CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will evaluate and manage acute upper gastrointestinal bleeding effectively

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Managing acute upper GI bleeding, preventing recurrences

ABSTRACT

Acute upper gastrointestinal (GI) bleeding is common and potentially life-threatening and needs a prompt assessment and aggressive medical management. All patients need to undergo endoscopy to diagnose, assess, and possibly treat any underlying lesion. In addition, patients found to have bleeding ulcers should receive a proton pump inhibitor, the dosage and duration of treatment depending on the endoscopic findings and clinical factors.

KEY POINTS

The first priority is to ensure that the patient is hemodynamically stable, which often requires admission to the intensive care unit for monitoring and fluid resuscitation.

Peptic ulcers account for most cases of upper GI bleeding, but bleeding from varices has a much higher case-fatality rate and always demands aggressive treatment.

Patients with ulcer disease should be tested and treated for *Helicobacter pylori* infection.

Patients with a history of bleeding ulcers who need long-term treatment with aspirin or a nonsteroidal anti-inflammatory drug should also be prescribed a proton pump inhibitor.

Upper gastrointestinal (GI) bleeding is common, costly, and potentially life-threatening. It must be managed promptly and appropriately to prevent adverse outcomes.

More people are admitted to the hospital for upper GI bleeding than for congestive heart failure or deep vein thrombosis. In the United States, the annual rate of hospitalization for upper GI bleeding is estimated to be 165 per 100,000—more than 300,000 hospitalizations per year, at a cost of $2.5 billion.[1,2]

Furthermore, despite advances in therapy, the case-fatality rate has remained unchanged at 7% to 10%.[3] This may be because today's patients are older and have more comorbidities than those in the past.[4]

CAUSES OF UPPER GI BLEEDING

Peptic ulcers account for about 60% of severe cases of upper GI bleeding,[5] and they are the focus of this paper. Fortunately, up to 80% of bleeding ulcers stop bleeding spontaneously without any intervention.[6]

Gastroduodenal erosions account for about 12%.[3]

Varices due to cirrhosis are less common but more dangerous. Variceal bleeding accounts for a relatively small percentage (6%) of upper GI bleeding, but the mortality rate from a single episode of variceal bleeding is 30%, and 60% to 70% of patients die within 1 year, mostly of underlying liver disease.

Less frequent causes include Mallory-Weiss tears, erosive duodenitis, Dieulafoy ulcer (a type of vascular malformation), other vascular lesions, neoplasms, aortoenteric fistula, gastric antral vascular ectasia, and prolapse gastropathy.[5]

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HEMATEMESIS AND MELENA

The most common presenting signs of acute upper GI bleeding are hematemesis (vomiting of blood), "coffee grounds" emesis, and melena (tarry black stools). About 30% of patients with bleeding ulcers present with hematemesis, 20% with melena, and 50% with both.[7]

Hematochezia (red blood in the stool) usually suggests a lower GI source of bleeding, since blood from an upper source turns black and tarry as it passes through the gut, producing melena. However, up to 5% of patients with bleeding ulcers have hematochezia,[7] and it indicates heavy bleeding: bleeding of approximately 1,000 mL into the upper GI tract is needed to cause hematochezia, whereas only 50 to 100 mL is needed to cause melena.[8,9] Hematochezia with signs and symptoms of hemodynamic compromise such as syncope, postural hypotension, tachycardia, and shock should therefore direct one's attention to an upper GI source of bleeding.

Nonspecific features include nausea, vomiting, epigastric pain, vasovagal phenomena, and syncope.

WHAT IS THE PATIENT'S RISK?

More people are admitted for upper GI bleeding than for congestive heart failure

An assessment of clinical severity is the first critical task, as it helps in planning treatment. Advanced age, multiple comorbidities, and hemodynamic instability call for aggressive treatment. Apart from this simple clinical rule, scoring systems have been developed.

The Rockall scoring system, the most widely used, gives estimates of the risks of recurrent bleeding and death. It is based on the three clinical factors mentioned above and on two endoscopic ones, awarding points for:

- Age—0 points if less than 60; 1 point if 60 to 79; or 2 points if 80 years or older
- Shock—1 point if the pulse is more than 100; 2 points if the systolic blood pressure is less than 100 mm Hg
- Comorbid illness—2 points for ischemic heart disease, congestive heart failure, or other major comorbidity; 3 points for renal failure, hepatic failure, or metastatic disease
- Endoscopic diagnosis—0 points if no lesion found or a Mallory-Weiss tear; 1 point for peptic ulcer, esophagitis, or erosive disease; 2 points for GI malignancy
- Endoscopic stigmata or recent hemorrhage—0 points for a clean-based ulcer or flat pigmented spot; 2 points for blood in the upper GI tract, active bleeding, a nonbleeding visible vessel, or adherent clot.

