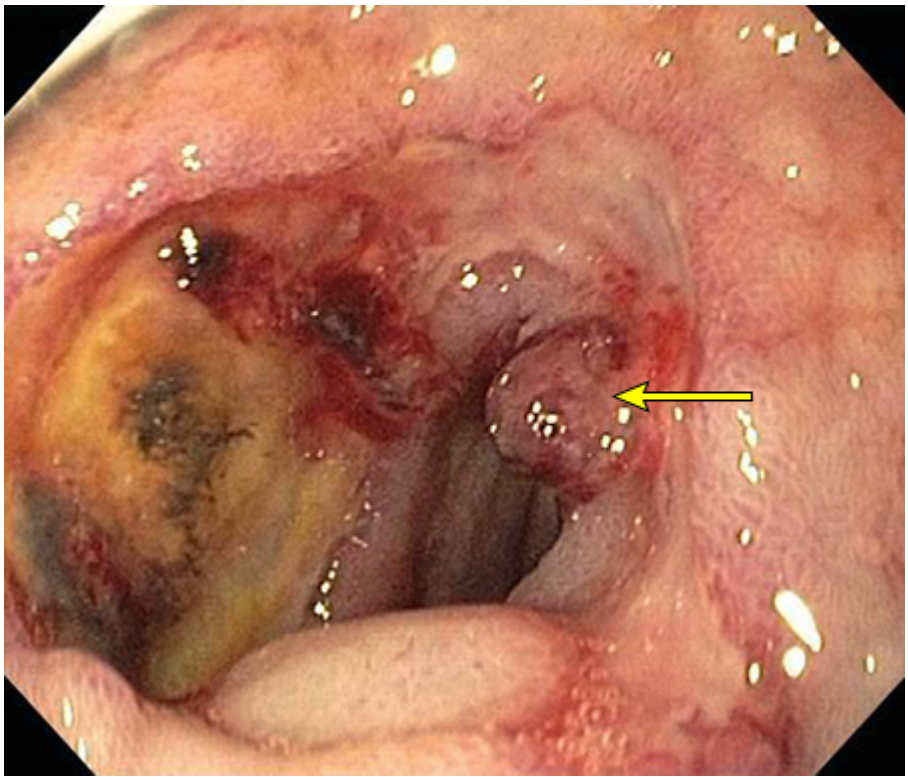


Endoscopy shows an actively bleeding gastric ulcer (Forrest classification Ia) along the lesser curvature.

Courtesy of Rome Jutabha, MD and Dennis M Jensen, MD.

Graphic 61646 Version 2.0

Duodenal ulcer with visible vessel

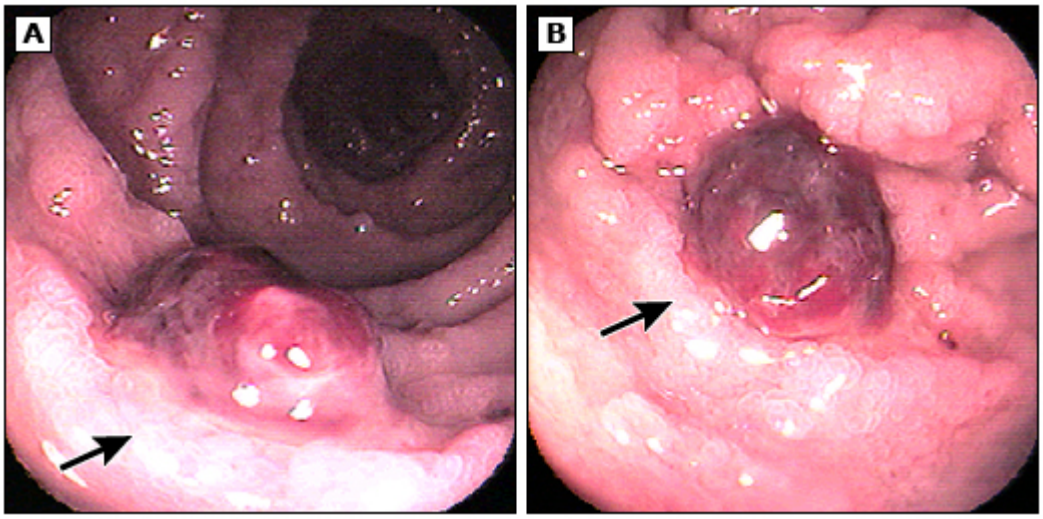


Upper endoscopy showing a duodenal ulcer with a nonbleeding visible vessel (arrow) in a large circumferential ulcer (Forrest classification IIa).

