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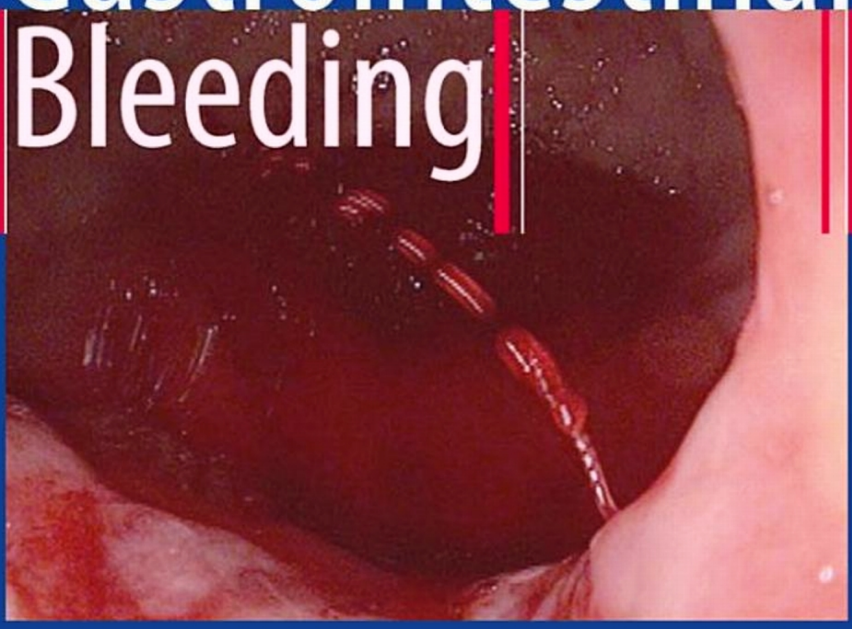
Theodore N. Pappas
Malcolm Stanley Branch *Editors*

Gastrointestinal Bleeding



A Practical Approach to Diagnosis and Management

Springer

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Editors

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Cover illustration: Endoscopic view of a bleeding colonic ulcer, courtesy of Malcolm S. Branch

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Preface

Gastrointestinal bleeding is an age-old problem. The original description of gastrointestinal bleeding may have been from Galen and his work connecting dyspepsia and melanotic stool. The changes in our management of gastrointestinal bleeding over the centuries have been driven by natural alterations in the spectrum of diseases, expanding our understanding of these diseases and the never ending advances in technology and pharmacology that have occurred relative to GI diseases. Academic interest in gastrointestinal bleeding peaked in the last half of the twentieth century with the expanding role of surgery, the discovery of acid-based peptic ulcer therapies, and the rise of flexible endoscopy and culminated in the description of h. pylori as a causative agent for ulcer disease. More recently there has been a decrease incidence in bleeding diseases of the gut and therefore a decreasing interest in the scholarly writing about these diseases. There has not been a major textbook written about gut bleeding in over 10 years and therefore the intention of this text book is to fill that void by providing a review of a comprehensive approach to upper gut, mid, and lower gut bleeding.

Clinicians at Duke University who have a common interest in the gastrointestinal tract have collaborated in the construction of this text. This effort has brought together surgeons, gastroenterologists, and radiologists, to carefully chronicle the presentation, diagnosis, and management of modern day causes of gastrointestinal bleeding. These co-authors concentrate on some of the latest innovations in the endoluminal and minimally invasive techniques that characterize the current approaches to these diseases. Emphasis has been placed on capsule endoscopy, double-balloon endoscopy, laparoscopic peptic ulcer surgery, and angiographic diagnosis and management techniques. The text has been written in such a way that the reader can quickly review a specific cause of GI bleeding prior to managing of such a patient. We expect this text will be used with the same immediacy as the diseases present.

We hope that this text provides a foundation for learning for medical students, interns, residents, and practitioners who encounter these critically ill and difficult to manage patients.

Durham, NC, USA — Aurora D. Pryor
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Part I
Upper GI Bleeding

Stabilization of Patients Presenting with Upper Gastrointestinal Bleeding

Errol L. Bush and Mark L. Shapiro

Introduction

Paleopathological evidence and descriptions of upper gastrointestinal bleeds (UGIB), i.e., proximal to the ligament of Treitz, are limited and sometimes inconclusive. The earliest potential reference to UGIB can be traced to the *Ebers papyrus* (circa 1550 BC) describing a "blood-nest" in a patient who acutely turned pale and later expired [1]. A more conclusive familiarity of peptic ulcer pathology was noted by Roman scientists during the first century [2] and thus we know that UGIB have been known for at least 2000 years. Risk factors for UGIB were most likely omnipresent and, as such, suffering from UGIB has more than likely always plagued humans.

UGIB are estimated to result in 40–150 episodes per 100,000 population [3], resulting in more than 300,000 hospital admissions [4] and accounting for 1–2% of all annual US hospital admissions [5]. At least 50% of UGIB result from peptic ulcer disease [6] (Fig. 1), even amongst those with sequelae from advanced liver disease [7]. This diagnosis is followed more than 10% of the time by variceal bleeding, erosive disease, and Mallory–Weiss tears, and less commonly by diagnoses such as angiodysplasias, posttraumatic, neoplasms, and Dieulafoy lesions [8, 9].

Repetitive vomiting or retching can lead to injury at or near the gastroesophageal junction, known as Mallory–Weiss tears, and has been associated with alcoholic binges, diabetic ketoacidosis, pro-emetic agents, hiatal hernias, and NSAID use [10]. Increased intra-abdominal pressures are thought to result in herniation of the gastric cardia into the chest, resulting in mucosal injury. Boerhaave's syndrome is the result of this process culminating in perforation. Bleeding from Mallory–Weiss tears spontaneously ceases in 90% of cases [11], but persistence is usually associated with bleeding diathesis from other medical comorbidities. Bleeding may be controlled endoscopically and if uncontrolled may require surgery (Fig. 2).

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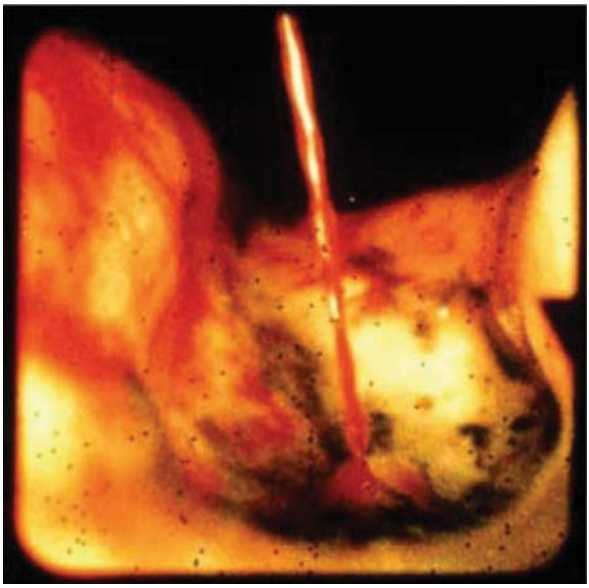

Fig. 1 Bleeding ulcer

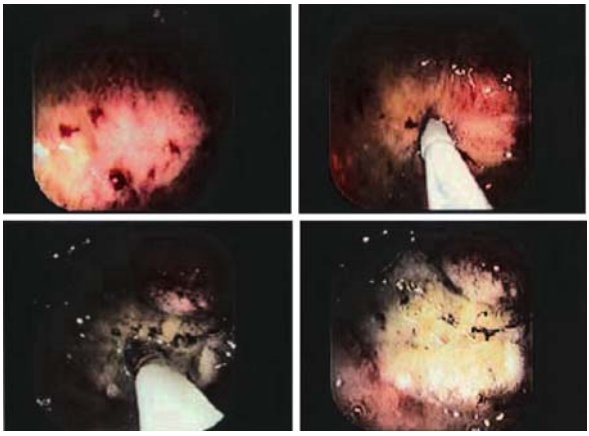

Fig. 2 Injection therapy of gastric ulcer

Angiodysplasias are acquired lesions with submucosal dilated and tortuous vessels that most commonly occur in the cecum and ascending colon, but can occur in the upper gastrointestinal tract as well. When this occurs they are most commonly noted in the stomach or duodenum. Bleeding from these lesions is intermittent and of varying intensity, but the majority of the bleeds from these lesions spontaneously cease. Uncontrolled bleeding of this source can be severe enough to be catastrophic, and given the intermittent nature of these lesions, they may be missed on endoscopy

and therefore must remain in the differential of otherwise unexplained causes of UGIB as oversight can be devastating.

Dieulafoy lesions are congenitally enlarged submucosal arteries that account for approximately 2% of non-variceal UGIB [12]. The vast majority are less than 5 mm and located 6–10 cm below the gastroesophageal junction on the lesser curvature [13]. Several endoscopic therapies are utilized for bleeding control, but up to 20% of patients may require surgery for recurrent bleeding [14] (Fig. 3).

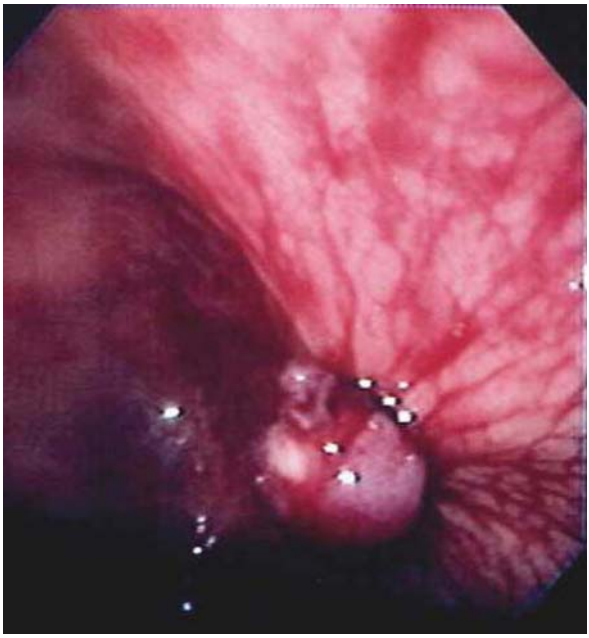

Fig. 3 Dieulafoy lesion treated with endoscopic banding

While UGIB can be both acute and chronic, mortality from the pathology of acute UGIB is much greater than that of chronic UGIB. Large series have estimated that a patient with a UGIB has a mortality rate between 2 and 15% [15, 16], but that confounding comorbidities such as age, medications, malignancies, and inpatient status may increase this rate to as high as 33% [15, 17, 18]. This takes its toll on society and the health-care system as this diagnosis portends approximately 30,000 deaths [19] and billions of dollars of health-care expenditures annually [20].

A UGIB may be a life-threatening emergency and requires prompt evaluation, diagnosis, stabilization, and therapeutic measures in a rapid fashion. Management depends on the location and severity of the source and the methodical identification of these. Outcomes are dependent upon time to diagnosis and appropriate management. This chapter focuses on the initial evaluation and management of patients presenting with a UGIB.

Goals of Therapy

Prevention of the morbidity and mortality associated with UGIB should involve assessment and therapy aimed at three approaches: hemodynamic resuscitation, cessation of bleeding source, and prevention of future recurrence. Although each aim is independent, there is inherent overlap and each should proceed in a concurrent manner to achieve the best outcomes.

History

Much information on the etiology of a UGIB can be attained by taking a complete patient history and performing a physical examination. The history should involve inquiring about prior gastrointestinal bleeds, since up to 60% of UGIB are from the same lesion previously identified [21], as well as alcohol use, liver disease or presence of varices, history of ulcers or symptoms related to them, history of vascular anomalies, prior surgeries or interventions, and the use of certain medications, such as aspirin or non-aspirin NSAIDs. Wilcox et al. noted that the majority of patients presenting with a UGIB had used an aspirin or non-aspirin NSAID in the week prior to presentation and interestingly, 44% of patients reported non-prescription use [22]. Therefore, history should also include knowledge of the chronic use of over-the-counter medications that might unsuspectingly contain similar products. Cirrhotic patients have a 30% chance of having a variceal bleed [23]; 60% of these patients in particular will rebleed within the first year of the index bleed, carrying a 20% mortality rate per subsequent event [24].

Hemodynamic Resuscitation

It has been demonstrated that, of the modifiable factors affecting outcome, prompt hemodynamic resuscitation affords decreased mortality, as well as morbidity in the form of reduced incidence of myocardial infarction [25]. These authors thus recommend prompt resuscitation of adequate hemodynamic parameters and correction of hematocrit and coagulopathy. We also support this recommendation and thus the initial evaluation begins with a prompt assessment of hemodynamic instability and aggressive resuscitation afforded within a critical care setting. Delays in resuscitation lead to delays in therapeutic interventions, and thus increased morbidity [25, 26].

The American Society for Gastrointestinal Endoscopy recommends administration of crystalloid fluids to maintain an adequate blood pressure and the use of blood products to meet the demands of ongoing blood loss, significant hemorrhage, or cardiac ischemia [4]. In keeping with these recommendations, we suggest that these patients be treated as seriously as patients who have experienced an acute traumatic injury and have hemodynamic instability. Recommendations include placement of

two equal than or larger than 16 gauge intravenous lines and consideration of providing central venous access, especially if the use of a vasoactive drug is anticipated. Administration of a 1 L bolus of crystalloid fluid should then ensue, unless contraindicated by a medical comorbidity. If hemodynamics has not improved, this bolus should be repeated. If hemodynamic compromise still exists, then blood product transfusion is recommended. If a coagulopathy has been detected, then the appropriate fractionated blood products should also be administered. During periods of extreme duress, recombinant human factor VIIa (rFVIIa) has been employed. This should only be used in extreme situations as prior investigations continue to question its role in the coagulopathic patient. The largest of these studies did not identify a therapeutic benefit greater than placebo in this setting, although there was a suggestion of potential benefit of reduced therapeutic failure in advanced cirrhosis [27]. However, recently, even this finding was re-examined in a larger population set and not supported [28]. Furthermore, comorbidities such as stroke, pulmonary embolism, and myocardial infarction remain common and severe. Thus a careful, well-balanced risk assessment is necessary prior to the administration of rFVIIa.

During resuscitation efforts, all patients should remain *nil per os*. This will not only aid endoscopic measures, but also help protect the patient's airway. If there is any concern for the protection of the patient's airway, either because of potential aspiration or due to mental status, then the patient should be promptly intubated endotracheally.

Cessation of Bleeding

Once the patient has been stabilized by resuscitation efforts, therapeutic measures to control bleeding can be activated. These measures include endoscopic, percutaneous, and surgical. The choice of intervention should be made with the consultation of a multidisciplinary team and consideration of immediately available resources.

Endoscopy

While 80% of UGIB cease spontaneously, 20% will recur, and thus the standard of care and first-line therapy is usually upper endoscopy within the first 24 h of an episode [29]. This not only allows visualization of anatomy, source localization, and establishment of predictors of recurrent bleeding (stigmata), but also allows the potential for a therapeutic intervention. The efficacy and safety of achieving endoscopic hemostasis has been reported and carries a high range of both specificity and sensitivity [30–32]. However, the sensitivity is dependent upon both the operator and the endoscopic field. Prior to endoscopy, nasogastric lavage may be performed until lavage fluid is clear or no longer clearing in the case of ongoing hemorrhage. Lavage serves not only as a tool to empty the stomach prior to endoscopy, but also as a diagnostic tool for a UGIB, especially in patients with hematemesis [33], though a closed

pylorus could result in a negative lavage for a bleeding source distal to the pylorus and proximal to the ligament of Treitz. Intravenous erythromycin (250 mg IV bolus or 3 mg/kg over 30 min) 30–90 min prior to endoscopy may be administered to aid gastric motility and emptying [34, 35].

Esophageal Tamponade

In patients with uncontrollable esophageal variceal bleeding after failed pharmacologic and endoscopic interventions, balloon tamponade remains a temporary option. The technique was first described by Westphal in 1930 using an esophageal sound for a cirrhotic patient with a variceal bleed [36] and has since spurred the development of three multiluminal nasogastric balloon tubes used for the same purpose. The Sengstaken–Blakemore tube was originally described in 1950 [37] and has a 250 mL gastric balloon, an esophageal balloon, and a gastric suction port. It was later modified to add an esophageal suction port in an effort to decrease the need for parallel insertion of a nasogastric tube for collection of esophageal secretions above the proximal inflated balloon. This modification is known as the Minnesota tube [38]. The third is the Linton–Nachlas tube, which has a 600 mL gastric balloon and both gastric and esophageal aspiration ports. It is used mainly for gastric variceal bleeds. Given that this balloon tamponade has not been shown to be more effective than pharmacological or endoscopic therapy in the long term [39–41] and is frequented by rebleeding after deflating the balloon, as well as a potentially devastating complication of esophageal rupture, balloon tamponade is typically utilized as a temporizing measure until more definitive procedures can be employed.

Percutaneous

The majority of UGIB will either spontaneously cease or be controlled endoscopically. However, in the setting of failed endoscopic therapy, the American College of Radiology has recently recommended the use of transcatheter-based angiographic interventions, especially in high-risk surgical patients [42]. Angiography is a beneficial tool as it may not only provide diagnostic information in the setting of non-localized lesions, but concomitantly be therapeutic through the arterial instillation of vasoactive drugs, arterial embolization, or a combination of the two. Overall this therapy is low risk and may lead to greater than 65% success [42].