The Rockall score can thus range from 0 to 11 points, with an overall score of 0, 1, or 2 associated with an excellent prognosis.[10]

The Blatchford scoring system uses only clinical and laboratory factors and has no endoscopic component (TABLE 1). In contrast to the Rockall score, the main outcome it predicts is the need for clinical intervention (endoscopy, surgery, or blood transfusion). The Blatchford score ranges from 0 to 23; most patients with a score of 6 or higher need intervention.[11]

Other systems that are used less often include the Baylor severity scale and the Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Does the patient have varices?

All variceal bleeding should be considered severe, since the 1-year death rate is so high (up to 70%). Clues pointing to variceal bleeding include previous variceal bleeding, thrombocytopenia, history of liver disease, and signs of liver disease on clinical examination.

All patients suspected of having bleeding varices should be admitted to the intensive care unit for close monitoring and should be given the highest priority, even if they are hemodynamically stable.

Is the patient hemodynamically stable?

Appropriate hemodynamic assessment includes monitoring of heart rate, blood pressure, and mental status. Tachycardia at rest, hypotension, and orthostatic changes in vital signs indicate a considerable loss of blood volume. Low urine output, dry mucous membranes, and sunken neck veins are also useful signs. (Tachycardia may be blunted if the patient is taking a beta-blocker.)

If these signs of hypovolemia are present, the initial management focuses on treating shock and on improving oxygen delivery to the vital organs. This involves repletion of the intravascular volume with intravenous infusions or blood transfusions. Supplemental oxygen also is useful, especially in elderly patients with heart disease.[12]

Inspection of nasogastric aspirate

In the initial assessment, it is useful to insert a nasogastric tube and inspect the aspirate. If it contains bright red blood, the patient needs an urgent endoscopic evaluation and an intensive level of care[13,14]; if it contains coffee-grounds material, the patient needs to be admitted to the hospital and to undergo endoscopic evaluation within 24 hours.

However, a normal aspirate does not rule out upper GI bleeding. Aljebreen et al[15] found that 15% of patients with upper GI bleeding and normal nasogastric aspirate still had high-risk lesions (ie, visible bleeding or nonbleeding visible vessels) on endoscopy.

ACID-SUPPRESSION HELPS ULCERS HEAL

Acid and pepsin interfere with the healing of ulcers and other nonvariceal upper GI lesions. Further, an acidic environment promotes platelet disaggregation and fibrinolysis and impairs clot formation.[16] This suggests that inhibiting gastric acid secretion and raising the gastric pH to 6 or higher may stabilize clots. Moreover, pepsinogen in the stomach is converted to its active form (pepsin) if the pH is less than 4. Therefore, keeping the pH above 4 keeps pepsinogen in an inactive form.

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists were the first drugs to inhibit acid secretion, reversibly blocking histamine-2 receptors on the basolateral membrane of parietal cells. However, these drugs did not prove very useful in managing upper GI bleeding in clinical trials.[17,18] In their intravenous form, they often fail to keep the gastric pH at 6 or higher, due to tachyphylaxis.[19] The use of this class of drugs has declined in favor of proton pump inhibitors.

Proton pump inhibitors

Proton pump inhibitors reduce both basal and stimulated acid secretion by inhibiting hydrogen-potassium adenosine triphosphatase, the proton pump of the parietal cell.

Multiple studies have shown that proton pump inhibitors raise the gastric pH and keep it high. For example, an infusion of omeprazole (Prilosec) can keep the gastric pH above 6 for 72 hours without inducing tachyphylaxis.[20,21]

TABLE 1

The Blatchford scoring system

VARIABLES	POINTS
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
< 90	3
Blood urea nitrogen (mmol/L)	
6.5–7.9	2
8.0–9.9	3
10.0–24.9	4
> 25	6
Hemoglobin (men; g/dL)	
12.0–12.9	1
10.0–11.9	3
< 10.0	6
Hemoglobin (women; g/dL)	
10.0–11.9	1
< 10.0	2
Other variables	
Pulse > 100	1
Presentation with melena	1
Hepatic disease	2
Cardiac failure	2
Total	___

Most patients need intervention if their score is 6 or higher. Conversely, few patients need intervention if their systolic blood pressure is 110 mm Hg or less, their blood urea nitrogen is less than 6.5 mmol/L, their hemoglobin level is 13 g/dL or higher (in men) or 12 g/dL or higher (in women), and their pulse is less than 100.