Courtesy of Rome Jutabha.

Graphic 54960 Version 4.0

Duodenal ulcer with visible vessel

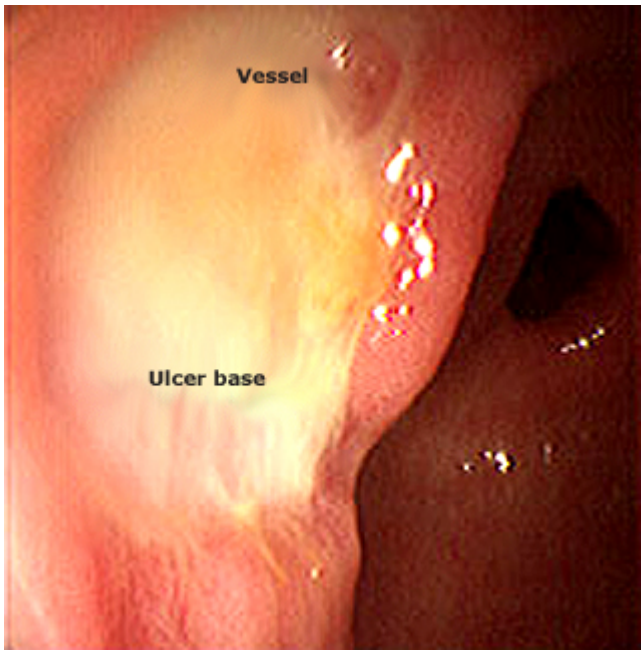


Duodenal ulcer in a patient with recent upper gastrointestinal bleeding. The ulcer base (arrows) is visible as the whitish rim underlying the protruding vessel. The erythematous mound in the center of the ulcer represents an artery that has eroded into the lumen of the duodenum.

Courtesy of Eric D Libby, MD.

Graphic 79058 Version 3.0

Gastric ulcer with a visible vessel

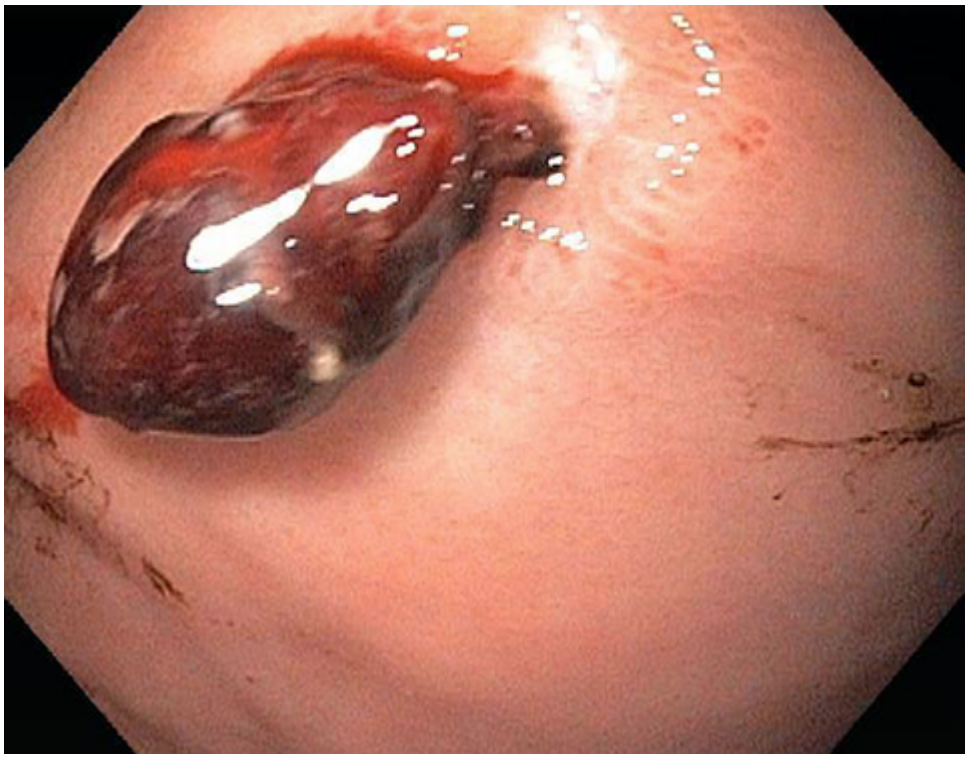


Ulcer in the gastric antrum seen on endoscopy. The visible vessel appears as a small protuberance in the one o'clock position.

Courtesy of Eric D Libby, MD.