Surgery

Involvement of surgical consultation is necessary for ongoing blood loss despite endoscopic and percutaneous interventions, recurrent bleeding, bleeding related to

a prior surgical procedure, or development of an acute abdomen. Any surgical intervention is aimed at providing a procedure predicted to be most effective at achieving hemostasis and preventing future recurrence, while considering its morbidity with the current clinical scenario.

Pharmacological Adjuncts

Octreotide, a somatostatin analogue, is traditionally used to reduce the risk of recurrent variceal bleeding, though recently it has been indicated in non-variceal bleeding, as it not only reduces splanchnic perfusion, but also reduces gastric acid secretion and may have a gastric cytoprotective effect and protects renal flow [43].

Intravenous proton pump inhibitors (PPI) are recommended when a diagnosis of a UGIB is made and one should not wait until confirmation of the source to be a peptic ulcer. Not only does this strategy reduce total length of hospital stay, but it aids the endoscopist as there are fewer actively bleeding ulcers and more ulcers without stigmata of recent bleeding [44]. Opponents of this strategy cite the additional costs associated with this costly therapy in patients without bleeding sources related to acid secretion; however, recent cost analyses have demonstrated this strategy to be more effective pre-endoscopy than afterwards and a less costly treatment strategy for all UGIB [18, 45].

Vasopressin has pharmacological effects which theoretically would aid bleeding cessation. Intravenous vasopressin administration results in mesenteric arteriolar constriction and thus decreased portal venous flow and pressure. Vasopressin used in acute variceal bleeds can have an initial hemostatic rate as high as 80%, but in a meta-analysis no difference was noted in any major outcome, including mortality reduction [46]. Unfortunately, the vasoconstriction effects of vasopressin may result in systemic end-organ damage, notably of the heart, brain, bowel, and limbs, which can lead to reluctance in its regular use. The same study did demonstrate a 34% mortality reduction with the use of terlipressin, a vasopressin analogue, suggesting that this analogue may be preferred for vasopressor therapy [46].

Prevention of Recurrence

Both oral and intravenous infusions of PPI have been shown to reduce recurrent bleeding, decrease hospital stay, and reduce the need for blood transfusion. However, the same effect has not been demonstrated with the use of H_2 receptor antagonists, and neither has shown any effect on mortality [29, 43, 47].

Patients with cirrhosis have increased infection rates within the community that are even more greatly elevated when admitted to a hospital. Variceal bleeding disrupts normal mucosal integrity, thus allowing higher rates of bacterial infection. Prophylactic antibiotics in cirrhotic patients hospitalized for UGIB have been demonstrated to reduce overall infections complications, recurrent bleeding, and mortality [48, 49].

Conclusions

Patients presenting with a UGIB undoubtedly represent a serious medical emergency and outcomes depend on the rapid diagnosis, hemodynamic resuscitation, and successful intervention. The choice of endoscopy, transcatheter-based interventions, or surgery for patients with acute UGIB depends on the site of bleeding being localized or not, patient comorbidities and stability, institutional expertise, and the availability of those modalities and resources.

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Urgent Workup for Upper Gastrointestinal Bleeding

Loretta Erhunmwunsee and Sandhya A. Lagoo-Deenadayalan

Introduction

Each year hundreds of thousands of patients suffer from acute upper gastrointestinal bleeding (UGIB) [1], which by definition arises from a site proximal to the ligament of Treitz. Etiological factors include peptic ulcer disease, gastritis, gastroesophageal varices, and Mallory–Weiss tears. Less common causes are marginal ulcers, esophagitis, gastric cancer, aorto-enteric fistulas, hemobilia, AV malformations (Fig. 1), and Dieulafoy lesions [2, 3]. Peptic ulcer disease, including gastric/duodenal ulcers (Fig. 2) and erosive esophagitis/gastritis (Fig. 3), is the source of bleed 50–75% of the time [1, 2, 4, 5]. The incidence of esophageal varices is 10–30%, Mallory–Weiss tears 4–13%, AVMs 2–4%, malignancies 1–5%, and Dieulafoy lesions 1–2% [5]. These etiologies lead to UGIB in 100 out of 100,000 patients [6, 7] and cost billions of dollars a year to treat [1, 6, 8]. In spite of the fact that 80% of acute UGIBs resolve spontaneously [1], there is still significant morbidity and mortality associated with the process, especially in those with multiple comorbidities and in the elderly [9]. Because UGIB can carry a mortality of 6–10% [1, 10] it is imperative that patients are seen soon after presentation, that they are stabilized, and that the source of the bleeding and its location are determined expeditiously.

Medical Workup

Patients with acute UGIB may present with postural hypotension, anemia, hematochezia, hematemesis, or melena. Patients with gross UGIB present with melena 75% of the time and with hematemesis 50% of the time [11]. In patients with evidence of upper gastrointestinal hemorrhage, it is important to obtain a thorough history and perform a focused physical exam. These patients should be asked about

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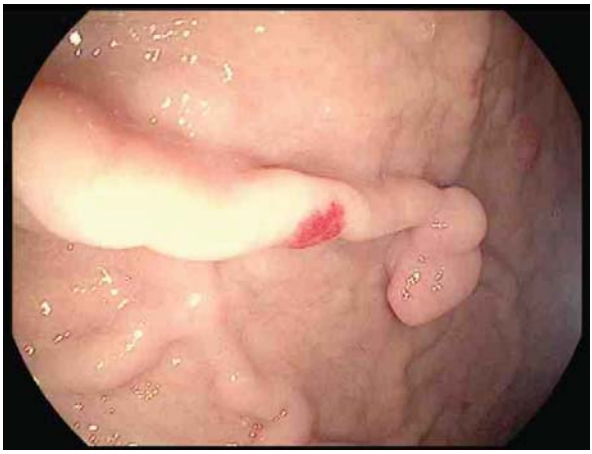

Fig. 1 Endoscopy revealing an arteriovenous malformation (AVM)

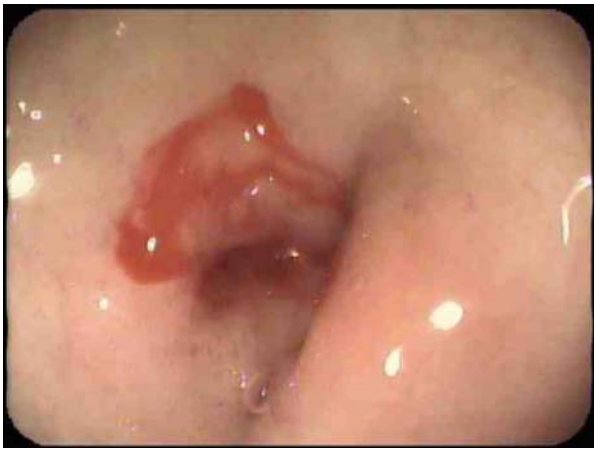

Fig. 2 Patient with endoscopic evidence of a non-bleeding duodenal ulcer

NSAID and anticoagulation use as well as about history of alcohol use, tobacco use, liver disease, or prior bleeding episodes. Laboratory values, such as complete blood count (CBC), coagulation markers, liver function tests, and a basic metabolic panel, including BUN and creatinine, should be obtained. A thorough abdominal exam should be performed to ascertain tenderness and to rule out peritoneal signs, which would be cause for immediate operative management. A complete rectal exam is performed to look for rectal causes of GI bleeding.

Next a nasogastric (NG) lavage may be performed as the first diagnostic procedure, since a bloody aspirate confirms the source of bleeding as being proximal to the pylorus. Bilious fluid aspiration is a prerequisite in order to state that a lavage is negative. There is, however, some debate as to the usefulness of the NG lavage

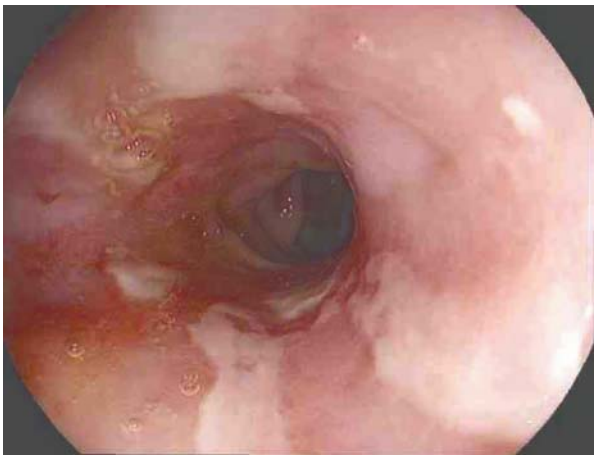

Fig. 3 Patient with evidence of esophagitis on EGD

as a diagnostic procedure [4]. An esophagogastroduodenoscopy (EGD) has a much higher sensitivity and the added potential for therapy and thus some consider NG lavage unnecessary in the diagnostic role. On the other hand, there is agreement that NG lavage is useful in clearing out the stomach of blood and clot, thus making the subsequent EGD easier to perform. The American College of Physicians consensus recommended considering NG lavage for use as an adjunct to endoscopy [4].

Esophagogastroduodenoscopy in Non-variceal Bleeding

After a positive NG lavage, and even with a negative one if there is high enough suspicion, the next step should be performance of an esophagogastroduodenoscopy (EGD) for localization of the bleeding source. Upper endoscopy is the primary method of evaluating a patient with UGI bleeding as it has a 90–95% success rate [11]. The American Society of Gastrointestinal Endoscopy (ASGE) suggests that early upper endoscopy is a critical step in the workup of a patient with UGIB. An early upper endoscopy allows for localization and diagnosis of the source of bleeding, risk stratification of recurrence based on the appearance of the lesion, and potential therapy [12].

There is debate as to the timing of early upper endoscopy [13]. Most agree that an endoscopy should be performed within 24 hours [12] to evaluate UGIB but several studies are evaluating whether some patients benefit from even earlier endoscopy. Clearly, patients who have persistent or severe bleeding should undergo very early endoscopy to avail themselves of the potential of endoscopic therapy [13]. But the majority of patients will have resolution of their bleed and therefore benefit from neither therapeutic nor early diagnostic endoscopy. Bjorkman et al. evaluated 93 outpatients with acute non-variceal upper GI bleeding. The patients

were randomized to either urgent endoscopy (within 6 hours) or elective endoscopy (within 48 hours). The group found that urgent routine diagnostic endoscopy did not reduce hospitalization or resource utilization. But they suggest that in the 20% of patients whose bleed does not resolve spontaneously or that recurs, an urgent therapeutic endoscopy can save lives [14]. Tai and colleagues published a similar study where they reviewed the charts of 189 patients with non-variceal upper gastrointestinal hemorrhage. The patients were divided into two groups: those who had undergone an endoscopy within 8 hours (emergency endoscopy) or within 24 hours (urgent endoscopy). Their study found no difference regarding the rate of recurrent bleeding, total amount of transfusion, length of hospital stay, or mortality between the two groups [15]. These findings suggest that in the majority of patients whose UGIB resolves, obtaining a diagnostic EGD up to 24 hours does not lead to worse outcomes. Currently, the recommendation is to perform endoscopy in all patients with UGIB within 24 hours. In those with persistent bleeding or a high risk of recurrence, endoscopy should be performed as soon as it is safe [12].

In spite of the excellent results with EGD, the procedure is not without complications. It can cause gastrointestinal perforations, precipitation of gastrointestinal bleeding, aspiration pneumonia, respiratory arrest, and cardiovascular complications [11]. The incidence of complications is low, but it is important to be certain that in each patient the benefit of the procedure outweighs the risk.

Endoscopic Findings

During the procedure, the endoscopist is looking for any lesion that might have caused the bleeding and for characteristics that suggest the likelihood of recurrence. Forrest [16] classified peptic ulcers according to features that were associated with risk of rebleeding (see Table 1). They are classified as Ia–III, with lesions in higher groups showing a decrease in risk of recurrence. The first group contains the actively bleeding ulcers (I). This group is further separated into vessels that are either spurting (Ia) or oozing (Ib). The second group includes the non-actively bleeding ulcers. This group is further broken down into three groups: non-bleeding but visible vessel (IIa), ulcer with surface clot (IIb), or ulcer with pigmented spots (IIc). Forrest group III includes ulcers with a clean base [16]. Laine and Peterson looked at thousands

Table 1 Forrest classification of peptic ulcers

Type	Description
Ia	Active spurting bleeding
Ib	Active oozing bleeding
IIa	Non-bleeding but visible vessel
IIb	Non-bleeding with adherent clot
IIc	Non-bleeding with pigmented ulcer base
III	Clean base, no sign of bleeding

of patients with bleeding peptic ulcers and determined their prevalence, rate of further bleeding, and mortality associated with the lesions. They found that most ulcers with a clean base, are associated with a 5% risk of rebleed and 2% mortality. Patients with ulcers that have a flat, pigmented spot on endoscopy have a 10% risk of further bleeding and 3% mortality. The presence of adherent clots on top of an ulcer is associated with a 22% risk of further bleeding and 7% mortality. A visible, non-bleeding vessel is correlated with a 43% risk of rebleed and 11% mortality, while actively bleeding vessels have the highest risk of recurrence at about 55% and a mortality of 11% [1]. Other lesions such as Mallory–Weiss tears are associated with a low risk (2%) of further bleeding [14]. These associations suggest that proper evaluation via endoscopy is crucial, as endoscopic findings are directly associated with patients' prognosis and therefore will aid in decisions concerning therapy.

The Rockall score is the most frequently used score to determine the prognosis of a patient with an upper GI bleeding. It allows for recurrence risk stratification and for determination of prognosis. The score, which is based on clinical and endoscopic findings, reflects the likelihood of recurrence of bleeding and of death [10]. It is based on the patient's age, evidence of shock, and the presence of comorbidities. It takes into consideration the cause of bleeding and whether there were any stigmata of recent hemorrhage seen on endoscopy [10]. The maximum score prior to EGD or diagnosis is 7. After diagnosis via scope, the maximum score is 11. Higher scores are associated with higher rates of recurrence and death. The stratification of patients with this score can help in determining how soon a patient undergoes endoscopy and their subsequent disposition. A patient with a low Rockall score (0, 1, or 2) has a less than 5% chance of rebleeding and mortality is virtually zero, even if there is a rebleed. Thus these patients may be treated on an outpatient basis with good outcomes. However, a patient with a high Rockall score (8 or greater) has a 40% risk of rebleeding and their mortality is as high as 41%. Thus these patients should be observed and may even require admission to the Intensive Care Unit (ICU) [10].

EGD is the first-line diagnostic tool in patients with evidence of UGIB. It allows for risk stratification and prognosis as mentioned above. It also has the added benefit of offering therapeutic intervention to approximately 20% of patients who have recurrent or persistent bleeding. Therapy in these patients focuses on managing the stigmata of recent hemorrhage, i.e., adherent clot; visible, non-bleeding vessels; and vessels that are bleeding. Endoscopic therapeutic options such as sclerotherapy, heat probes, and hemoclipping will be discussed in detail in a later chapter.

Arteriography

Ninety percent of the time an EGD is the only procedure necessary to localize the source of UGI bleeding [3, 17]. The remaining 10% of lesions may be elusive to the endoscopist for many reasons, such as structural abnormalities, i.e., strictures or post-surgical changes [17], or secondary to potentially obscure lesions,

such as angiodysplasias, gastric antral vascular ectasias (GAVE), portal hypertensive gastropathy, or Dieulafoy lesions [18]. Large amounts of blood may prevent proper visualization and therefore localization of the lesion. In these instances when an EGD is unable to locate the source of bleeding, a diagnostic arteriogram is frequently helpful.

Arteriography is an invasive, contrasted radiologic study that can identify briskly bleeding lesions, when the bleeding rate is 0.5 mL/min or greater. In the setting of upper GI bleeding, arteriography is positive for extravasation or abnormal mucosa blush in up to 61% of cases [17]. Some suggest that it has utility in locating structural abnormalities that may not be actively bleeding, such as angiodysplasias, tumors, or inflammatory lesions as well [18].

In the detection of the source of upper GI bleeding, selective angiography focuses on the celiac axis [17]. Percutaneous access of the femoral artery is obtained via Seldinger technique. A 5 F catheter is placed under fluoroscopic guidance into the celiac artery and the superior mesenteric artery. The inferior mesenteric artery is frequently examined to rule out lower gastrointestinal source for bleed as well [5, 17]. Bleeding from the left gastric artery, splenic artery, its closely associated short gastrics, the common hepatic artery, and the gastroduodenal artery can be observed. A positive study is seen as an extravasation of contrast into the bowel lumen or as an abnormal blush. A duodenal ulcer may produce bleeding by eroding into the gastroduodenal, which may be seen as extravasation around that artery. Embolization of the gastroduodenal artery distal to its take-off from the proper hepatic artery can control bleeding from a duodenal ulcer (Fig. 4a, b). Arteriography can also be helpful with the diagnosis of hemorrhagic/stress gastritis, which is a very important diagnosis in ICU patients. On arteriography, one may see multiple small foci of extravasation in a diffusely hypervascular gastric mucosa [3]. A bleeding left gastric artery, associated with a Mallory–Weiss tear, can be seen on arteriogram as well. Once the source of bleeding has been discovered, transcatheter interventions,

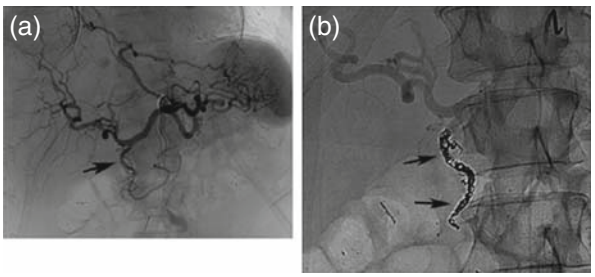

Fig. 4 (**a**) Arteriogram of a patient with bleeding from a duodenal ulcer after celiac injection. There was continued bleeding in spite of endoscopic clipping and injection of epinephrine into ulcer bed. The *arrow* indicates gastroduodenal artery with no active extravasation. The clip noticed on fluoroscopy is in the third/fourth portion of duodenum. (**b**) *Arrows* indicate gastroduodenal artery coil embolized using multiple coils. The vessel is occluded just beyond its origin from the proper hepatic artery

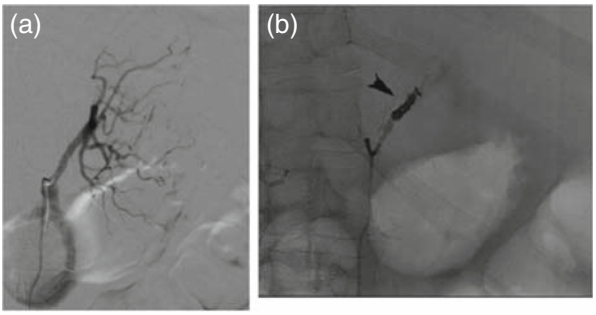

Fig. 5 (**a**) Arteriogram of a patient with bleeding from a gastric ulcer. Arteriogram depicts celiac injection with catheter in left gastric artery. (**b**) Left gastric artery occluded with multiple coils

such as embolization, can be performed. Figure 5a, b shows embolization of the left gastric artery in a patient with a bleeding gastric ulcer.