ADAPTED FROM BLATCHFORD O, MURRAY WR, BLATCHFORD M. A RISK SCORE TO PREDICT NEED FOR TREATMENT FOR UPPER-GASTROINTESTINAL HAEMORRHAGE. LANCET 2000; 356:1318–1321. WITH PERMISSION FROM ELSEVIER, WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/01406736.

Started after endoscopy. Randomized controlled trials have found proton pump inhibitors to be effective when given in high doses intravenously for 72 hours after successful endoscopic treatment of bleeding ulcers with high-risk endoscopic signs, such as active bleeding or nonbleeding visible vessels.[22,23]

A meta-analysis indicated that these drugs decrease the incidence of recurrent peptic ulcer bleeding, the need for blood transfusions, the need for surgery, and the duration of hospitalization, but not the mortality rate.[24,25] These studies also illustrate the benefit of fol-

Old age, comorbidities, and hemodynamic instability should prompt aggressive treatment

lowing up endoscopic treatment to stop the bleeding with an intravenous infusion of a proton pump inhibitor.

The recommended dose of omeprazole for patients with high-risk findings on endoscopy is an 80-mg bolus followed by an 8-mg/hour infusion for 72 hours. After the patient's condition stabilizes, oral therapy can be substituted for intravenous therapy. In patients with low-risk endoscopic findings (a clean-based ulcer or flat spot), oral proton pump inhibitors in high doses are recommended.

In either case, after the initial bleeding is treated endoscopically and hemostasis is achieved, a proton pump inhibitor is recommended for 6 to 8 weeks, or longer if the patient is also positive for *Helicobacter pylori* or is on daily treatment with aspirin or a nonsteroidal anti-inflammatory drug (NSAID) that is not selective for cyclo-oxygenase 2 (see below).

Started *before* endoscopy, these drugs reduced the frequency of actively bleeding ulcers, the duration of hospitalization, and the need for endoscopic therapy in a randomized controlled trial.[26] A meta-analysis found that significantly fewer patients had signs of recent bleeding on endoscopy if they received a proton pump inhibitor 24 to 48 hours before the procedure, but it did not find any significant difference in important clinical outcomes such as death, recurrent bleeding, or surgery.[27] Nevertheless, we believe that intravenous proton pump inhibitor therapy should be started before endoscopy in patients with upper GI bleeding.

All variceal bleeding should be considered severe

Somatostatin analogues

Octreotide (Sandostatin), an analogue of the hormone somatostatin, decreases splanchnic blood flow, decreases secretion of gastric acid and pepsin, and stimulates mucus production. Although it is beneficial in treating upper GI bleeding due to varices, its benefit has not been confirmed in patients with nonvariceal upper GI bleeding.

A meta-analysis revealed that outcomes were better with high-dose intravenous proton pump inhibitor therapy than with octreotide when these drugs were started after endoscopic treatment of acute peptic ulcer bleeding.[28] Nevertheless, octreotide may be useful in patients with uncontrolled nonvariceal bleeding who are awaiting endoscopy, since it is relatively safe to use.

ALL PATIENTS NEED ENDOSCOPY

All patients with upper GI bleeding need an upper endoscopic examination to diagnose and assess the risk posed by the bleeding lesion and to treat the lesion, reducing the risk of recurrent bleeding.

How urgently does endoscopy need to be done?

Endoscopy within the first 24 hours of upper GI bleeding is considered the standard of care. Patients with uncontrolled or recurrent bleeding should undergo endoscopy on an urgent basis to control the bleeding and reduce the risk of death.

However, how urgently endoscopy needs to be done is often debated. A multicenter randomized controlled trial compared outcomes in patients who underwent endoscopy within 6 hours of coming to the emergency department vs within 24 hours after the initial evaluation. The study found no significant difference in outcomes between the two groups; however, the group that underwent endoscopy sooner needed fewer transfusions.[29]