Graphic 61604 Version 1.0

Gastric ulcer with adherent clot

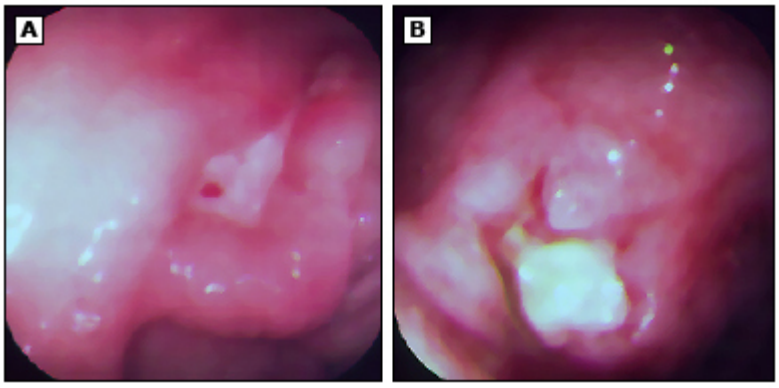


Upper endoscopy showing a gastric ulcer with an adherent clot (Forrest classification IIb).

Courtesy of Rome Jutabha, MD.

Graphic 76246 Version 1.0

Peptic ulcers at low risk for rebleeding

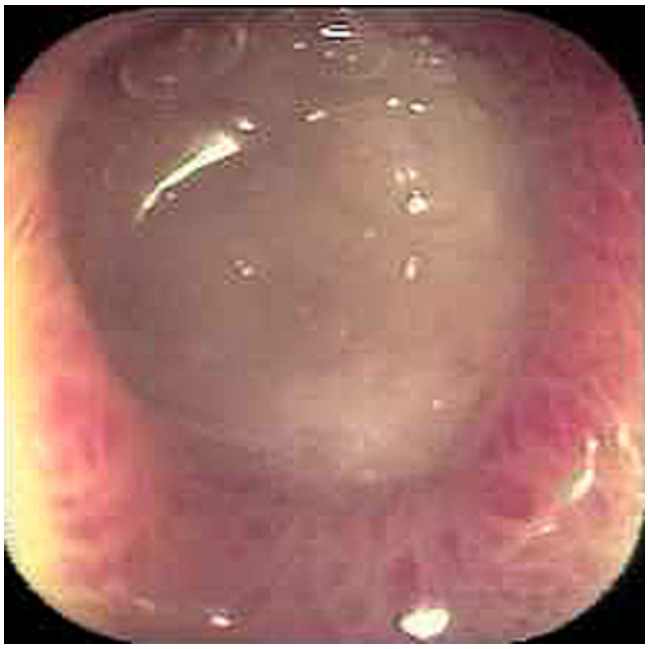


Ulcers with a flat pigmented spot (Forrest classification IIc; panel A) or a clean base (Forrest classification III, panel B) are at low risk for rebleeding and do not need to be treated endoscopically.

Courtesy of Rome Jutabha, MD and Dennis M Jensen, MD.

Graphic 52497 Version 2.0

Ulcer with a clean base



The opalescent ulcer in the center of this image taken during endoscopy has a "clean" base, which has a low risk of bleeding.

Courtesy of Eric D Libby, MD

Graphic 74032 Version 1.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone[*] ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone[¶] ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine[¶] ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine[¶] ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant[¶] ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Encorafenib ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone[Δ] ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack[◇] ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Repotrectinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.

- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

Data from: UpToDate Lexidrug. More information available at https://online.lexi.com/.