In spite of the many benefits of arteriography in the detection of occult upper GI bleeding, there is the potential for complications. Arterial injury, contrast reactions, nephrotoxicity, thromboemboli, and hemorrhage are possible but occur quite infrequently. Arteriograms for upper or lower GI bleeding have a complication rate of <5% [17]. Relative contraindications to the procedure include severe coagulopathy, congestive heart failure, recent myocardial infarction, renal insufficiency, and pregnancy [19].

Tagged Red Cell Scan

Technetium 99m-labeled red blood cell scan, also known as tagged red cell scan, can also be used in patients with obscure UGIB. Red blood cells are labeled with technetium 99 and injected into the celiac artery in order to detect upper GI bleeding. This nuclear medicine scan allows for the detection of bleeds that are much slower, with a rate greater than 0.1–0.4 mL/min.

When compared to the red cell scan, angiography has less sensitivity for slow bleeding but is more precise at the localization of the bleeding site. The red cell scan allows for determination of active bleeding and many prefer to use it as a prelude to angiography [5]. If the red cell scan is positive suggesting current active bleeding, then angiography is more likely to be positive [17, 20]. When the red cell scan is used in conjunction with arteriogram, the sensitivity of the arteriogram increases to 61–72% from 40–78% [2]. When the red cell scan is negative, then putting the angiogram on hold may be the most effective strategy as it lowers the risk of complications from arteriogram in patients who are unlikely to be positive. Red cell scan has the benefit of allowing the patient to come back later if the bleed was not detected initially. The prolonged bioavailability of the radiolabeled red blood cells allows for continued imaging for up to 24 h [20]. This procedure is therefore well suited for instances when the bleeding is intermittent, which is a common occurrence. Nuclear scintigraphy is therefore recommended before arteriogram in patients

with intermittent bleeding [20]. However, angiogram remains the diagnostic tool of choice in patients with obscure, continuous UGIBs [17].

CT Angiography (CTA)

CTA is not routinely used in the workup of a patient with UGIB. But new research suggests that CTA may be useful in detecting lesions not found via endoscope [5]. Ettorre et al. evaluated 18 patients with gastrointestinal bleeding via CTA and then via conventional angiography. CTA detected the source of bleed in 72% of patients whose source of bleed could not be located via endoscopy. Ettorre et al. also suggest that CTA is faster, easier, and more sensitive than conventional angiography at detecting active bleeding [19]. CTA does not offer therapeutic options for management of any bleeding detected.

Variceal Bleeding

Gastroesophageal varices form secondary to elevated portal pressure. They obtain blood flow from the left gastric and the short gastric veins. Gastroesophageal varices (Fig. 6) are responsible for a large percentage of UGIB. They are also associated with significant morbidity and mortality, since greater than one-third of patients with

Fig. 6 Banding of esophageal varix via endoscopy

variceal bleeding will die from the event. Similar to UGIB caused by non-variceal causes, variceal bleeds must be evaluated by EGD once the patient is stabilized. Following stabilization, therapeutic options, such as banding and sclerotherapy, are possible via endoscopy. Angiography is generally not indicated for evaluation of venous bleeding and thus variceal bleeds are not best studied by arteriograms [3]. TIPS is a therapeutic procedure used in managing gastroesophageal varices but can also be diagnostic of portal hypertension. The procedure is considered when endoscopic therapy has been unsuccessful in the treatment of variceal bleeds. TIPS is now frequently used as a non-surgical bridge to liver transplantation.

Small Bowel Bleeding

Patients with upper GI bleeding may present with hematemesis, melena, hematochezia, iron deficiency anemia, or hypotension. Many of these signs/symptoms, however, are not exclusive to UGIB sources. The cause of melena, hematochezia, or iron deficiency anemia may be a bleeding source distal to the ligament of Treitz. If an upper GI source cannot be localized, then the rest of the small bowel as well as the large bowel may need examining via imaging studies. Options for further small bowel evaluation include endoscopic studies, such as capsule endoscopy or push enteroscopy, or radiologic imaging such as small bowel follow-through. Capsule endoscopy seems to be the method of choice [21]. The aforementioned procedures will be discussed in detail in future lower GI bleeding chapters.

Summary

With the improvement of preventive therapy for peptic ulcer disease, there has been a decrease in the frequency of lesions that cause UGIB. But the mortality from UGIB that result from these lesions and others has remained relatively unchanged [1]. UGIB is 60–90% more common than are lower GI bleeds, and upwards of 75% of apparently lower GI blood comes from an upper GI source. This leads to a 2–3 times higher mortality for UGIB than LGIB [5]. Patients with signs or symptoms of UGIB need to have thorough evaluations so that lesions that have risk of rebleeding can be treated in a timely manner. Endoscopy is first line in the diagnosis of sources of UGIB with a sensitivity of about 90%. When the source cannot be detected via upper endoscopy, bleeding scans and angiogram can be performed to find the source of bleeding. For variceal bleeds, endoscopy is the first choice for the diagnosis of the varix and its treatment.

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Management of Esophageal Variceal Bleeding

Keki Balsara and Lisa Pickett

Introduction

Esophageal variceal bleeding is a potentially life-threatening complication of portal hypertension. One-third of cirrhotic patients with documented varices bleed within 2 years from the time of initial diagnosis. Mortality rates from an initial episode of bleeding are 20–35% and approximately 30% with each additional episode of bleeding. Risk factors for acute bleeding episodes include advanced cirrhosis, large or proximal extension of varices, high portal pressure, continuation of alcohol consumption, and hepatocellular carcinoma.

Portal hypertension is characterized by the development of venous collaterals around areas of increased resistance, with resultant hemodynamic changes, including an increase in splanchnic flow and a hyperdynamic circulation. Increased resistance in the portal system commonly results from cirrhosis, but can also be secondary to acute hepatitis, congenital hepatic fibrosis, hepatic vein anomaly or obstruction, or hepatic vein thrombosis. Portal venous pressure is normally 5–10 mmHg. When the pressure rises above 10 mmHg, portal hypertension is present and one begins to see the development of characteristic pathophysiologic features to include variceal bleeding, ascites, and liver failure.

Gastroesophageal varices are the classic collateral pathways that develop from the left gastric and short gastric veins to the lesser and greater curves of the stomach. These veins then run submucosally across the gastroesophageal junction up the esophagus (Fig. 1). Additional collateral pathways are found in the periumbilical, retroperitoneal, and hemorrhoidal venous plexuses.

When the pressure in varices rises, these veins may rupture, causing brisk and possibly life-threatening bleeding. This bleeding can be made more catastrophic by the concomitant coagulopathy present in many patients with cirrhosis.

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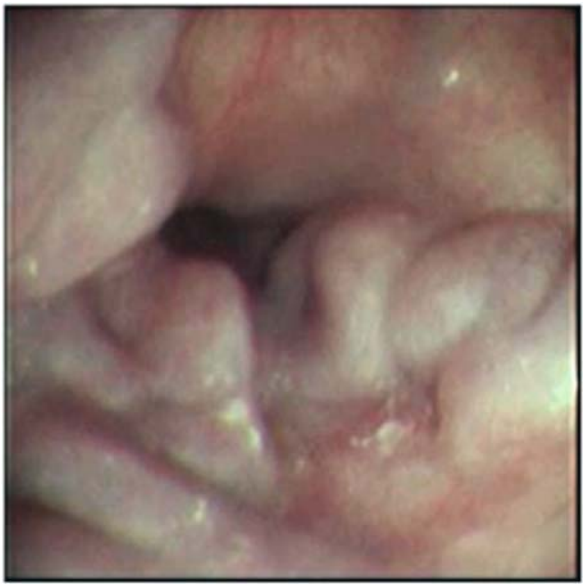

Fig. 1 Endoscopic view of esophageal varices

Management

The management of variceal bleeding is dependent upon three objectives – prevention of the initial bleed, management of acute bleeding while limiting complications, and prevention of recurrent bleeding.

Prevention of Initial Bleed

Due to the high mortality associated with initial bleed, much interest exists in developing methods of prophylaxis. Operative prophylaxis, while initially thought to be effective, has been abandoned over the past two decades secondary to prohibitive mortality rates [1, 2].

There is evidence to suggest that aggressive beta blockade may lower portal venous pressure by approximately 20%. A meta-analysis looked at the effects of propranolol or nadolol on patients with documented esophageal varices. It demonstrated a significant decrease in initial bleeding events for those patients receiving beta blockade, although no difference in mortality was seen between the groups [3]. Because contraindications to beta blockade are present in up to 20% of patients, alternative pharmacotherapies have been explored. Long-acting nitrates have been equally effective in reducing portal venous pressure and resultant initial bleed [4].

Management of Acute Bleeding

Patients present with bloody emesis, which can be brisk, often requiring ICU admission. Bleeding esophageal varices are somewhat unique, in that no single physician can perform every procedure possibly required by the patient, but must understand the role of and indications for each intervention. Thus, management requires a coordinated multidisciplinary effort, with clear communication between critical care physicians, gastroenterologists, surgeons, and vascular radiologists for optimal patient outcomes.

The initial management of acute gastrointestinal hemorrhage includes airway protection (when necessary), adequate vascular access, and aggressive resuscitation of the patient with fluids, blood, and blood products. Nasogastric tube placement and gastric lavage are performed to clear the stomach of blood and discern the presence of ongoing bleeding. Once hemodynamic stability has been achieved, endoscopic evaluation of the upper GI tract is performed for initial diagnosis. It is crucial to determine the source of bleeding, as 25% of patients with esophageal varices may have additional sources of GI bleeding, including gastritis, portal gastropathy, and peptic ulcer disease [5].

In those cases where bleeding is brisk and endoscopy cannot be performed in a timely fashion or endoscopic treatment/medical therapy is unsuccessful, several balloon compression devices can be utilized to temporize bleeding. Balloon devices are available with gastric and esophageal balloons (Minnesota and Sengstaken–Blakemore tubes) and gastric balloon alone (Linton–Nachlas). These tubes are inserted and balloons inflated to compress the bleeding varices. They carry a high risk of complications from aspiration, pressure necrosis, injury to surrounding structures, moderate mortality (up to 6%), and little chance of long-term cessation of bleeding. Thus, balloons should be placed with caution, only utilized until another treatment option is available.

Antibiotics are initiated upon admission [6]. Up to 20% of patients with cirrhosis who are hospitalized with bleeding have bacterial infections and up to another 50% will develop an infection while hospitalized. Multiple trials and a Cochrane review demonstrate this frequency of bacterial infections during hospitalization and suggest that antibiotics decrease infectious complications and mortality in cirrhotic patients hospitalized for bleeding, and may prevent re-bleeding after acute variceal hemorrhage [7–10].

This patient population also frequently requires prophylaxis of alcohol withdrawal, vitamin prophylaxis of Wernicke's encephalopathy, treatment/prevention of hepatic encephalopathy, and nutrition.

Once the source of bleeding has been confirmed to be esophageal, medical management is initiated. The initial objective is to administer vasoactive medications to lower portal pressure and, therefore, in the collateral circulation. Vasopressin and, more recently, octreotide are the drugs of choice in the United States. Terlipressin is also well studied, but not currently available in the United States.

Vasopressin is a potent, non-selective vasoconstrictor. It is administered systemically with the intent of causing global vasoconstriction, resulting in cessation of

bleeding. Octreotide, a synthetic somatostatin analogue, is more selective in its sight of action. It produces selective splanchnic vasoconstriction and decreases azygous blood flow, a surrogate marker of variceal blood flow. Octreotide treatment is instituted as a bolus dose followed by a 3–5 day continuous infusion. Terlipressin is an analogue of the natural hormone arginine vasopressin. It stimulates vasopressin-1 receptors, which are located in vascular smooth muscle and mediate vasoconstriction. Administration of terlipressin increases mean arterial pressure and decreases portal flow and pressure, which ultimately result in improvement of management of bleeding esophageal varices [11]. A Cochrane review of studies investigating Terlipressin demonstrated 34% relative risk reduction in mortality [12].

Medical management, alone, fails in up to 20% of cases. In these cases, there are a variety of interventional procedures with documented efficacy in the treatment of variceal bleeding. Foremost amongst these is endoscopic management of variceal bleeding, which includes sclerotherapy and banding.

Endoscopic sclerotherapy has been an accepted means of treatment for variceal bleeding since the 1930s. The goal of treatment is to control bleeding by thrombosing the veins or thickening the mucosa overlying the veins by injecting sclerosing agents into the varices of the distal (third/two-thirds) of the esophagus. The most commonly used agents are sodium morrhuate, sodium tetradecyl sulfate, and ethanolamine oleate. The sclerosing agent is usually injected intra-variceally, beginning at the gastroesophageal junction and proceeding circumferentially. If active bleeding is identified on endoscopy, the sclerosing agent can be injected inferiorly to the site of bleeding. Care should be taken to avoid injection of agent in the proximal to mid-esophagus. Sclerosant can accidentally be introduced into the azygous vein, ultimately into the pulmonary circulation, causing unwanted complications [13]. Endoscopic sclerotherapy is effective in controlling active bleeding in approximately 80–90% of patients [14]. However, a Cochrane review demonstrated no difference between medical management of bleeding esophageal varices and sclerotherapy [15].

Complications from sclerotherapy occur in approximately 40% of patients undergoing this treatment. Injection site ulceration occurs in nearly 100% of patients and is associated with re-bleeding in 2–13% of patients. Esophageal stricture occurs in 10–20% of patients. Most respond to serial dilation. Finally, chest pain, fevers, and respiratory complications have all been attributed to sclerotherapy but their etiology is poorly understood and their incidence is low. Re-bleeding occurs in 8–30%.

Endoscopic band ligation utilizes small elastic bands that are endoscopically placed over a suctioned varix (Figs. 2, 3, and 4). By avoiding the use of a sclerosing agent, the incidence of associated complications is reduced. Ligation is started at the level of the GE junction and continued circumferentially and cephalad. Bands can be directly applied to sites of active bleeding or deployed to obtain proximal and distal control. Banding is made difficult by limited visualization due to the size of the device and obscured vision by bleeding and/or clots. Recurrence rates are 30–48% [16, 17].

Fig. 2 Band applicator on endoscope

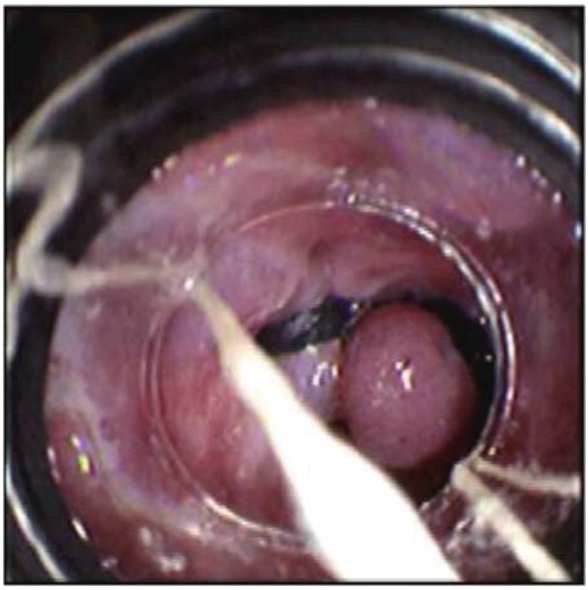

Fig. 3 Band application

Definitive management strategies for patients who fail medical or endoscopic treatment include TIPS and surgical shunts. Due to a nearly 50% mortality with surgical shunts, TIPS is the preferred means of interventional treatment.