For a better view of the stomach

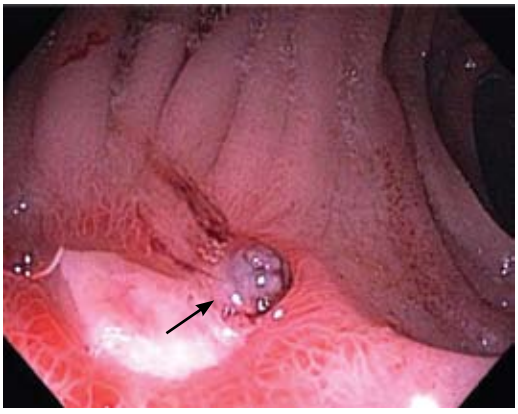
Gastric lavage improves the view of the gastric fundus but has not been proven to improve outcome.[30]

Promotility agents such as erythromycin and metoclopramide (Reglan) are also used to empty the stomach for better visualization.[31–35] Erythromycin has been shown to improve visualization, shorten the procedure time, and prevent the need for additional endoscopy attempts in two randomized controlled studies.[33,34] Furthermore, a cost-effectiveness study confirmed that giving intravenous erythromycin before endoscopy for acute upper GI bleeding saved money and resulted in an increase in quality-adjusted life-years.[35]

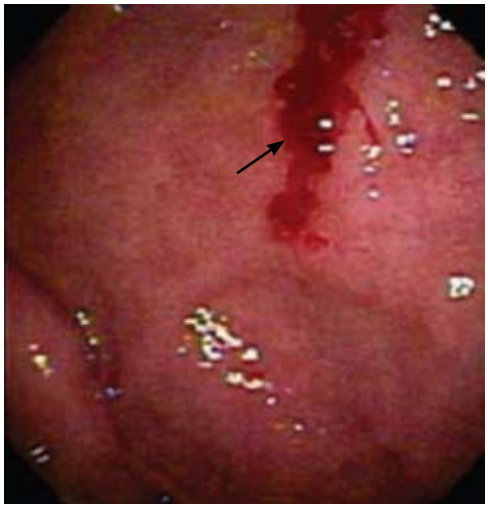
Endoscopy to diagnose bleeding and assess risk

Upper endoscopy is 90% to 95% diagnostic for acute upper GI bleeding.[36]

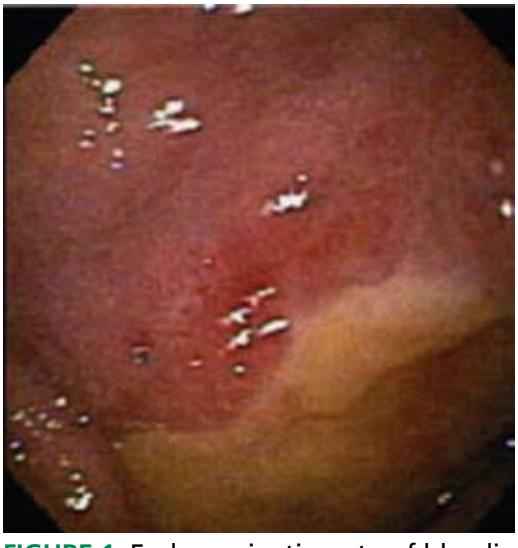
Nonbleeding visible vessel (high risk)



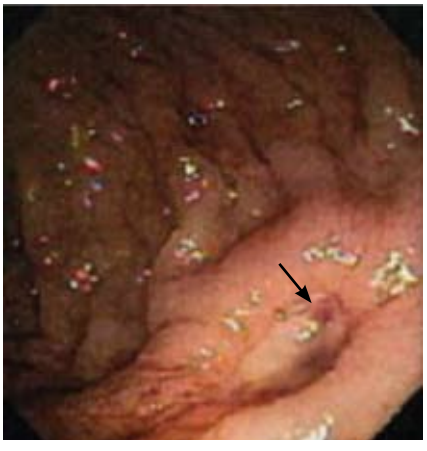
Dieulafoy ulcer (high risk)



Clean-based ulcer (low risk)



Red spot in a gastric ulcer (low risk)



A normal aspirate does not rule out upper GI bleeding

FIGURE 1. Endoscopic stigmata of bleeding peptic ulcer (arrows) and risk of recurrent bleeding and death.

Furthermore, some of the clinical scoring systems are based on endoscopic findings along with clinical factors on admission. These scoring systems are valuable for assessing patients with nonvariceal upper GI bleeding, as they predict the risk of death, longer hospital stay, surgical intervention, and recurrent bleeding.[37,38] Patients with endoscopic findings associated with higher rates of recurrent bleeding and death (**FIGURE 1**) need aggressive management.