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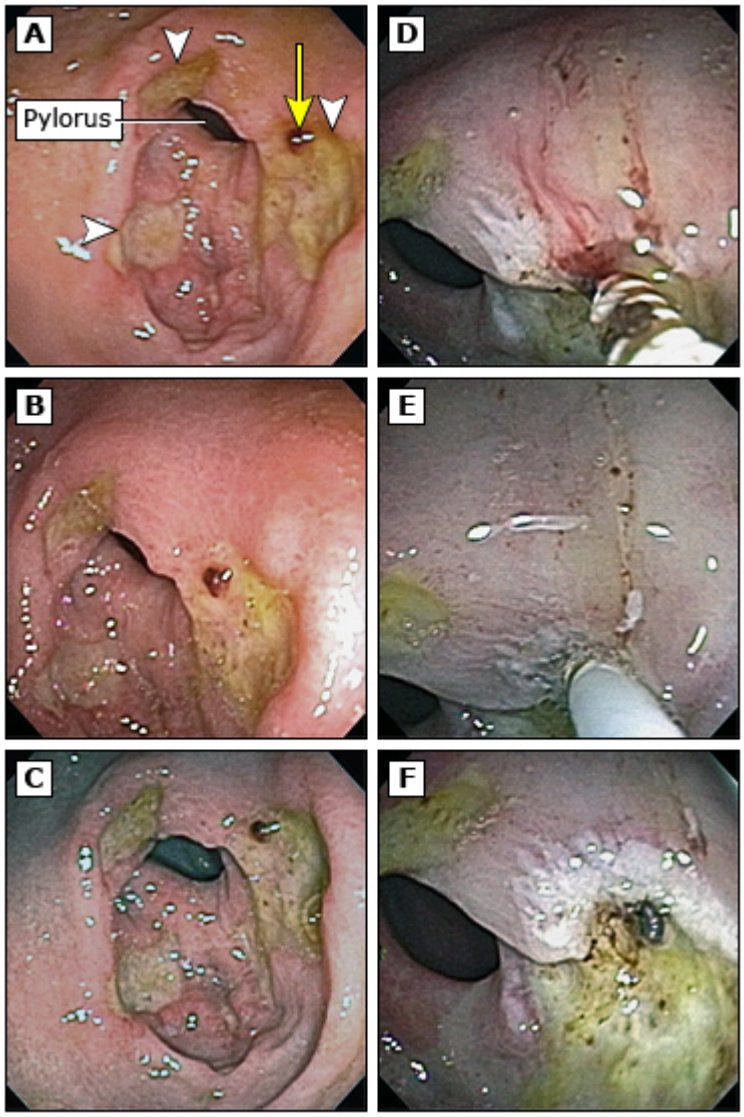
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 99.0

Combination therapy for a nonbleeding visible vessel

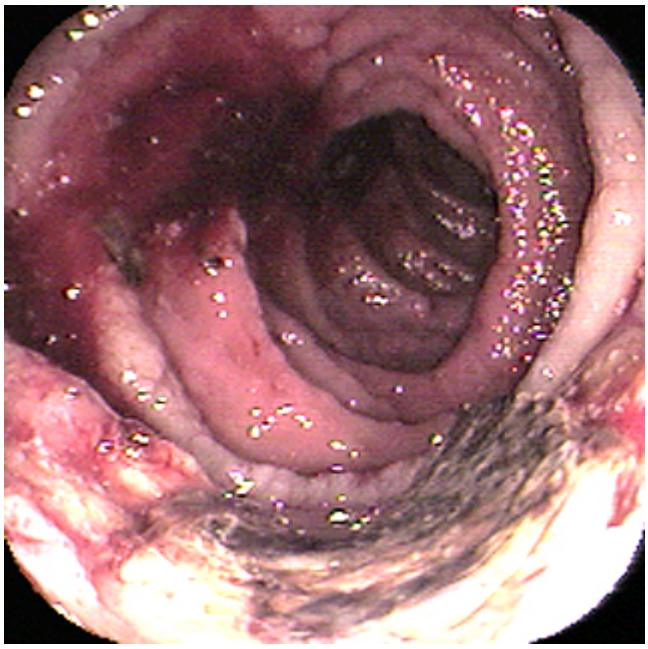


Upper endoscopy showing a deformed gastric antrum with three circumferential ulcers (arrowheads) near the pylorus (panels A-C). One of the ulcers contains a nonbleeding visible vessel (arrow), which was treated by a combination of epinephrine injection and bipolar electrocoagulation (panels D-E). Panel F shows the coagulated vessel after treatment.

Courtesy of Dennis M Jensen, MD, and Gustavo A Machicado, MD.

Graphic 56986 Version 3.0

Combination therapy for a bleeding duodenal ulcer with a visible vessel



Appearance of a duodenal ulcer that had a visible vessel following injection therapy with epinephrine and thermal coagulation. Note that the visible vessel has been flattened.

Courtesy of Eric D Libby, MD.

Graphic 70660 Version 2.0

Contributor Disclosures

John R Saltzman, MD, FACP, FACG, FASGE, AGAF No relevant financial relationship(s) with ineligible companies to disclose. **Loren Laine, MD** Consultant/Advisory Boards: Medtronic [Endoscopic hemostatic therapy]; Phathom Pharmaceuticals [Gastric acid inhibition medication]. Other Financial Interest: Biohaven [Assess liver events in clinical trials]; Celgene [Data safety monitoring board]; GSK [Assess GI events in clinical trials]; Intercept [Assess liver events in clinical trials]; Prometheus [Data safety monitoring board]. All of the relevant financial relationships listed have been mitigated. **Anne C Travis, MD, MSc, FACG, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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