Transjugular intrahepatic portosystemic shunt (TIPS) is an interventional radiologic procedure that creates a communication through the hepatic parenchyma between the hepatic and portal veins. The systemic venous system is accessed via the internal jugular vein. A catheter is advanced and preferentially placed in the right hepatic vein. Subsequently, a needle is advanced into the portal vein and ultimately a stent is placed between the hepatic vein and portal vein across the liver

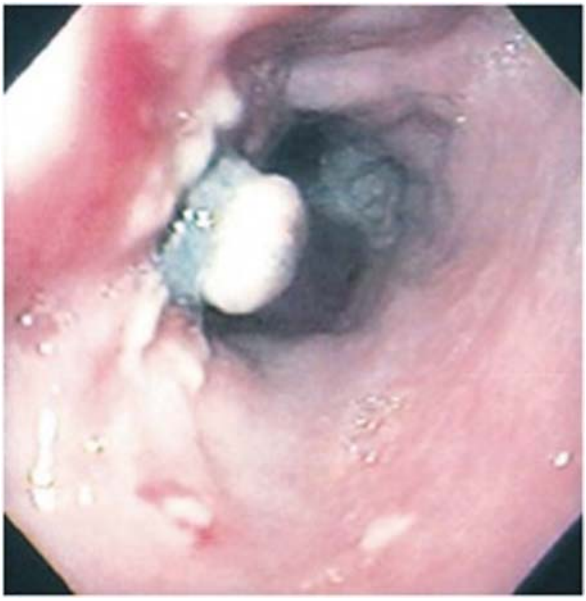

Fig. 4 Banded varix

parenchyma. Success rates for placement of the stent and reduction in portal venous pressure approaches 90%.

Complications can be both acute and chronic. Acute complications include intraperitoneal hemorrhage, hemobilia, and right-sided heart failure. The most severe acute complication is acute, decompensated liver failure. Chronic complications include shunt dysfunction and hepatic encephalopathy. The latter often occurs because of poor portal perfusion due to significant shunt through the stent [18].

Due to the success and relative ease of TIPS, the use of surgical shunts for the treatment of varices is on the decline. Nonetheless, it remains one of the only treatment options available for those patients who have failed alternative, less invasive interventions.

Surgical shunts can be broadly divided into three categories: non-selective, selective, and partial shunts. Non-selective shunts completely eliminate hepatic portal perfusion. Selective shunts decompress esophageal and gastric varices but maintain portal flow to the liver. Partial shunts preserve some portal flow and incompletely decompress the portal venous system.

The two basic non-selective shunts are the end-to-side portacaval shunt (Eck fistula) which directly diverts all portal flow to the inferior vena cava and the side-to-side shunt which preserves portal perfusion while decompressing varices. While highly effective in reducing the incidence of bleeding and ascites, they are both associated with a very high rate of liver dysfunction due to reduced hepatic blood flow. With the advent of TIPS, there are few indications for non-selective shunts.

The selective shunt, more commonly known as the Warren shunt, was described in the late 1960s. It is effectively a distal splenorenal shunt which results in effective variceal decompression and preservation of hepatic portal perfusion. Several controlled trials have compared the Warren shunt with a variety of non-selective shunts. All of these demonstrated no difference in survival between groups but a reduction in post-operative hepatic encephalopathy in those undergoing selective shunts [19, 20].

The objective of partial shunts is similar to that of selective shunts. They incompletely decompress the entire portal venous system while preserving some hepatic portal flow. Originally described by Sarfeh, it utilizes a small diameter PTFE graft for shunting. However, due to its use of synthetic material, there is a higher incidence of thrombosis and, therefore, it is less favored than the selective Warren shunt.

The most common surgical, non-shunt procedure is the Sugiura procedure. It is a devascularization procedure which consists of splenectomy, proximal gastric devascularization, selective vagotomy, pyloroplasty, esophageal devascularization, and esophageal transaction. It reduces esophageal inflow and, thus, reduces bleeding. Its primary advantage is that it preserves portal flow and, therefore, reduces post-operative hepatic encephalopathy.

Finally, liver transplantation is used for those patients with portal hypertension and decompensated liver failure. Often, these patients are temporized with TIPS prior to transplant. One-year mortality rates for Child's C cirrhotics is 20% following transplant versus 80% following various shunt procedures [21].

Conclusion

Bleeding from esophageal varices as a sequelae of liver disease and portal hypertension is a potentially life-threatening problem. Treatment modalities are many and, in part, depend on the stability and underlying disease process of the patient. Once stabilized in the acute setting, the goal of treatment is to control current bleeding, prevent associated complications, and reduce the risk of future bleeding. Due to the high-risk patient population and the advent of newer technologies, endoscopic and interventional radiology treatments of variceal bleeding have become the mainstays of therapy. While surgical treatments still exist, they are used less frequently due to failure of improvement in long-term survival.

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Management of Dieulafoy's Lesions

Seraina K. Faes, Brian R. Untch, Claire Edwards, John Turner, Martin Poleski, and Douglas S. Tyler

Introduction

In 1884 Gallard wrote the first description of a patient with a Dieulafoy's lesion [1]. The lesion's name, however, comes from Paul Georges Dieulafoy (1839–1911), a professor of pathology at the Faculty of Medicine in Paris. In 1898 Dieulafoy described several patients with fatal GI hemorrhage and a bleeding gastric vessel without associated ulceration [2, 3]. He named the lesion *exulceratio simple*x. Other names and descriptions can also be found in the literature and include gastric aneurysm, caliber-persistent artery, cirsoid aneurysm, and submucosal arterial malformation.

Pathophysiology

Histologically, a Dieulafoy's lesion is not aneurismal, but instead an enlarged, tortuous artery lying just under the gastrointestinal mucosa, with only a minute defect at the point of contact with the mucosa [4, 5] (Fig. 1). The vessel is typically 1–3 mm in diameter, significantly larger than vessels in neighboring submucosa.

The etiology of Dieulafoy's lesion is thought to be congenital. The argument for a congenital origin is due to these vessels' normal media and adventitia and a lack of branching that is typically seen in the submucosa. The prominent artery is thought to erode the mucosa. Once the mucosa is sufficiently denuded, exposure to intraluminal contents leads to vessel disruption and subsequent bleeding. The lack of inflammatory reaction (or ulcer) around the vessel is characteristic and diagnostic [4, 6, 7]. In support of a congenital etiology, Dieulafoy's lesions have been observed (although extremely rarely) in children [5, 8].

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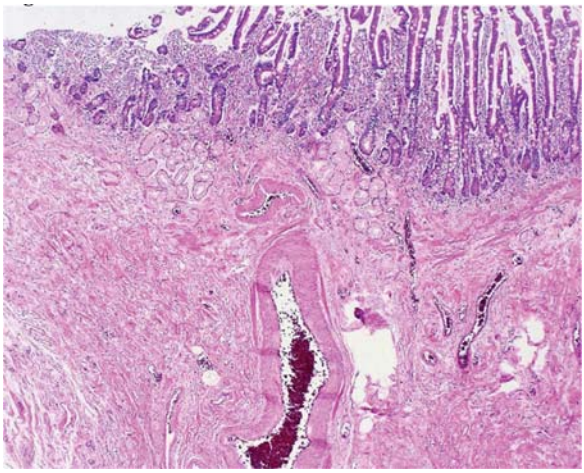

Fig. 1 Histopathologic examination of surgical specimen (40X) showing a tortuous thick-walled vessel superficially located underneath duodenal mucosa

Risk Factors

Risk factors for Dieulafoy's lesions include age, alcohol, aspirin, NSAIDs, and cardiopulmonary disease [3, 9]. Perhaps as patients' mucosa and vessels age or are exposed to various agents, a previously asymptomatic caliber-persistent artery will more likely bleed. In support of this suggestion is that men are more likely than women to be affected and the mean age of presentation is thought to be in the fifth decade [9]. However, these factors are by no means universal in this patient group and have no known diagnostic or prognostic significance.

Reports suggest that Dieulafoy's lesions account for only a small percentage of cases of acute upper gastrointestinal bleeding. Several retrospective studies have demonstrated an incidence between 1 and 6% [4–6]. Incidence at other locations is more difficult to estimate due to their infrequency. It has been postulated, however, that the lesion is underappreciated due to the difficulty of visualizing the lesion during endoscopy, especially when it is not bleeding [5, 7, 10]. Case series suggest that the great majority of Dieulafoy's lesions are located within 6 cm of the gastroesophageal junction, most often on the lesser curvature [4, 11]. Dieulafoy's lesions are also often found in the duodenum, and lesions in the small bowel, colon, esophagus, and even the bronchial tree have been reported [12, 13, 14].

Clinical Presentation

Patient presentation is consistent with other causes of massive GI hemorrhage and includes melena, hematochezia, hematemesis, and hemorrhagic shock. Management and stabilization strategies are beyond the scope of this chapter and are discussed elsewhere within the text. Arterial disruption results in a majority of patients

presenting with hemodynamic instability [13]. With gastric Dieulafoy's lesions, hematemesis with melena is frequent [15].

Clinical Management

Endoscopy is essential in the diagnosis of Dieulafoy's lesion. On endoscopy, the lesion may appear as active arterial spurting of blood, a protruding vessel, or a pinpoint clot (Fig. 2). In the absence of blood, a small defect in the mucosa [6] is sometimes seen, notably surrounded by normal, uninflamed tissue [16]. Especially given the prevalence of risk factors for gastrointestinal mucosal injury in these patients, the possibility of additional bleeding lesions must be considered. In one case series [7], a patient continued to hemorrhage after treatment of a Dieulafoy's lesion because of an overlooked second lesion in the gastric fundus.

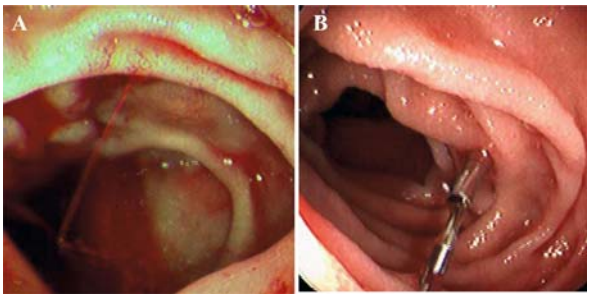

Fig. 2 Endoscopy of the duodenum showing arterial bleeding from a pinpoint lesion of the intestinal mucosa (**a**) and an endoscopically placed clip which appears to have temporarily stopped the bleeding (**b**)

Although once managed surgically, there is now consistent recommendation within the literature that endoscopy is the treatment of choice for Dieulafoy's lesions [12, 11, 17–19]. Reports in the last 8 years (Table 1) have described successful treatment with epinephrine injection, heat probe coagulation, mechanical methods (banding, hemoclipping), and various combinations. Hemostasis with other methods, including laser photocoagulation and sclerosing agents, has also been described [6]. Small retrospective and randomized controlled trials have demonstrated a decreased risk of recurrent bleeding when "mechanical" hemostasis (hemoclipping or band ligation) is used, compared with epinephrine injection [21, 23, 24]. Park et al. found no difference between patients treated with hemoclipping vs. with band ligation [16]: rates of hemostasis and recurrence were equal among the two groups.

Publications about Dieulafoy's lesion consist mainly of small case series: the largest published series to date consists of only 101 cases [5]. A review of case series of substantial size (10 or more patients) published since 1988 reveals that despite modernization of endoscopic therapy, a small number of patients with Dieulafoy's lesion experience recurrent bleeding regardless of treatment modality (Table 2). Although a decrease in the rate of recurrence as endoscopic methods improve with

Table 1 Efficacy of treatment modalities of Dieulafoy's lesion: reports since 2000

Study (no. of patients)	Study type	Endoscopic modality	Percent of patients effectively treated endoscopically
Ljubicic [18] (21)	Retrospective review	Hemoclipping	90.5
Sone et al. [17] (61)	Retrospective review	Hemoclipping, injection	100
Cheng et al. [20] (29)	Retrospective review	Various	86.2
Park et al. [21] (26)	Randomized controlled trial	Hemoclipping vs. band ligation	100
Nikolaidis et al. [22] (23)	Retrospective review	Band ligation	95.7
Schmulewitz and Baillie [4] (40)	Retrospective review	Various, usually epinephrine injection and heater probe	90
Chung et al. [23] (24)	Randomized controlled trial	Hemoclipping/band ligation vs. injection	91.7

time might be expected, Table 2 demonstrates no clear pattern in the rate of recurrence. However, a 2005 report citing an unusually low level of recurrence (1/61 patients), in a relatively lengthy follow-up period of 47 months, is encouraging [17]. Whether any specific clinical factors predispose patients to recurrence is unclear. Nor is any pattern evident in terms of the time at which bleeding recurs; authors have reported recurrence within the same hospital stay and as late as 6 years after discharge.

Surgery continues to play a role in the management of the disease. In most Dieulafoy case series, at least one patient underwent surgery, either due to failure of endoscopy or recurrence of bleeding (Table 2). The indications for surgical management of the Dieulafoy's lesion have yet to be defined. One author has suggested considering surgery when the patient has rebled despite endoscopic therapy [13]. Another has suggested that a transfusion requirement of greater than 6–8 units of blood should be considered an indication for operative intervention in all upper GI bleeding [26]. Most authors, however, provide no objective rationale for the decision to go to surgery. Neither is there agreement on the appropriate operation to perform. Gastrotomy with ligation or coagulation of the lesion likely carries a rebleeding risk similar to that of endoscopic treatment. Indeed, recurrence has been reported after this operation [12, 27], which also fails to yield a tissue diagnosis. "Blind" partial gastric resection carries a risk of not including the lesion and has also led to recurrence [5], but if the lesion is inked on endoscopy, this pitfall can be avoided. Combined endoscopy and laparoscopy has also been advocated [28–30] as a means to simultaneously localize and perform resection.

Recently, angiography has been used for the treatment of Dieulafoy's lesions in poor surgical candidates and those not accessible with endoscopy. It can also be

Table 2 Rates of recurrent bleeding and of surgical treatment in case series

Study (no. of patients)	Endoscopic treatment modality	Number with recurrence after one treatment	Number with multiple recurrences	Number undergoing surgery (indication)
Ljubicic [18] 2006 (21)	Hemoclipping	2	0	1 (severe bleeding)
Sone et al. [17] (61)	Hemoclipping, injection	1	0	0
Cheng et al. [20] (29)	Various	3	0	3 (2 severe bleeding; 1 recurrence)
Nikolaidis et al. [22] (23)	Band ligation	1	0	1 (recurrence)
Schmulewitz and Baillie [4] (40)	Various, usually epinephrine injection and heater probe	18	6	3 (failure of endoscopy)
Norton et al. [12] (89)	Various	9	2	4 (3 failure of endoscopy, 1 recurrence)
Parra-Blanco et al. [10] (26)	Hemoclipping, heat probe, injection	4	1	1 (failure of endoscopy)
Baettig et al. [11] (28)	Injection	1	0	3 (1 severe bleeding, 1 concurrent bleeding ulcer, 1 recurrence)
Stark et al. [13] (19)	Various	2	0	1 (failure of endoscopy)
Asaki et al. [7] (45)	Ethanol injection	5	0	1 (hemorrhage from second lesion missed on endoscopy)
Pointner et al. [25] (22)	Sclerotherapy and/or coagulation	4	1	4 (3 unable to locate lesion endoscopically, 1 multiple recurrence)

employed for diagnostic purposes if endoscopy is non-diagnostic. Tortuous ecstatic arteries without early venous return are characteristic after dye injection [31]. Using this criterion, these lesions can be easily distinguished from angiodysplasia and erosive bleeding. Multiple authors report case reports with successful treatment or partial treatment with embolization [32, 20]. However, rebleeding is not uncommon and often patients require subsequent resection.

Summary

Dieulafoy's lesions are a rare cause of GI bleeding and patients frequently present with hemorrhagic shock. It must be suspected in a patient with massive gastrointestinal hemorrhage, non-specific symptoms, and minimal endoscopic findings.

Further evaluation with repeated endoscopy or angiography and continued monitoring are paramount. Failure to consider the lesion in the differential diagnosis can be dangerous, as bleeding from this entity can be sudden and lead to rapid exsanguination. Multiple treatment approaches can be employed once a diagnosis is made; however, endoscopy has demonstrated excellent efficacy and should be the first-line treatment in nearly all cases. The difficulty in diagnosis and anatomic variability observed in some cases can require careful collaboration between gastroenterologists, radiologists, intensivists, and surgeons.

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Management of Bleeding Peptic Ulcer Disease

James C. Padussis and Theodore N. Pappas

Epidemiology

Peptic ulcers are defects in the gastrointestinal mucosa that extend through the muscularis mucosae. They persist as a function of the acid or peptic activity in gastric juice. The natural history of peptic ulcer disease (PUD) ranges from resolution without intervention to the development of complications with potential for significant morbidity and mortality, such as bleeding and perforation. Peptic ulcer disease is an important cause of morbidity and health-care costs. Estimates of expenditures related to work loss, hospitalization, and outpatient care are $5.65 billion per year in the United States [1].

Helicobacter pylori and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease in the United States, accounting for 48 and 24% of cases, respectively (Table 1) [2]. A variety of other infections and comorbidities are associated with a greater risk of peptic ulcer disease (e.g., cytomegalovirus, tuberculosis, Crohn's disease, hepatic cirrhosis, chronic renal failure, sarcoidosis, myeloproliferative disorder). Critical illness, surgery, or hypovolemia leading to splanchnic hypoperfusion may result in gastroduodenal erosions or ulcers (stress ulcers). Smoking increases the risk of ulcer recurrence and slows healing. A peptic ulcer may arise at various locations including the stomach (gastric ulcer), duodenum (duodenal ulcer), and esophagus (esophageal ulcer). Gastric ulcers are further divided into five types based on location, secretory status, and cause (Table 2, Fig. 1).

H. pylori is a gram-negative bacillus that colonizes the stomach, induces inflammatory cytokines, and causes gastric inflammation. Individuals with *H. pylori* associated antral-predominant gastritis exhibit increased gastric acid production and are prone to PUD. Worldwide, more than 1 billion people are estimated to be infected with *H. pylori* with higher prevalence in developing countries [3, 4].