Certain factors, primarily clinical and endoscopic, predict that endoscopic treatment will fail to stop ulcer bleeding. Clinical factors include a history of peptic ulcer bleeding and hemodynamic compromise at presentation. Endoscopic factors include ulcers located high on the lesser curvature of the stomach, ulcers in the posterior or superior duodenal bulb, ulcers larger than 2 cm in diameter, and ulcers that are actively bleeding at the time of endoscopy.[37] Other endoscopic findings that predict clinical outcome are summarized in **TABLE 2**.

Patients at high risk (ie, older than 60 years, with severe comorbidity, or hemodynamically compromised) who have active bleeding (ie, witnessed hematemesis, red blood per nasogastric tube, or fresh blood per rectum) or a nonbleeding visible vessel should be admitted to a monitored bed or intensive care unit. Observation in a regular medical ward is appropriate for high-risk patients found to have an adherent clot. Patients with low-risk findings (eg, a clean ulcer base) are at low risk of recur-

TABLE 2

Endoscopic findings as predictors of clinical outcome

ENDOSCOPIC FINDING	PREVALENCE %	RECURRENT BLEEDING (%)	SURGERY (%)	MORTALITY (%)
Active bleeding	18	55	35	11
Visible vessel	17	43	34	11
Adherent clot	17	22	10	7
Flat spot	20	10	6	3
Clean-base ulcer	42	5	0.5	2

ADAPTED FROM LAINE L, PETERSON WL. BLEEDING PEPTIC ULCER. N ENGL J MED 1994; 331:717–727.

rent bleeding and may be considered for early hospital discharge with appropriate outpatient follow-up.

Endoscopy to treat bleeding

About 25% of endoscopic procedures performed for upper GI bleeding include some type of treatment,[39] such as injections of epinephrine, normal saline, or sclerosants; thermal cautery; argon plasma coagulation; electrocautery; or application of clips or bands. They are all equally effective, and combinations of these therapies are more effective than when they are used individually. A recent meta-analysis found dual therapy to be superior to epinephrine monotherapy in preventing recurrent bleeding, need for surgery, and death.[40]

In cases of active bleeding or nonbleeding visible vessels, continue IV omeprazole for 72 hours

Endoscopic therapy is recommended for patients found to have active bleeding or nonbleeding visible blood vessels, as outcomes are better with endoscopic hemostatic treatment than with drug therapy alone (**TABLE 3**).[41–44]

How to manage adherent clots is controversial, but recent studies have revealed a significant benefit from removing them and treating the underlying lesions compared with drug therapy alone.[43,45]

Flat, pigmented spots and nonbleeding ulcers with a clean base do not require endoscopic treatment because the risk of recurrent bleeding is low.

Endoscopic therapy stops the bleeding in more than 90% of patients, but bleeding recurs after endoscopic therapy in 10% to 25%.[46] Reversal of any severe coagulopathy with transfusions of platelets or fresh frozen plasma is essential for endoscopic hemostasis. However, coagulopathy at the time of initial bleeding and endoscopy does not appear to be associated with higher rates of recurrent bleeding following endoscopic therapy for nonvariceal upper GI bleeding.[47]

Patients with refractory bleeding are candidates for angiography or surgery. However, even when endoscopic hemostasis fails, endoscopy is important before angiography or surgery to pinpoint the site of bleeding and diagnose the cause.

A second endoscopic procedure is generally not recommended within 24 hours after the initial procedure.[48] However, it is appropriate in cases in which clinical signs indicate recurrent bleeding or if hemostasis during the initial procedure is questionable. A meta-analysis found that routinely repeating endoscopy reduces the rate of recurrent bleeding but not the need for surgery or the risk of death.[49]

ALL PATIENTS SHOULD BE ADMITTED

All patients with upper GI bleeding should be admitted to the hospital, with the level of care dictated by the severity of their clinical condition (**FIGURE 2**).

VARICEAL BLEEDING

Variceal bleeding, a severe outcome of portal hypertension secondary to cirrhosis, carries a 6-week mortality rate of 10% to 20%.[50] In view of the risk, primary prevention is indicated in patients with high-risk varices.

The mainstays of primary and secondary prevention are the nonselective beta-blockers such as nadolol (Corgard) and propranolol (Inderal). Several randomized controlled trials have shown lower rates of recurrent bleeding and death with propranolol or nadolol

TABLE 3

Signs of ulcer hemorrhage and risk of recurrent bleeding with endoscopic hemostasis vs medical therapy

SIGNS	RISK OF RECURRENT BLEEDING WITH MEDICAL THERAPY ALONE	RISK OF RECURRENT BLEEDING WITH ENDOSCOPIC HEMOSTASIS
Active arterial bleeding (spurting)	85%–95%	10%–20%
Nonbleeding visible vessel	50%	5%–-10%
Nonbleeding adherent clot	35%	< 5%
Ulcer oozing	10%–25%	< 5%
Flat spots	7%	Not indicated
Clean-based ulcer	3%	Not indicated

Data are from Kovacs and Jensen[41,42] and Jensen and Machicado.[44]

than with placebo.[51] In doses that decrease the heart rate by 25%, beta-blockers have been shown to delay and decrease variceal hemorrhage. However, most patients require prophylactic endoscopic variceal ligation because they cannot tolerate beta-blocker therapy.

In suspected acute variceal bleeding, a somatostatin analogue should be started to decrease the portal pressure, and antibiotics should be started to reduce the risks of infection and death. Vasoactive drugs, ie, somatostatin analogues, should be started before endoscopy and continued for 5 days to reduce the chances of recurrent bleeding.[52,53]

Terlipressin is the only drug proven to improve the odds of survival in acute variceal bleeding. Although widely used in Europe, it has not been approved for use in the United States.

Octreotide, another option, improves hemostasis to the same extent, although it does not increase the survival rate.[54,55] The recommended dose of octreotide for patients with variceal bleeding is a 50-µg intravenous bolus, followed by a 50-µg/hour infusion for 5 days.

Combining endoscopic and drug therapy improves the chances of stopping the bleeding and reduces the risk of recurrent bleeding compared with endoscopic therapy alone.[56]

Transjugular intrahepatic portosystemic shunting is indicated in recurrent variceal hemorrhage or in those with initial bleeding that is refractory to standard medical and endoscopic therapy. It is not the primary therapy because it doubles the risk of encephalopathy and has a high stent occlusion rate (up to 60%, lower with covered stents).

GI BLEEDING CAN CAUSE ACUTE MYOCARDIAL INFARCTION

The simultaneous presentation of acute myocardial infarction (MI) and GI hemorrhage is very serious and unfortunately common.

Bleeding recurs after endoscopic treatment in 10% to 25% of cases

An acute MI occurring simultaneously with or after GI bleeding is usually precipitated by massive bleeding causing hypovolemia, hemodynamic compromise, and hypoperfusion. Conversely, the anticoagulant, antiplatelet, or thrombolytic drugs given to treat MI can precipitate GI bleeding (see below).

This distinction is important because the two scenarios have different clinical courses and prognoses. GI bleeding that precipitates an acute MI tends to be massive, whereas GI bleeding after treatment of acute MI tends to be self-limited and often resolves with reversal of underlying coagulopathy.[57]

Endoscopy carries a higher than average risk in patients with recent acute MI, with all-cause mortality rates as high as 1%.[58] (The usual rate is 0.0004%.[59]) Nevertheless, endoscopy can be safely performed early on in patients with acute MI if it is done under strict monitoring in a coronary care unit.

Several studies have shown that MI patients who present with upper GI bleeding as the inciting event or patients with acute MI