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Table 1 Causes of peptic ulcer disease

Cause	Comments
Common	
H. pylori infection	Found in 48% of patients with PUD
NSAIDs	5–20% of patients who use NSAIDs over an extended period develop PUD
Other medications	Corticosteroids, bisphosphonates, potassium chloride, chemotherapeutic agents
Rare	
Zollinger–Ellison syndrome	Hypersecretory state causing multiple gastroduodenal, jejunal, or esophageal ulcers
Malignancy	Gastric cancer, lymphoma, lung cancer
Stress	After acute illness, multi-organ failure, ventilator support, extensive burns (Curling's ulcer), or head injury (Cushing's ulcer)

Table 2 Classification and characteristics of gastroduodenal ulcers

Type	Location	Acid hypersecretion	Complications	Incidence (%)
I	Gastric body, lesser curvature	No	Bleeding uncommon	55
II	Body of stomach + duodenal ulcer	Yes	Bleeding, perforation, obstruction	20
III	Prepyloric	Yes	Bleeding, perforation	20
IV	High on lesser curvature	No	Bleeding	<5
V	Anywhere (medication induced)	No	Bleeding, perforation	<5

However, the prevalence of *H. pylori* both in the general population and in peptic ulcer disease is decreasing rapidly, presumably due to improved hygiene and decreased *H. pylori* transmission in early childhood. In regions such as southern Europe and Japan, where prevalence rates for *H. pylori* in PUD had been over 90%, there is evidence of decreasing *H. pylori* prevalence in the population and in peptic ulcers [3, 4]. In regions where this trend is more mature, such as the United States and western Europe, the prevalence of *H. pylori* in PUD now ranges from 50 to 75% and is continuing to fall rapidly [5–7].

Nonsteroidal anti-inflammatory drugs, including aspirin, cause gastric hyperemia shortly after ingestion. With repeated use this can lead to erosions in the mucosa. These erosions tend to improve over time as adaptation to the NSAID exposure occurs. However, some patients, for reasons that are not known, fail to develop this resistance, and the erosions progress to ulcers. The Food and Drug Administration (FDA) estimates the risk of a clinically significant NSAID-induced gastrointestinal event, including gastrointestinal bleeding, perforation, or pyloric obstruction, as being 1–4% per year for the nonselective NSAID class of drugs [8]. Although

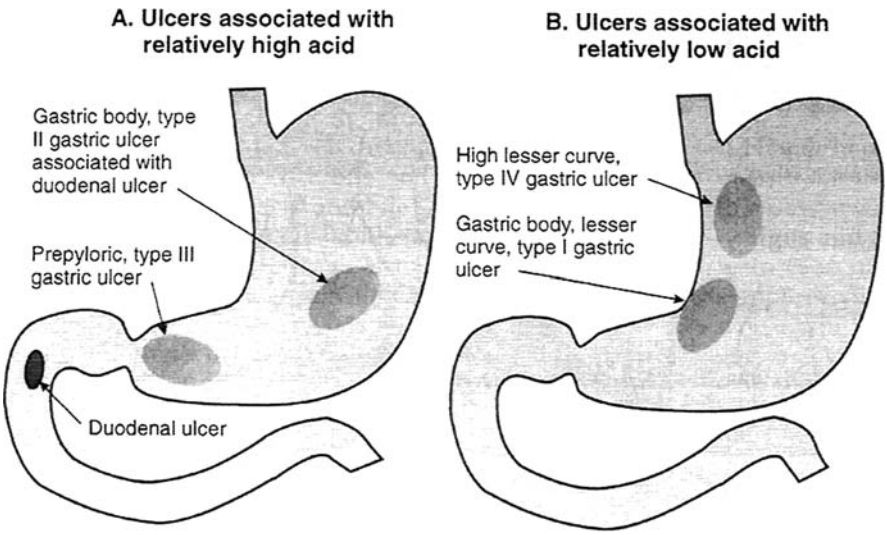

Fig. 1 The four major types of gastric ulcers and their association with either (**a**) high acid or (**b**) low acid. From Sabiston DC [122], with permission

aspirin has been in use for more than a century, use of low-dose aspirin in prevention of thrombotic cardiovascular and peripheral vascular disease has emerged over the last two decades as an important cause of symptomatic PUD and its associated complications [9, 10]. Furthermore, the use of nonaspirin NSAIDs has also risen dramatically in the past decade, principally because patients with degenerative joint disease take these drugs regularly [9]. It has been shown that aspirin in doses ranging from 75 to 300 mg daily causes a 2–3 fold increased risk of GI bleeding due to both upper GI ulceration and lower GI causes [9, 10]. There are several risk factors that influence the risk of PUD in patients taking NSAIDs, the most important of which is a prior history of clinical ulcer disease or ulcer complications. Other risk factors include the NSAID dose, duration of therapy, age greater than 75 years, co-therapy with drugs that enhance toxicity, and genetic predisposition. Polymorphism of cytochrome P450 2C9 may delay the metabolism of several NSAIDs, with a prolonged duration of drug enhancing the ulcerogenic effect [11]. Co-therapy of NSAIDs with corticosteroids, anticoagulants, other NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and alendronate dramatically increases the risk of ulcer complications.

The annual rate of hospitalization for acute upper gastrointestinal hemorrhage in the United States is estimated to be 160 hospital admissions per 100,000 population, which translates into more than 400,000 per year [12]. In most settings, the vast majority of acute episodes of upper gastrointestinal bleeding (80–90%) have nonvariceal causes, with gastroduodenal peptic ulcers accounting for the majority of lesions [13]. A number of studies have suggested that the annual incidence of bleeding from a peptic ulcer may be decreasing worldwide, yet other

recent population-based estimates have suggested that the incidence is about 60 per 100,000 population, with an increasing proportion of episodes related to the use of aspirin and nonsteroidal anti-inflammatory medications [14, 15]. Moreover, peptic ulcer bleeding is seen predominantly among the elderly, with 68% of patients over the age of 60 years and 27% over the age of 80 years [16]. Mortality associated with peptic ulcer bleeding remains high at 5–10% [13]. Estimated direct medical costs for the in-hospital care of patients with bleeding from a peptic ulcer total more than $2 billion annually in the United States [17].

Presentation

Typical symptoms of peptic ulcer disease include episodic gnawing or burning epigastric pain; pain occurring 2–5 h after meals or on an empty stomach; and nocturnal pain relieved by food intake, antacids, or antisecretory agents. A history of episodic or epigastric pain, relief of pain after food intake, and nighttime awakening because of pain, with relief following food intake, are the most specific findings for peptic ulcer disease and help rule in the diagnosis [18]. Less common features include indigestion, vomiting, loss of appetite, intolerance of fatty foods, heartburn, and a positive family history [18]. The natural history and clinical presentation of peptic ulcer disease differ in individual populations [19]. Abdominal pain is absent in at least 30% of older patients with peptic ulcers [20]. Postprandial epigastric pain is more likely to be relieved by food or antacids in patients with duodenal ulcers than in those with gastric ulcers. Weight loss precipitated by fear of food intake is characteristic of gastric ulcers.

Hematemesis and melena are the most common presenting signs of acute upper gastrointestinal hemorrhage secondary to a bleeding peptic ulcer. Melena is sometimes seen in patients with hemorrhage in the lower gastrointestinal tract (e.g., distal small bowel and colon) and hematochezia in patients with brisk upper gastrointestinal hemorrhage [21]. Patients with a bleeding peptic ulcer that is not brisk in nature may present with fatigue caused by anemia, orthostasis, or syncope. Appropriate hemodynamic assessment includes the careful measurement of pulse and blood pressure, including orthostatic changes, to estimate the intravascular volume status and guide resuscitative efforts. Patients who present with acute upper gastrointestinal bleeding and a substantial loss of intravascular volume have resting tachycardia (pulse >100 beats/min), hypotension (systolic blood pressure <100 mmHg), or postural changes (an increase in the pulse of >20 beats/min or a drop in systolic blood pressure of >20 mmHg on standing) [22, 23]. Mucous membranes, neck veins, and urine output should also be evaluated as additional ways of estimating the intravascular volume status [22].

Initial Management

The first priority in treatment is correcting fluid losses and restoring hemodynamic stability. Volume resuscitation should be initiated with crystalloid intravenous fluids with the use of two large-bore peripheral intravenous-access catheters or a

central catheter if peripheral access is not available. In order to maintain adequate oxygen-carrying capacity, especially in older patients with coexisting cardiac illnesses, the use of supplemental oxygen and transfusion of packed red blood cells should be considered if tachycardia or hypotension is present or if the hemoglobin level is less than 10 g/dL [22, 24]. When indicated, correction of coagulopathy is undertaken [25].

The insertion of a nasogastric tube may be helpful in the initial assessment of the patient, although the incremental information such a procedure provides remains controversial [23]. It has been suggested that the presence of blood in the nasogastric aspirate is an adverse prognostic sign that may be useful in identifying patients who require urgent endoscopic evaluation [23, 26]. However, the absence of bloody or coffee-ground material does not definitively rule out ongoing or recurrent bleeding, since approximately 15% of patients without those findings are found to have high-risk lesions on endoscopy [23]. The use of a large-bore orogastric tube with gastric lavage (with the use of tap water at room temperature) appears only to improve visualization of the gastric fundus on endoscopy and has not been documented to improve the outcome [27]. Intravenous erythromycin, through its effect as a motilin receptor agonist, has been shown to promote gastric motility and substantially improve visualization of the gastric mucosa on initial endoscopy. However, erythromycin has not been shown to improve the diagnostic yield of endoscopy substantially or to improve the outcome [28].

Risk Stratification

With the use of clinical variables alone, scoring tools have been developed to facilitate the triage of patients with acute upper gastrointestinal hemorrhage, identify those in need of urgent endoscopic evaluation, predict the risk of an adverse outcome, and assist in guiding treatment [29, 30]. Because gastrointestinal endoscopy by itself occasionally induces GI bleeding and rebleeding, emergency endoscopy is not a procedure without risk [31]. Thus the uniform recommendation of emergency endoscopy for all patients with signs of upper GI bleeding is questionable and the establishment of criteria to isolate those who do not need urgent endoscopy of great practical value.

The Blatchford risk score (BRS) is a validated risk-stratification tool based only on clinical and laboratory variables, used to predict adverse outcomes and the need for intervention in patients with upper gastrointestinal hemorrhage (Table 3) [32]. Blatchford et al. reported that a BRS of 0 had a 100% negative predictive value for rebleeding and mortality [32]. Masaoka et al. validated the Blatchford scoring system and showed that when a BRS score of 2 was used as the cutoff, sensitivity for determining a patient to be low risk remained 100%, while 87% of patients later considered to be low risk underwent emergent endoscopy [33]. This might be considered to represent over-diagnosis, but to avoid missing incipient or critical hemorrhagic lesions, this vigilance may be warranted. The Rockall score is probably the most widely known risk-stratification tool for upper gastrointestinal hemorrhage

Table 3 Blatchford score

At presentation	Points
Systolic blood pressure	
100–109 mmHg	1
90–99 mmHg	2
<90 mmHg	3
Blood urea nitrogen	
6.5–7.9 mmol/L	2
8.0–9.9 mmol/L	3
10.0–24.9 mmol/L	4
≥25 mmol/L	6
Hemoglobin (men)	
12.0–12.9 g/dL	1
10.0–11.9 g/dL	3
<10.0 g/dL	6
Hemoglobin (women)	
10.0–11.9 g/dL	1
<10 g/dL	6
Other variables at presentation	
Pulse ≥100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

and has been validated in numerous health-care settings (Table 4) [34]. The complete Rockall score makes use of both clinical and endoscopic criteria to predict the risk of rebleeding and death; the scale ranges from 0 to 11 points, with higher scores indicating higher risk. Patients with a clinical Rockall score of 0 or a complete Rockall score of 2 or less are considered to be at low risk of rebleeding or death. Dulai et al. showed that patients with a complete Rockall score less than or equal to 2 had a 4% chance of rebleeding and could be effectively managed as outpatients [35]. The clinical Rockall score and the Blatchford score are useful prognostic tools in patients presenting with acute upper gastrointestinal hemorrhage, since the two tools have selected common features, including a determination of the patient's hemodynamic status and coexisting illnesses, and may reduce the need for urgent endoscopic evaluation in patients who are deemed to be at low risk [36]. The use of such validated tools as adjuncts to clinical evaluation and the judgment of the medical practitioner is encouraged in clinical practice.

The endoscopic appearance of a bleeding ulcer can be used to predict the likelihood of recurrent bleeding on the basis of the Forrest classification, which ranges from IA to III (Table 5, Fig. 2). High-risk lesions include those characterized by active spurting of blood (grade IA), oozing blood (grade IB), a nonbleeding visible vessel described as a pigmented protuberance (grade IIA), or an adherent clot (which is defined as a lesion that is red, maroon, or black and amorphous in texture and that cannot be dislodged by suction or forceful water irrigation) (grade IIB).

Table 4 Rockall score

Complete Rockall score	Clinical Rockall score	Age	Points
		<60 years	0
		60–79 years	1
		≥80 years	2
		Shock	
		Heart rate <100 beats/min	1
		Systolic blood pressure <100 mmHg	2
		Coexisting illness	
		Ischemic heart disease, congestive heart failure, other major illness	2
		Renal failure, hepatic failure, metastatic cancer	3
		Endoscopic diagnosis	
		No lesion observer, Mallory–Weiss tear	0
		Peptic ulcer, erosive disease, esophagitis	1
		Cancer of upper GI tract	2
		Endoscopic stigmata of recent hemorrhage	
		Clean-base ulcer, flat pigmented spot	0
		Blood in upper GI tract, active bleeding, visible vessel, clot	2

Table 5 Forrest classification

Grade	Rebleeding risk (%)
Grade I: active pulsatile bleeding	70–90
Grade Ib: active nonpulsatile bleeding	10–20
Grade IIa: nonbleeding visible vessel	40–50
Grade IIb: adherent clot	10–20
Grade IIc: pigmented spot	1–2
Grade III: no signs of recent bleeding	1–2

Low-risk lesions include flat, pigmented spots (grade IIC) and clean-base ulcers (grade III) [21, 37–39]. The interobserver variation in diagnosing these endoscopic stigmata is low to moderate [40].

At initial endoscopy, high-risk lesions are seen in approximately one-third to one-half of all patients, with rebleeding rates of 22–55% if the ulcer is left untreated endoscopically [13, 21, 37, 39]. Additional data are needed to confirm the possible improvement in risk stratification provided by endoscopic Doppler ultrasonography applied directly to the ulcer stigmata before and after endoscopic hemostasis [41].

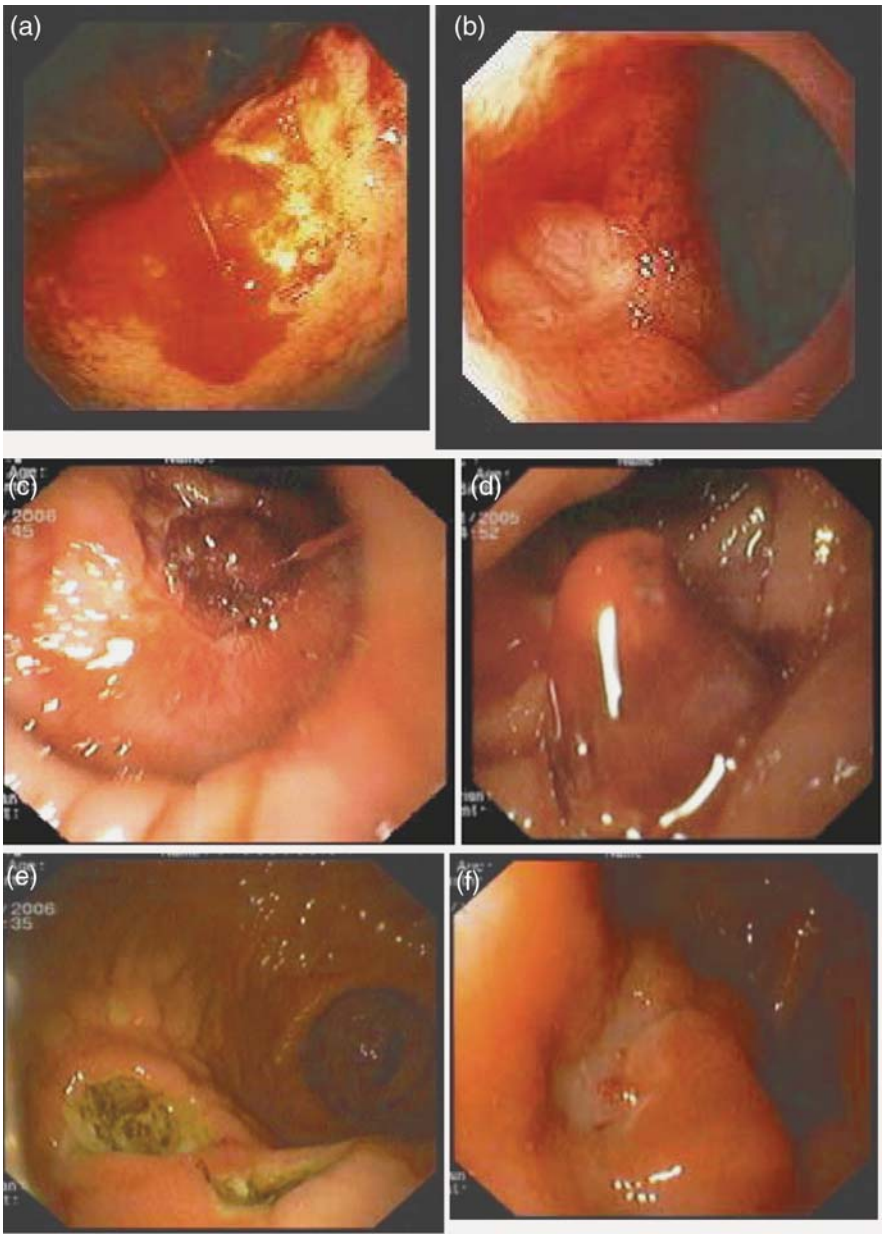

Fig. 2 (**a**) Gastric ulcer with pulsatile, arterial bleeding (grade IA). (**b**) Active oozing of blood from the upper edge of a fibrin-based ulcer in the duodenal bulb (grade IB). (**c**) Duodenal ulcer with nonbleeding visible vessel (grade IIA). (**d**) Duodenal ulcer with adherent clot (grade IIB). (**e**) Duodenal ulcer with black pigmented spots (grade IIC). (**f**) Duodenal ulcer with clean base (grade III)

Endoscopic Therapy

A multidisciplinary approach with timely involvement of a trained endoscopist and endoscopy assistant is widely recommended [22, 29, 42]. Such involvement should entail after-hours availability, since early endoscopy (performed within 24 h after presentation of the patient) is the cornerstone of treatment for patients with acute upper gastrointestinal hemorrhage and may improve certain outcomes, such as the number of units of blood transfused and the length of the hospital stay, for selected patients who are classified as being at high risk. Early endoscopy also allows for the safe and expedited discharge of patients who are classified as being at low risk and reduces the use of health-care resources [29, 43]. Goals of early endoscopy are to determine the cause of bleeding, ascertain prognosis, and administer endoscopic therapy, if indicated. Treatment recommendations have focused on the first 72 h after presentation and endoscopic evaluation and therapy, since this is the period when the risk of rebleeding is greatest [39, 44].

High-risk patients should be admitted to the hospital and should receive endoscopic therapy. They should then be triaged to a monitored setting or intensive care unit for the first 24 h of what is usually at least a 3-day hospital stay. Patients who have bleeding ulcers with high-risk stigmata as determined on endoscopy (active bleeding or a nonbleeding visible vessel) should undergo endoscopic hemostasis, a procedure that has been shown to decrease rates of rebleeding, the need for urgent surgery, and mortality [29, 42, 45]. Contemporary endoscopic treatments include injection therapy (saline, vasoconstrictors, sclerosing agents, tissue adhesives, or a combination thereof), thermal therapy (with the use of contact methods, such as multipolar electrocoagulation and heater prober, or noncontact methods, such as argon plasma coagulation [APC]), and mechanical hemostasis (principally endoscopic clips).

Injections with solutions of diluted epinephrine (1:10,000) are widely used because of their simplicity. The principle mechanism of action by which diluted epinephrine solutions work is a tamponade effect induced by the volume of solution injected. It is therefore logical that in a recent study, a large-volume (35–45 mL) epinephrine injection appeared to be more effective than a standard-volume (15–25 mL) injection [46]. Solutions of agents other than epinephrine, such as sclerosants, saline, or even dextrose, can produce the same effect. In spite of the large body of published literature, no single solution for endoscopic injection has been shown to be superior to another in achieving hemostasis. The use of sclerosants in injection therapy for bleeding ulcers should be discouraged, however. Addition of a sclerosant has repeatedly been shown to confer no advantage over injection with epinephrine alone and extensive, uncontrolled tissue necrosis may occur resulting in ulcer perforation [47, 48]. The use of injectable fibrin sealant is a relatively new approach to achieve initial hemostasis and decrease the rate of rebleeding from peptic ulcers. An open label, 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 [49]. While the safety profiles of

all three treatment strategies were similar, the patients who received multiple applications of fibrin sealant had significantly less rebleeding than the polidocanol group and had fewer acute treatment failures (8% vs. 13%). 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. While injection therapy is a cornerstone of endoscopic treatment of bleeding peptic ulcers, the rebleeding rate is high (approximately 18%) if injection therapy alone is performed [50]. Injection therapy alone was shown to be less effective at preventing recurrent bleeding compared to bipolar electrocoagulation in a randomized controlled trial involving 100 patients with high-risk bleeding ulcers [51].

Thermal coagulation achieves acute hemostasis and prevents rebleeding by coaptive coagulation of the underlying artery in the ulcer base [52]. Thermal devices can be divided into contact (heater probe, monopolar and bipolar electrocoagulation) and noncontact types (laser treatment and APC). Contact probes which are commercially available include the heater probe (Olympus Corp.), Gold probe (Boston Scientific), and BICAP probe (Circon ACMI). While the hemostatic effects of contact probes are well established by clinical trials, the use of APC in the treatment of peptic ulcer bleeding has only recently been reported. Argon plasma coagulation has a theoretical disadvantage for the treatment of bleeding ulcers since it does not permit tamponade; nevertheless, at least two controlled trials suggested that APC can be equally as effective. One randomized, controlled study comparing APC with heater probe coagulation showed no significant differences in terms of initial hemostasis at index endoscopy, frequency of recurrent bleeding, requirement for emergency surgery, number of units of blood transfused, length of hospital stay, and mortality rate [53]. To summarize, no single method of endoscopic thermal coagulation is superior to the others.

Mechanical devices have been used for the treatment of variceal hemorrhage, but rarely in the treatment of bleeding peptic ulcer disease. Hemoclips, however, have gained increasing popularity in the past few years. Initial enthusiasm for the use of hemoclips was generated by a study by Cipolletta and colleagues, in which they compared hemoclips with heater probe thermocoagulation [54]. They reported a significantly lower rate of recurrent bleeding with the use of hemoclips (1.8% vs. 21%). The deployment of hemoclips on fibrotic ulcer floors can be difficult, however, particularly when they are used tangentially or with the endoscope in a retroflexed position. Indeed, two subsequent trials yielded conflicting results on the use of hemoclips. Lin and colleagues compared hemoclips with heater probe coagulation, and in 6 out of 40 patients the hemoclips could not be applied [55]. Gevers et al. randomly assigned patients with bleeding ulcers to treatment with hemoclips, injection, or both [56]. They reported a failure rate of 13 out of 35 patients with the hemoclips compared with 5 out of 34 with injection and 8 out of 32 patients with combined therapy. The efficacy of hemoclips seems to be limited by the difficulty of successful application. With improvements in design, this technical problem might be overcome. More studies are required to give a fair verdict on the effectiveness of hemoclips.

Many endoscopists favor combined therapy, in which the injection of diluted epinephrine precedes thermal coagulation. In actively bleeding ulcers, an injection can diminish or even stop bleeding, allowing a clear view of the bleeding vessel, which in turn facilitates accurate thermal coagulation. The cessation of blood flow can also prevent dissipation of thermal energy, so that tissue injury can be minimized. In a prospective randomized trial, 134 patients with actively bleeding ulcers who received epinephrine alone were compared with 136 patients who received the combined therapy of epinephrine injection followed by heater probe coagulation [57]. There was no difference in the outcome of the two treatment strategies as measured by rebleeding, the need for surgery, requirement for repeated endoscopic hemostasis, length of hospital stay, mortality rate, or healing at 4 weeks. When the subgroup of patients with spurting ulcers was analyzed separately, however, there was less rebleeding in the combined group as well as a lesser need for surgery. For the severe form of spurting hemorrhage, combined therapy therefore seems to be beneficial. The benefit of combination therapy has further been evaluated in many trials and confirmed by meta-analysis. In a systematic review that aimed to determine whether the addition of a second hemostatic procedure immediately after epinephrine injection improves efficacy of hemostasis or patient outcomes, 16 randomized studies involving 1,673 patients were analyzed [58]. The addition of a second procedure reduced the rate of recurrent bleeding from 18.4 to 10.6% (OR 0.53, 95% CI 0.40–0.69) and that of emergency surgery from 11.3 to 7.6% (OR 0.64, 95% CT 0.46–0.90). The mortality rate fell from 5.1 to 2.6% (OR 0.51, 95% CI 0.31–0.84). Eleven studies used injected substances (such as sclerosant, tissue adhesive, or thrombin), two studies added hemoclips, and three studies evaluated the added use of thermal coagulation devices. Pooled data revealed that combined therapy is the treatment of choice for high-risk bleeding peptic ulcers. The meta-analysis also confirmed a greater risk of the significant complications of perforation and gastric-wall necrosis in the combined therapy group (6 out of 558 patients) than in the epinephrine-alone group (1 out of 560 patients). Furthermore, improvement in prognosis seems to be more evident in those with active bleeding.

In summary, a consensus statement recommends combination therapy with epinephrine to provide local vasoconstriction, volume tamponade, and facilitation of a clear view of the bleeding vessel, followed by targeted contact thermal therapy [29]. At present it is probably best for endoscopists to carry out the hemostasis technique they are most comfortable using, since all methods have been shown to be efficacious. However, epinephrine injection alone should not be performed. The exact roles of newer and emerging endoscopic hemostasis techniques, including loops, cryotherapy, suturing and stapling devices, await appropriately powered clinical trials.

Despite the effectiveness of endoscopic hemostasis, rebleeding occurs in 10–25% of cases, irrespective of the method of treatment. Various clinical and endoscopic factors have been proposed as predictors of failure of endoscopic treatment in patients with bleeding from a peptic ulcer. These include a history of peptic ulcer

disease, previous ulcer bleeding, the presence of shock at presentation, active bleeding during endoscopy, large ulcer greater than 2 cm in diameter, a large underlying bleeding vessel greater than 2 mm in diameter, and ulcers located on the lesser curve of the stomach or on the posterior or superior duodenal bulb.

The benefit of a routine second-look endoscopy after the initial hemostasis is disputed. In a meta-analysis of four studies comparing systematic second-look endoscopy and re-treatment versus expectant treatment, Marmo et al. showed that the risk of recurrent bleeding with the former approach was reduced by 6.2%, but risk reduction for surgery and mortality were insignificant [59]. The authors concluded that appropriate selection of patients for second-look endoscopy is crucial. The selective use of second-look endoscopy and re-treatment has been supported by a single-center trial that included only Forrest I and IIa ulcers; patients were treated by a standardized endoscopic therapy in combination with intravenous omeprazole [60]. A scheduled second-look endoscopy the day after initial endoscopic hemostasis was found to prevent recurrent bleeding (relative risk 0.33, 95% CI 0.1–0.96). Repeat endoscopy may be considered on a case-by-case basis if there are clinical signs of recurrent bleeding or if there is uncertainty regarding the effectiveness of hemostasis during the initial treatment.

A significant portion of patients who are admitted to the hospital with acute, nonvariceal upper gastrointestinal hemorrhage are at low risk for rebleeding and death [61–63]. Results from randomized trials have shown that after endoscopy, low-risk patients can be discharged home, depending on when the initial endoscopy is performed [64–68]. Selection criteria for those patients who are considered low risk include age<60, absence of hemodynamic instability, absence of severe coexisting medical illness, a hemoglobin of greater than 8 g/dL without the need for transfusion, normal coagulation studies, onset of bleeding outside the hospital, presence of a clean-base ulcer, and adequate social support at home [61, 62, 65–69]. Low-risk patients who do not fulfill these clinical criteria should be admitted to the hospital for observation.

Medical Therapy

In the past 10 years, pharmacotherapy has focused on the use of profound acid suppression with proton-pump inhibitors in the treatment of patients with nonvariceal upper gastrointestinal hemorrhage. Experimental data have shown that gastric acid impairs clot formation, promotes platelet disaggregation, and favors fibrinolysis [70]. Therefore, inhibiting gastric acid and raising the intragastric pH to 6 or more and maintaining it at that level may promote clot stability, thus decreasing the likelihood of rebleeding. However, the goal of an intragastric pH of 6 or more is theoretical and has not been documented to be a reliable proxy for clinical efficacy in the treatment of peptic ulcer bleeding. Furthermore, although data from clinical trials support the use of a bolus followed by a continuous infusion of proton-pump inhibitors this may not sustain an intragastric pH of 6 or more [71]. The use of histamine H_2-receptor antagonists (H_2 blockers) in patients with peptic ulcer bleeding

has not resulted in a significant improvement in outcomes, probably because of early development of pharmacologic tolerance [72].

Potent acid-suppressing proton-pump inhibitors do not induce tachyphylaxis and have had favorable clinical results [73]. Recent meta-analyses showed that the use of proton-pump inhibitors significantly decreased the risk of ulcer rebleeding (odds ratio (OR) 0.40, 95% confidence interval [CI] 0.24–0.67), the need for urgent surgery (OR 0.50, 95% CI 0.33–0.76), and the risk of death (OR 0.53, 95% CT 0.31–0.91) [74, 75]. However, the reduction in mortality appears to occur only among patients with high-risk stigmata who have first undergone endoscopic therapy, a finding that supports the use of medical therapy as an adjunct to, but not a replacement for, endoscopic hemostasis in such patients [75].

There are only limited data from randomized clinical trials in the United States that have evaluated therapy with intravenous proton-pump inhibitors for acute bleeding from a peptic ulcer. A recent study comparing the use of high-dose intravenous proton-pump inhibitors with that of H_2 blockers was halted prematurely because of slow recruitment of subjects and, although there was a trend favoring therapy with high-dose intravenous proton-pump inhibitors, the study was underpowered to show any statistical difference between the two treatments [76]. In addition, the dosing method for treatment with proton-pump inhibitors appears to be important. A pooled analysis of 16 randomized, controlled trials that enrolled more than 3,800 patients suggested that intravenous bolus loading followed by continuous infusion of proton-pump inhibitors is more effective than bolus dosing alone in decreasing the rates of rebleeding and the need for surgery [77]. Therefore, it is reasonable to recommend the use of an intravenous bolus of a proton-pump inhibitor followed by a continuous infusion for 72 h after endoscopic hemostasis, although controversy persists regarding optimal dosing. The use of high-dose intravenous proton-pump inhibitors after endoscopic therapy has also been shown to be more effective and less costly than alternative approaches in a variety of clinical settings [78, 79].

The administration of high-dose intravenous proton-pump inhibitors while the patient is awaiting endoscopy does not appear to have an effect on outcome, even though its use may be associated with a significant down-staging of endoscopic lesions. One study found that patients who receive pre-endoscopic proton-pump inhibitors were less likely to have endoscopic evidence of high-risk stigmata than patients who received placebo (OR 0.67, 95% CI 0.54–0.84) and less likely to need endoscopic hemostasis therapy (19.1% vs. 28.4%, p=0.007) [80, 81]. The cost-effectiveness of proton-pump inhibitors for this indication remains somewhat controversial [82, 83].

The use of high-dose oral proton-pump inhibitors in peptic ulcer bleeding has been shown in Asian populations to lead to reductions in the risk of rebleeding (OR 0.24, 95% CI 0.16–0.26), the need for surgery (OR 0.29, 95% CI 0.16–0.53), and the risk of death (OR 0.35, 95% CI 0.16–0.74) [84]. However, these results may not be generalizable to North American or European populations because of underlying differences in physiological measures and pharmacodynamic profiles, and prevalence rates of *H. pylori* infection, factors that may favor the acid-suppressive effect of a given dose of a proton-pump inhibitor in Asian patients [84]. Additional

data from randomized clinical trials comparing the use of intravenous proton-pump inhibitors with that of oral proton-pump inhibitors are required in Western patient populations, since high oral doses could result in significant savings in health-care resources [79].

Somatostatin and its analogue, octreotide, inhibit both acid and pepsin secretion while also reducing gastroduodenal mucosal blood flow. However, these drugs are not routinely recommended in patients with peptic ulcer bleeding, since contemporary randomized, controlled trials have shown little or no benefit attributable to them, either alone or in combination with an H_2 blocker [85]. Furthermore, there are no strong data to support the adjunctive use of these drugs after endoscopic therapy for ulcer bleeding.

When an aggressive treatment plan consisting of anti-*H. pylori* therapy and avoidance of NSAIDs is employed, there is a rate of ulcer cure of 95%. There is ample evidence to prove that, for bleeding related to *H. pylori* infection, when the patient is not using aspirin or nonsteroidal anti-inflammatory drugs, curing the infection with a 10- to 14-day course of triple therapy obviates the risk of ulcer recurrence and ulcer rebleeding [86, 87]. Currently, triple therapy consisting of a proton-pump inhibitor and two antibiotics is recommended for treatment of *H. pylori* infection. The triple combination of omeprazole, amoxicillin, and clarithromycin has been most widely used, and it is associated with eradication of *H. pylori* in 90% of patients. Alternative regimens also include combinations of omeprazole, metronidazole, and amoxicillin or clarithromycin, with equivalent results. When patients must be administered NSAIDs for serious underlying medical conditions, the synthetic prostaglandin analogue, misoprostol, has shown promise in decreasing the incidence of recurrent bleeding, especially among the elderly [88, 89]. However, maintenance proton-pump inhibitor therapy may be required for select patients.

Interventional Therapy

Identifying the source of the upper GI bleeding often requires a multi-modality approach. No source of GI bleeding is found in 5–10% of patients after upper GI endoscopy, while missed lesions account for only a very small portion of these patients (<2%) [90]. Nuclear medicine scans (tagged red blood cell scans) use radiolabeled blood products to generate images of extravasated blood. Alavi and colleagues first demonstrated that nuclear medicine could detect bleeding at a rate as low as 0.1 mL/min [91]. The bioavailability of radiolabeled colloid, though, is less than 1 h, limiting its use to cases of active bleeding [92]. Nuclear imaging compliments clinical findings by assessing ongoing bleeding with possible localization and risk assessment for future intervention. Localization with nuclear imaging is usually warranted in those patients with active, intermittent bleeding with hemodynamic stability between episodes. Nuclear medicine often gives a good idea of the source of upper GI bleeding, but is not 100% accurate.