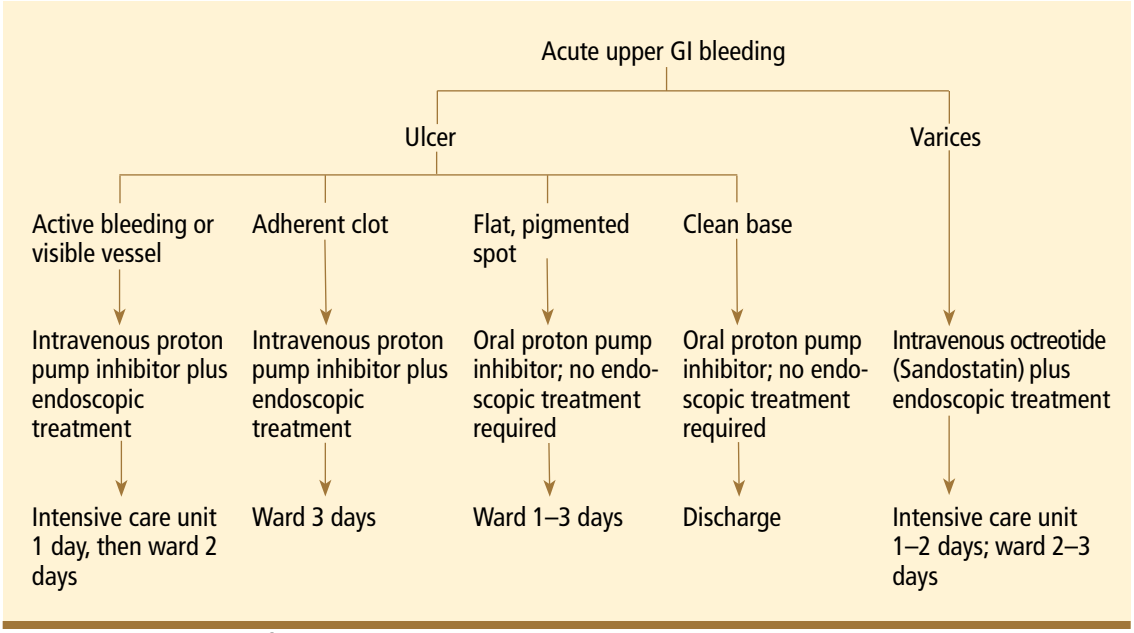


FIGURE 2. Algorithm for patients with acute upper gastrointestinal bleeding.

who are vomiting blood or who are hemodynamically unstable due to GI bleeding are significantly more likely to have a high-risk lesion and so have the greatest need for endoscopic therapy. Therefore, endoscopic intervention may be offered to MI patients at high risk who have been started on antiplatelet agents.

When starting warfarin, evaluate patients for risk factors for upper GI bleeding

WARFARIN CAN PRECIPITATE BLEEDING

Acute upper GI bleeding can be a severe complication of long-term oral anticoagulation, not because the drugs cause ulcers, but rather because they exacerbate ulcers that are already present.[60] Therefore, when starting warfarin (Coumadin), patients should be evaluated to determine if they have other risk factors for GI bleeding, such as ulcers.

The number of people presenting with upper GI bleeding while on warfarin therapy is increasing because of the expanding indications for long-term anticoagulation therapy, such as atrial fibrillation and deep venous thrombosis.

The risk of GI bleeding in patients who use oral anticoagulants is estimated to be 2.3 to 4.9 times higher than in nonusers.[61]

The goal international normalized ratio (INR) for patients on warfarin therapy is usually 2.0 to 3.0. Recent studies found that endoscopy can be safely performed in patients with acute GI bleeding whose INR is between 2.0 and 3.0.[62,63] Some suggest that both the length of warfarin therapy and the INR affect the risk of bleeding.[64,65]

Managing patients with an INR higher than 3.0 who have an episode of GI bleeding is always a challenge. It is not uncommon to find pathologic lesions causing GI bleeding in patients who are on warfarin with a supratherapeutic INR, and thus, endoscopy is indicated. However, before endoscopy, reversal of anticoagulation should be considered.

BLEEDING IN PATIENTS ON ANTIPLATELET DRUGS

Aspirin

Aspirin decreases production of prostaglandins in the GI tract, thereby decreasing the protective and restorative properties of the gastric and duodenal mucosa and predisposing to ulcers and bleeding.

The higher the aspirin dose, the higher the risk. Aspirin doubles the risk of upper GI bleeding at daily doses of 75 mg and quadruples it at doses of 300 mg.[66] Even doses as low as 10 mg can decrease gastric mucosal prostaglandin production.[67] Thus, it appears that there is no

risk-free dose of aspirin, and enteric-coated or buffered formulations do not appear to reduce the risk.[68–70]

The most important risk factor for upper GI bleeding in patients taking aspirin is a history of peptic ulcer bleeding. Approximately 15% of aspirin users who have bleeding from ulcers have recurrent bleeding within 1 year.[71]

As aspirin-induced GI bleeding becomes more common, health care providers often feel caught between the GI risk and the cardiovascular benefit. When considering whether to discontinue antiplatelet therapy, a cardiologist should be consulted along with a gastroenterologist to weigh the risks of GI bleeding vs thrombosis. To date, there have been no clinical trials published to suggest when antiplatelet therapy should be stopped to optimize GI and cardiovascular outcomes. An alternative is to replace aspirin with another antiplatelet drug that does not induce ulcers.

Clopidogrel

Clopidogrel (Plavix) is recommended for hospitalized patients with acute coronary syndrome who cannot tolerate the GI side effects of aspirin, according to the joint guidelines of the American College of Cardiology and the American Heart Association, with the highest level of evidence.[72] This recommendation was largely based on the safety data from the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial, in which the incidence of major GI bleeding was lower in the clopidogrel group (0.52%) than in the aspirin group (0.72%; $P < .05$).[73]

Aspirin plus a proton pump inhibitor

Patients who have had an episode of upper GI bleeding and who need long-term aspirin therapy should also receive a proton pump inhibitor indefinitely to prevent ulcer recurrence.