Angiography is often performed after endoscopy or nuclear imaging to identify and treat causes of upper GI bleeding. Nusbaum and colleagues first reported

angiographic visualization of extravasated blood in canine models with bleeding rates as low as 0.5 mL/min [93]. Angiographic technique for the diagnosis of upper GI bleeding usually requires selective angiograms of the three mesenteric vessels. After femoral access is obtained, consecutive catheterization and angiograms of the celiac, superior mesenteric, and inferior mesenteric arteries are performed. The inferior mesenteric artery is often not the source of upper GI bleeding, but it is examined to exclude other sources of lower GI bleeding. Unfortunately, blood extravasation is not always visualized. In recent reviews of angiographic results, blood extravasation or intraluminal blush was seen in 40–60% of angiographic cases of nonvariceal upper GI bleeding [93–96]. Direct angiographic signs of active GI bleeding include blood extravasation or intraluminal contrast pooling. Commonly encountered indirect angiographic signs of GI bleeding include mucosal or extramucosal hyperemia, identifying a submucosal vessel, and intramural pooling of contrast or arterial wall abnormalities. When angiographic abnormalities are identified and correlated with endoscopy or nuclear medicine imaging, angiographic treatment is recommended to decrease rebleeding rates and improve survival.

Angiographic intervention has become a major option for treating the minority of patients who will continue to bleed after aggressive endoscopic treatment or in whom a locus of acute bleeding has not been identified. Angiographic interventions are successful at controlling bleeding detectable by angiography in 89–90% of cases with an overall clinical success rate of 52–90% [97–99]. Less than 2% of patients with peptic ulcer bleeding would fail both endoscopic and angiographic interventions.

Selective infusion of intra-arterial vasoconstrictors was one of the first angiographic treatments for GI bleeding, which met with initial success, but multiple, late complications. The mechanism of action for vasoconstrictor infusion in the mesentery combines vasoconstriction along with contraction of the smooth muscle in the bowel wall, causing local compression [100]. The procedure consists of a selective angiogram to identify the source of bleeding and placing an infusion catheter near the site of bleeding. Vasopressin is then infused at a starting rate of 0.2 U/min and a mesenteric angiogram is repeated after 20 min to see if bleeding has stopped. If bleeding persists, vasopressin infusion is increased to 0.4 U/min. Generally, infusion rates greater than 0.6 U/min are associated with increased complications such as intestinal and cardiac ischemia. If control of bleeding is successful, the mesenteric intra-arterial infusion of vasopressin is continued for 12–36 h. The infusion is then slowly tapered off over the next 24–36 h, looking for clinical signs of rebleeding. Gomes and others have reported success rates at controlling bleeding with intra-arterial vasoconstrictors approaching 52–100%, but rebleeding rates of greater than 50% are often reported when the infusion is discontinued [90, 101]. For this reason, vasoconstrictor infusion is rarely used in clinical practice.

With a dual blood supply from the celiac and superior mesenteric arteries, the upper GI tract can tolerate embolization treatment with less risk of intestinal ischemia compared with the lower GI counterparts [102]. For this reason, transcatheter embolization therapy has quickly become a safe and effective treatment for many cases of bleeding peptic ulcer disease. The role of transcatheter

embolization is to selectively reduce blood supply to the source of bleeding while maintaining enough collateral blood flow to maintain viability. With new advances in hydrophilic, steerable wires and microcatheters, superselection and embolization in short segments of visceral arteries can now be performed. Coaxial systems allow 2–3 Fr catheters to pass through previous larger catheters to allow access to distal branch arteries. Presumably, submucosal collateral blood supply to short segments of bowel prevents most ischemic complications after embolization [103]. Series by Lang in 1992 and Schenker et al. in 2001 showed that transcatheter embolization with microcatheters was beneficial and safe when applied to the upper GI system [104, 105]. Lang reported that terminal vessel embolization provided more effective long-term control of bleeding in the duodenum with only mildly increased risk of late duodenal stenosis [104]. Since the introduction of microcatheter systems, use of angiographic embolization to successfully treat peptic ulcer disease has increased. Along with the improvements in microcatheter systems, development of new embolization agents has likewise increased. Many embolization agents have been used successfully including particulate embolization such as polyvinyl alcohol particles or autologous clot, coil embolization, Gelfoam embolization, glue embolization such as *N*-butyl 2-cyanoacrylate, balloon embolization with detachable balloons, or sclerosant embolization such as ethanol or polidocanol. Lang et al. favored e-aminocaproic acid-induced autologous clot when occluding the proximal gastroduodenal artery, while Funaki favored microcoils because of their ease of deployment and better visualization under fluoroscopy [103]. Schenker et al. found that none of the procedural variables, including the type of embolization, had a significant impact on clinical success [105]. However, Aina et al. concluded that the use of coil embolization as a single therapy for NUGB was associated with a higher risk of early rebleeding [96]. Although results have varied, the combination of coils and embolic particles (“sandwiches”) has gained favor in controlling bleeding compared with single therapy [96, 102]. Absolute alcohol, autologous clot, and Gelfoam powder have been used as embolic agents, but are less favored because of their distal occlusive properties and increased ischemia risks. Further investigation is needed to determine the optimal size of embolic agents for each clinical application.

Theoretically, embolization reduces perfusion to the site of bleeding and the reduced blood flow promotes clot formation. With ongoing coagulopathy, Aina et al. and Schenker et al. have both shown adverse outcomes supporting the theory that native thrombus formation is imperative for success with transcatheter embolization [96, 105]. The upper GI tract contains a rich collateral blood supply that often requires embolization of multiple arteries for successful outcomes. Careful angiographic assessment of the collateral pathways prior to embolization is essential in patients with severe atherosclerotic occlusive disease or previous extensive upper GI surgery. In general, bleeding in the esophagus and fundus of the stomach is treated by embolization of the left gastric artery. Bleeding in the body and antrum of the stomach may be controlled by embolization of either the gastroepiploic, right gastric, or gastroduodenal (GDA) arteries depending on the source of bleeding. If the bleeding is from a duodenal ulcer, the GDA needs to be catheterized and embolized.

The GDA has a dual supply from both the hepatic artery and the SMA. Back pressure may allow continued bleeding if embolization is performed proximally. As such the embolization needs to take place both distal and proximal to the injury site using the so-called sandwich technique. This problem is also encountered when the bleeding involves the pancreaticoduodenal arcade in duodenal ulcers. The pancreaticoduodenal arcade is composed of the superior pancreaticoduodenal (celiac artery axis) and the inferior pancreaticoduodenal (SMA axis) arteries, which may each give off anterior and posterior branches to the pancreas and duodenum. Bleeding from this arcade should be treated by embolizing the arteries both proximal and distal to the lesion. Superselective angiography with 3 Fr catheters allows visualization of the pancreaticoduodenal arcade via the celiac and superior mesenteric arteries with treatment of multiple vessels supplying the bleeding focus.

Transcatheter embolization remains a safe adjunct to endoscopy in the control of peptic ulcer bleeding. These methods are associated with a control rate of initial bleeding of 89–98% and clinical success rates of 52–90% with most reports showing clinical successes of 70–80% [97, 99, 106]. Carreira et al. reported a large series over 10 years utilizing transcatheter embolization and showed a procedural success rate of 89% and clinical success rate of 80% [107]. Gomes et al. had previously compared vasopressin infusion to embolization techniques and found the primary success rate with embolization therapy to be 71% and secondary success rate 88% compared with the primary success rate of 52% with vasoconstrictor infusion [101]. While angiographic control of bleeding is achieved in a vast majority of patients, less than 10% will develop recurrent bleeding. Often these patients are amenable to angiographic reintervention. Schenker et al. and Carreira et al. report similar complication rates of approximately 10% in their 10-year experience [105, 107]. More than half of these complications were considered minor with the major complications consisting of coil migration, renal impairment secondary to contrast nephrotoxicity, bowel or hepatic ischemia, arterial dissection or bleeding, and contrast reactions. Intestinal ischemia was usually transient, requiring surgical intervention in less than 1%. While the overall mortality of all patients with NUGB remains 6–10%, the mortality rate for patients that require transcatheter embolization is 10–40%. Walsh et al. found a 17% overall mortality after successful angiographic embolization, which was significantly higher (62%) if embolization failed to control the bleeding [108]. Schenker et al. identified no technical factors, such as which arteries were embolized or the type of embolization material used, that impacted on mortality [105]. Clinical factors that predicted poor outcomes were multi-organ failure, cirrhosis, bleeding dyscrasia, older age, cancer, and the recurrence of bleeding [105].

In most institutions, radiologic intervention is reserved for patients in whom endoscopic therapy has failed, especially if such patients are high-risk surgical candidates. A retrospective analysis showed no significant difference between embolization therapy and surgery in the incidence of recurrent bleeding (29 and 23.1%, respectively), the need for additional surgery (16.1 and 30.8%), and mortality (25.8 and 20.5%), despite a more advanced age and higher prevalence of heart disease in the group receiving embolization therapy [109]. Although radiologic

embolization may not always be a permanent cure, it may allow for the stabilization of the patient's condition until more definitive therapy is performed, depending on available expertise [110].

Surgical Therapy

Because of a new understanding of peptic ulcer disease, the role of surgery has changed markedly within the past two decades and now obviates the need for routine early surgical consultation in all patients presenting with acute upper gastrointestinal hemorrhage. The drop in surgical rates to 6.5–7.5% of all bleeding peptic ulcer cases has been suggested by meta-analyses and national registry data, whereas epidemiologic studies have suggested an increase in the population-based annual incidence of emergency surgery from 5.2 to 7.0 operations per 100,000 population between 1987 and 1999 [13, 50, 111]. The aim of emergency surgery is no longer to cure the disease but rather to stop the hemorrhage when endoscopic therapy is unavailable or has failed.

Surgery remains an effective and safe approach for treating selected patients with uncontrolled bleeding or patients who may not tolerate recurrent or worsening bleeding [112]. There are data to suggest that patient characteristics such as advanced age (>60 years) and the presence of significant comorbid disease predict a better outcome with early surgery [113, 114]. Such patients are not capable of sustaining prolonged hypotension and the episodic anemia related to delayed surgical therapy. With early operation, these more tenuous patients may avoid the morbidity of a delay in definitive therapy. Uncontrolled bleeding may be defined as those patients in whom hemodynamic stabilization cannot be achieved through intravascular volume replacement using crystalloid fluids and greater than 6 units of packed red blood cells. For most patients with evidence of persistent ulcer bleeding or rebleeding, a second attempt at endoscopic hemostasis is often effective, may result in fewer complications than surgery, and is the recommended approach [13, 115]. Exceptions may include patients with ulcers that are more than 2 cm in diameter and those who have hypotension associated with a rebleeding episode, since such patients may be at increased risk for the failure of repeat endoscopic hemostasis [42, 115].

The goals of surgery in bleeding PUD are twofold. First, the bleeding site must be controlled. Second, a procedure to prevent ulcer recurrence should be performed. In general, direct suturing of the ulcer or bleeding site can control bleeding. When ulcer bleeding is from a gastric ulcer, the ulcer should be resected, if possible. Resection of the ulcer achieves the desired hemostasis and provides tissue for histology to rule out the presence of gastric cancer. Small gastric ulcers (<2 cm) can usually be excised easily and safely, with the addition of an ulcer operation for patients who are acid hypersecretors. Large gastric ulcers, lesser curvature ulcers, bleeding ulcers associated with gastritis, and gastric ulcers that penetrate into the pancreas often require a more radical and technically demanding operation (subtotal, 75% resection, or near-total, 95% resection, gastrectomy) to control hemorrhage. When

the ulcer is located high on the lesser curve of the stomach and near the gastroesophageal junction, resection may be difficult, and direct suture ligature of the ulcer base may be necessary. In this case, a biopsy of this high-lying ulcer should be performed to rule out cancer. For bleeding duodenal ulcers, a Kocher maneuver provides access to the duodenum. Through a duodenotomy, the bleeding vessel at the base of the ulcer can be ligated. When bleeding is in the duodenum, special care should be taken to avoid the common bile duct, which passes behind the first and second portions of the duodenum.

Once surgical hemostasis is achieved, attention is shifted to the antiulcer procedure. With the discovery of the relation between infection with *H. pylori* and PUD, there has been debate as to whether a definitive antiulcer procedure should be performed during the initial operation. Available, but dated, literature suggests that when an antiulcer procedure is performed in addition to oversewing the ulcer, there is a lesser rate of recurrent bleeding with similar rates of postoperative complication and mortality in comparison with oversewing the ulcer alone [116, 117]. These studies, which were performed before the importance of *H. pylori* was understood, are flawed because they do not address the effect of *H. pylori* eradication on bleeding recurrence after surgery and whether successful eradication of *H. pylori* would prevent the need for an antiulcer procedure. It is our practice to reserve definitive ulcer operation for those patients who have peptic ulcer disease refractory to medical management or are on chronic NSAID therapy. Patients who are *H. pylori* positive and have not received triple therapy prior to bleeding should undergo ligation of the bleeder only, with postoperative *H. pylori* eradication therapy, in lieu of a definitive ulcer operation.

There are several options available to reduce gastric acidity, including truncal vagotomy and pyloroplasty, highly selective vagotomy, and truncal vagotomy and antrectomy. The option of vagotomy and antrectomy involves resection of the antrum and disruption of the vagal innervation of the stomach; results in attenuation of the neural and endocrine aspects of the production of gastric acid; and is associated with low rates of rebleeding during the postoperative period, with an ulcer recurrence rate of 1% [118, 119]. This therapeutic advantage is counterbalanced by the fact that vagotomy and antrectomy are time-consuming, are associated with 2% mortality, and involve the formation of a gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II), which may be prone to leakage [118]. In addition, the chronic consequences of vagotomy and antrectomy are common, and they include dumping in 2–10% of patients, marginal ulceration in 1–5% of patients, and disorders of gastric motility [118, 120]. Vagotomy and pyloroplasty and highly selective vagotomy involve division of the vagus nerve at differing locations to decrease acid production. Vagotomy and pyloroplasty calls for division of the vagus nerve at the esophageal hiatus, while with highly selective vagotomy, the individual vagal branches to the stomach are divided along the gastric wall from 5 to 7 cm proximal to the gastroesophageal junction to within 7 cm of the pylorus. Therefore, highly selective vagotomy ablates the neural input to the acid-producing region of the stomach without denervating the antrum and without interfering with the pyloric mechanism, which obviates the need for a pyloroplasty. Truncal vagotomy and highly selective

vagotomy result in decreased basal acid output and maximal acid output by approximately 80 and 50%, respectively. Vagotomy and pyloroplasty is recommended when the surgeon is required to achieve the operative goal expeditiously, such as would be necessary in an unstable patient. When patients are hemodynamically stable and in the hands of a surgeon experienced in the procedure, highly selective vagotomy is recommended because this procedure is least disruptive to normal physiology. Of interest, laparoscopic highly selective vagotomy has been performed with encouraging early results, although the long-term outcome of these patients is unknown. Vagotomy and pyloroplasty is associated with mild postoperative side effects and usually is well tolerated. Operative mortality has been quoted at 1%, ulcer recurrence rates average 10–12%, and the incidence of dumping ranges from 1 to 10% [118, 119]. Highly selective vagotomy is associated with no mortality and with slightly higher recurrence rates of 10–15%, but it causes fewer postoperative symptoms, with the incidence of dumping less than 5% [118, 119]. Interestingly, a recent retrospective cohort analysis of 907 patients comparing vagotomy and drainage with vagotomy and resection procedures suggested equivalent outcomes [121]. No differences were observed in 30-day mortality, morbidity, or rebleeding rates between surgical groups, while having a resective procedure was a predictor of prolonged postoperative stay.

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Management of Unusual Sources of Upper GI Bleeding

Elisabeth Tracy and Janet Tuttle-Newhall

Recognizing unusual sources of upper GI bleeding is important in evaluating individual patients who present diagnostic dilemmas and in promptly managing patients with uncommon but potentially catastrophic bleeding sources. As upper GI bleeds are relatively common, the probability of encountering a patient with an unusual source of bleeding is likely at some point; therefore, understanding the diagnosis and management of these uncommon pathologic processes is essential in caring for patients with upper gastrointestinal bleeding. In this chapter, we will discuss the diagnosis and management of gastric antral vascular ectasia (GAVE), aortoduodenal fistula (ADF), arteriovenous malformation (AVM), and hemorrhagic gastritis.

GAVE: Gastric Antral Vascular Ectasia

The first unusual entity of upper gastrointestinal bleeding is gastric antral vascular ectasia (GAVE). GAVE is a rare disorder characterized by visible columns of fiery red ectatic vessels and mucosa radiating longitudinally from the pylorus toward the antrum of the stomach After the initial description of condition by Ryder et al. in 1953, early observers dubbed the condition "watermelon stomach" because the striped pattern made by the erythematous columns resembled the stripes on a watermelon, Although not common, GAVE is an important cause of upper GI bleeding, accounting for almost 4% of all non-variceal hemorrhages from an upper gastrointestinal source [1].