In a recent double-blind randomized controlled trial in patients with a history of aspirin-induced bleeding, the combination of low-dose aspirin plus esomeprazole (Nexium) twice a day was superior to clopidogrel by itself in terms of the rate of recurrent bleeding (0.7% vs 8.6%; $P < .05$).[74] A similar trial showed nearly identical results: 0% upper GI bleeding in the group receiving aspirin plus esomeprazole 20 mg daily, vs 13.6% in the clopidogrel group ($P = .0019$).[75] These studies suggest that a once-daily proton pump inhibitor combined with aspirin is a safer alternative than clopidogrel alone.

Clopidogrel plus a proton pump inhibitor

Interestingly, recent studies have shown that omeprazole decreases the antiplatelet effect of clopidogrel, possibly by inhibiting the CYP2C19 enzyme.[76] However, concomitant use of pantoprazole (Protonix), lansoprazole (Prevacid), and esomeprazole did not have this effect, suggesting that although all proton pump inhibitors are metabolized to a varying degree by CYP2C19, the interaction between proton pump inhibitors and clopidogrel is not a class effect.[77–79] Therefore, pantoprazole, lansoprazole, and esomeprazole may be the appropriate proton pump inhibitors to use with clopidogrel in patients who have a clear indication for the medication, consistent with current guideline recommendations.

Helicobacter pylori infection in antiplatelet drug users

Before starting any long-term antiplatelet therapy, patients with a history of ulcers should be tested and treated for *H pylori* (TABLE 4).[80] Confirmation of eradication is required after *H pylori* treatment in patients with upper GI bleeding. Some suggest that for patients with a history of bleeding ulcer who need aspirin, eradication of *H pylori* substantially reduces the risk of recurrent ulcer bleeding.[81]

Health care providers often feel caught between the GI risk and the cardiovascular benefit of aspirin

TREATMENT AND PREVENTION OF NSAID-RELATED GI INJURY

About 1 in 20 users of NSAIDs develop GI complications and ulcers of varying degrees of severity, as do one in seven NSAID users over the age of 65. In fact, NSAID use accounts for 30% of hospitalizations for upper GI bleeding and deaths from this cause.[82–85] In addition, approximately 15% to 30% of NSAID users have clinically silent but endoscopically evident peptic ulcers.[86]

NSAIDs contribute to ulcer development by depleting prostaglandins. Thus, misoprostol (Cytotec), a synthetic prostaglandin, has been used to reduce this side effect.

TABLE 4

Preferred therapies for *Helicobacter pylori* infection

REGIMEN	DURATION	ERADICATION RATE	COMMENTS
Triple therapy			
Proton pump inhibitor twice a day Clarithromycin (Biaxin) 500 mg twice a day Amoxicillin 1,000 mg twice a day or	10–14 days	70%–85%	Consider in non-penicillin-allergic patients who have not previously received a macrolide
Proton pump inhibitor twice a day Clarithromycin 500 mg twice a day Metronidazole (Flagyl) 500 mg twice a day	10–14 days	75%–85%	Consider in penicillin-allergic patients who have not previously received a macrolide or who cannot tolerate bismuth quadruple therapy
Quadruple therapy			
Proton pump inhibitor twice a day Bismuth subsalicylate 525 mg twice a day Metronidazole 250 mg four times a day Tetracycline 500 mg four times a day	10–14 days	75%–90%	Consider in penicillin-allergic patients

In a clinical trial, misoprostol reduced the incidence of NSAID-associated GI complications by 40%.[87] Furthermore, it has been shown to be better than placebo in preventing recurrent gastric ulcers in patients with a history of gastric ulcer who were receiving low-dose aspirin.[88]

However, misoprostol is rarely used because it can cause diarrhea and abdominal cramping. Rather, the preferred drugs for preventing and treating NSAID- and aspirin-related GI lesions are proton pump inhibitors.

Numerous clinical trials using endoscopic end points showed that proton pump inhibitors in standard doses significantly reduce the incidence of ulcers associated with the use of NSAIDs.[89] Proton pump inhibitor therapy has achieved a significant reduction in relative risk of upper GI bleeding in patients who received low-dose aspirin therapy, as confirmed by epidemiologic studies.[90,91] The number of NSAID-related ulcers found on endoscopy could be reduced by an estimated 90% simply by using proton pump inhibitors.[92]

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