While the pathophysiology of GAVE remains poorly understood, the underlying chronic disease is thought to be related to its development. GAVE is often associated with systemic illness, most commonly hepatic cirrhosis and portal hypertension – which are present in 30% of GAVE patients. These patients have a mean age of 65 and are predominantly male. In non-cirrhotic patients, GAVE is most

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commonly associated with autoimmune disorders, including connective tissue disorders (62%), Raynaud's phenomenon (31%), and scleroderma (19%) [1]. Other less common conditions associated with GAVE include bone marrow transplantation, chronic renal failure, ischemic heart disease, valvular heart disease, familial Mediterranean fever, and acute myeloid leukemia. In contrast to cirrhotic patients, these non-cirrhotic patients are typically older (mean age 73) and predominantly female.

The link between cirrhosis and the development of GAVE is poorly understood. While scattered reports of the complete resolution of mucosal damage after liver transplant have supported a causal link between cirrhosis and GAVE, they have provided little insight into the mechanism [1]. Portal hypertension does not appear to cause the vascular ectasia in GAVE, and GAVE should not to be confused with portal gastropathy. Unlike portal gastropathy, a reduction of portal pressures in cirrhotic patients does not improve the process or reverse the gastric mucosal damage. Also incompletely understood is the development of GAVE in the setting of autoimmune disease. Some studies have linked GAVE to elevated levels of gastrin or prostaglandin E2, both of which have vasodilatory properties. Others have emphasized the role of mechanical stress on the development of the disorder based on increased antral area half-time on motility studies in these patients [1, 2].

A wide spectrum of initial presentations have been described for GAVE including severe acute upper GI hemorrhage and iron deficiency anemia secondary to occult blood loss. Patients may also complain of intermittent melena or hematemesis. Many are transfusion-dependant despite iron supplementation. The diagnosis of GAVE is made on endoscopy and confirmed by gastric mucosal biopsy. The classic striped "watermelon" or "tiger" pattern of erythematous mucosa is found in the antrum. Non-cirrhotic patients are more likely to have this typical pattern while cirrhotic patients may have more diffuse disease (Fig. 1). A diagnostic dilemma in cirrhotic patients is differentiating GAVE from portal hypertensive gastropathy (PHG). Making the correct diagnosis is important since GAVE will not respond to reduction in portal pressure [1, 3]. Distribution of the vascular changes may help: GAVE is typically limited to the antrum while PHG is associated with changes to the fundus and corpus, although, as noted above, cirrhotic patients with GAVE are less likely than autoimmune patients to have this typical distribution. Histologically, GAVE is characterized by mucosal vascular ectasia, fibrin thrombi, hyalinosis, and proliferation of spindle cells. Active bleeding may not be immediately apparent on endoscopy, but often occurs spontaneously after strong antral contractions. In PHG, active bleeding is obvious on endoscopy and recent bleeding is often characterized by variceal stigmata.

Management of GAVE involves [1] treating symptoms of acute or chronic bleeding and [2] preventing future bleeding. For symptomatic blood loss from GAVE, initial management includes fluid resuscitation and transfusion for acute episodes, along with iron supplementation for chronic anemia. To stop active bleeding and prevent future episodes, endoscopic ablation is the first-line therapy as well as treating underlying medical co-morbidities. When endoscopic measures fail, pharmacological therapy can be tried to reduce chronic blood loss. Several case reports

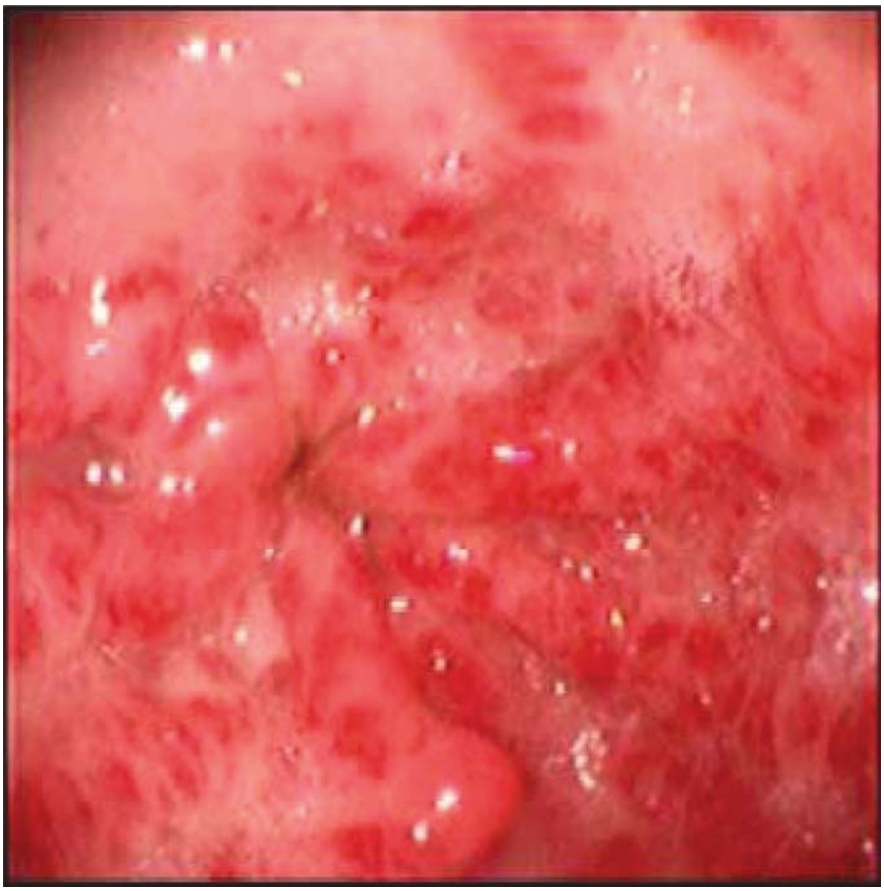

Fig. 1 Endoscopic findings of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) syndrome

have described positive results with estrogen, progesterone, transexamic acid, and chronic octreotide injections in controlling bleeding associated with GAVE [4–6]. For GAVE unresponsive to any of the above therapies, surgical resection (antrectomy) may be indicated; however, in the setting of a cirrhotic patient with portal hypertension, the mortality of an antrectomy is quite high. TIPS has been shown to reduce portal pressures but does not appear to affect transfusion requirements in GAVE [1].

Aortoenteric Fistula

An aortoenteric fistula is a direct connection between the abdominal aorta and the bowel, most commonly the retroperitoneal portion of the distal duodenum lying

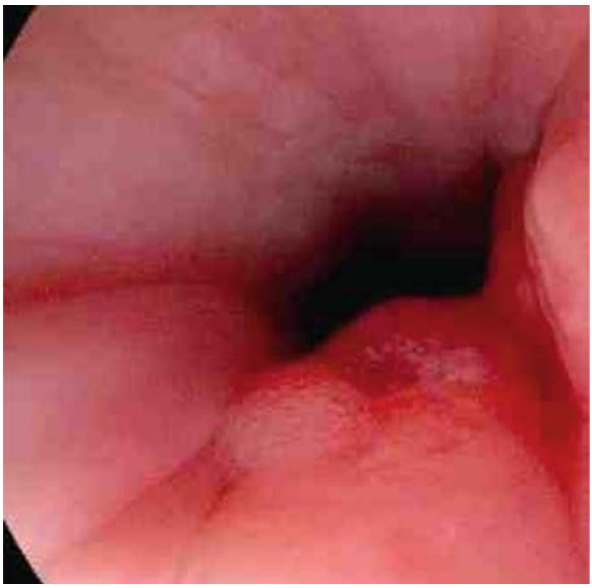

Fig. 2 Aortoesophageal fistula

anterior to the aorta. However, other sites of fistulae are possible (Fig. 2). The spontaneous development of a connection between the GI tract and the abdominal aorta is referred to as a *primary aortoenteric fistula* and is an uncommon event (0.04–0.07% incidence at autopsy) [7]. The majority of primary aortoduodenal fistulas (ADFs) are associated with existing abdominal aortic aneurysms (AAA). Inflammation and irritation of the fixed retroperitoneal portion of duodenum that lies adjacent to the expanding aneurysm may eventually result in the development of a fistula. Infectious aortitis, mycotic aneurysms, trauma, radiation, metastases, ulcers, gallstones, diverticulitis, and appendicitis can also be rare causes of primary ADFs.

In the United States, *secondary aortoduodenal* fistula is much more prevalent than primary ADF. Secondary ADF is an infrequent but feared complication of open and rarely endovascular AAA repair, with an incidence ranging from 0.6 to 1.6% after open repair (the incidence after endovascular repair is unknown but believed to be less than 0.5% from available reports) [8, 9]. Secondary ADF usually occurs at the site of the proximal anastomosis and is caused by pressure erosion from an anastomotic aneurysm, anastomotic suture line, or the vascular prosthesis itself. Although intuitively there would seem to be little risk of this complication after endovascular repair, at least 20 reports in the literature describe this complication [8]. Most of these secondary ADFs occur as a result of either device malfunction (such as stent fracture) or endo-leak. The median time from aneurysm repair to GI hemorrhage from ADF is 3 years following open repair or 16 months following endovascular repair, although bleeding may occur within days to weeks of the initial operation [9, 10].

The classic clinical triad for ADF is an upper GI bleed, abdominal pain, and pulsatile abdominal mass; however, the complete triad may be present in as few as 11% of patients with acute hemorrhage from an ADF. Clinical suspicion is essential for timely diagnosis and management [11]. Aortoduodenal fistula usually presents with an initial episode of GI bleeding (the "herald bleed") that subsides temporally but is followed in hours, days, or weeks by catastrophic hemorrhage. Patients may give a history of intermittent hematemesis or hematochezia and may report back pain or fever. The "herald bleed" most likely represents initial hemorrhage that is temporarily sealed by thrombus and bowel contracting around the fistulous tract. After the initial bleed has subsided, the risk of a subsequent exsanguinating hemorrhage is high.

Delayed or missed diagnosis of ADF carries a high mortality and morbidity. Since most delays in diagnosis occur in hemodynamically stable patients with atypical presentations, any patient with a history of AAA presenting with upper GI bleeding or significant melena should be suspected of having an ADF until proven otherwise. In an actively bleeding patient with suspected ADF, management starts with rapid assessment of hemodynamic stability. An unstable patient or the presence of massive hemorrhage in any patient requires a rapid initial assessment, placement of large-bore resuscitation lines (located with potential vascular reconstruction in mind), immediate fluid and non-typed blood resuscitation, and eventual typing and cross-matching of blood. These patients will most likely require urgent laparotomy for control of bleeding for survival. More commonly, a hemodynamically stable patient will present after one or more self-limited episodes of GI bleeding, allowing for a more comprehensive diagnostic work-up with imaging studies that can confirm the diagnosis of ADF and allow for operative planning. It is important to note that laboratory values may or may not show a low hemoglobin/hematocrit depending on the chronicity of GI bleeding. Also, a mild to moderate leukocytosis (white blood cell count $>10 \times 10^9$ per L) may result from a contaminated prosthetic graft and, potentially, bacteremia. In these patients, blood cultures should be sent and broad-spectrum coverage should be started empirically against the most common pathogens documented in these circumstances: *Escherichia coli, Staphylococcus aureus*, and *Staphylococcus epidermidis.* Although rare, fungal infections leading to secondary ADF have been reported, so initiating empiric antifungal therapy is reasonable [9, 12].

In a patient that is hemodynamically stable, the classic diagnostic study is an upper endoscopy (EGD). EGD should be carried out to the fourth portion of the duodenum. Active bleeding into the duodenum may be visualized. If not, the fistula may be detected by the presence of clot, ragged mucosa, purulent material inside the bowel, or exposed graft material. If no evidence of fistula is seen, EGD may be useful in searching for other sources of bleeding; however, it lacks the sensitivity or specificity to conclusively rule out ADF. More recent reviews in the literature have advocated for initial screening with a CT scan of the abdomen including arterial and portal phase intravenous contrast. CT is less invasive and carries less of a risk of dislodging a thrombus than EGD [9, 12]. A CT can provide both the diagnosis of ADF as well as important information on the location and nature of the

fistula. This anatomic information is essential in operative planning. Loss of a distinct aneurismal wall, obliteration of the fat plane between the aorta and duodenum, and retroperitoneal air are the radiologic signs of ADF. Detection rates with all modalities have traditionally been low. In a recent review, CT alone had a 61% detection rate for ADF compared with 25 and 26% for EGD and angiography, respectively. However, EGD detection rates are dependent on the skill and experience of the endoscopist. In studies of known ADF patients undergoing preoperative EGD, detection rates varied from under 25% to as high as 80%. While an abnormality is identified in nearly 50% of ADF patients undergoing EGD, it is non-specific and is diagnostic in only 25%. Although CT has a higher sensitivity for ADF, its specificity for the diagnosis is also low [9, 13, 14].

Angiography has less value in the diagnosis of ADF since extravasation of contrast from the aorta into the bowel lumen is rarely seen. However, angiography remains useful for the evaluation of arterial anatomy in preparation for the required intraoperative arterial reconstruction that results from removing the graft and closing the ADF (Fig. 3a, b). Given their low yield, MR, tagged white blood cell scans, and upper/lower GI series have little role in the diagnosis of ADF, especially in the acute setting. Awaiting these tests can inappropriately delay patient care without significant benefit [8, 10]. Clinical suspicion remains the key factor in timely diagnosis and management of ADF. The clinical factors most associated with poor outcomes in patients following ADF repair are delays in therapy longer than 24 h, greater number of diagnostic tests prior to operative intervention, and hypotension preoperatively [15].

Once in the operating room, the operative management for a hemodynamically unstable patient begins with prepping and draping widely, including the chest, axilla, and groins. The initial incision is a large midline incision in order to gain proximal control of the aorta. If there are too many adhesions to rapidly gain control of the supraceliac aorta, an anterolateral thoracotomy via the left chest will gain access to the supra-abdominal aorta. Once proximal control is obtained, dissection is carried to the level of the fourth portion of the duodenum. A medial visceral rotation from the right will expose both the vena cava and the aorta-duodenal junction. Once the fistula is identified, careful dissection around the aorta and involved segment of bowel can be carried out. Once distal control is obtained, the bowel defect can be closed in two layers unless the extent of the defect necessitates segmental resection with anastomosis. For primary ADF, aneurysmorraphy may be attempted, especially for a saccular or posttraumatic aneurysm. More commonly, repair involves replacement of the involved aorta with prosthetic graft after closure of the enteric defect. Extra-anatomic reconstruction may also be considered.

For secondary ADF, operative management is initially approached similar to that of a primary ADF, with control of the aorta prior to dissection of the fistula. For the subsequent repair, two approaches have been well described. The first involves removal of the infected graft with thorough debridement of aorta and perigraft structures with in situ graft replacement or, more commonly, extra-anatomic bypass. Mortality rates for this procedure range from 30 to 40% due to bleeding, sepsis, acute lung injury, and multi-organ system failure [9]. The second widely used

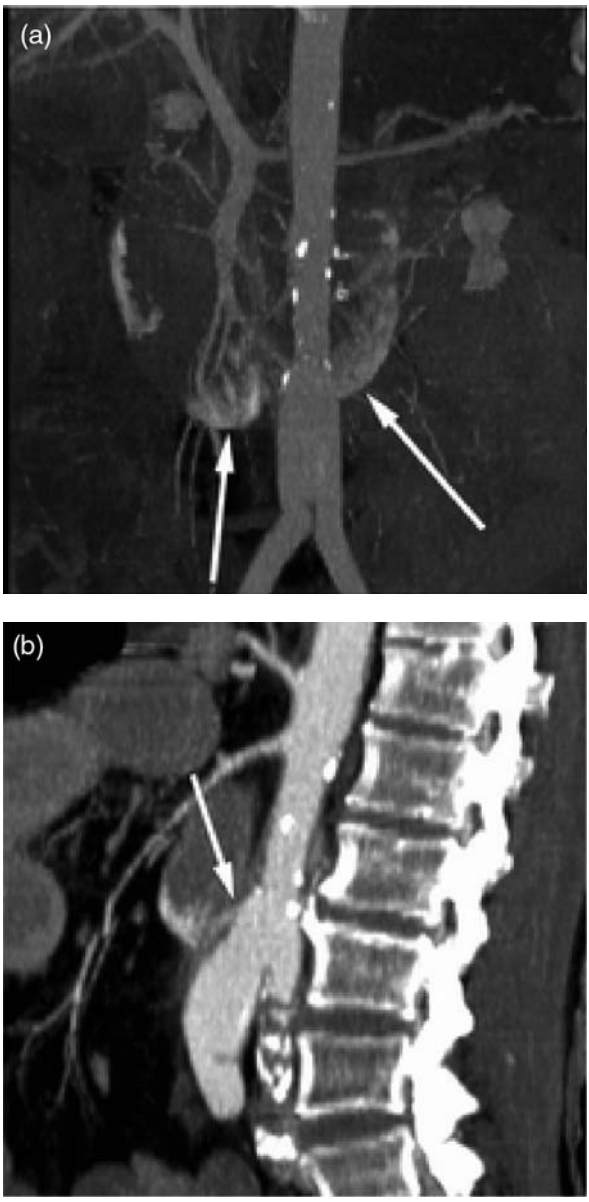

Fig. 3 Aortoduodenal fistula in a 70-year-old man 10 years after aortoiliac graft implantation: (**a**) contrast-enhanced axial CT with extravasation of contrast into duodenum; (**b**) contrast-enhanced sagittal view showing location of fistula. From Frauenfelder et al. [36]

approach involves closure of the enteric defect, complete graft removal, aortic stump closure, and extra-anatomic bypass through uninvolved tissue planes. However, this approach is associated with significant complications (including aortic stump rupture and limb loss). Even with recent advances, including wide debridement of tissue beds and staging the extra-anatomical bypass and graft excision to reduce

periods of lower body ischemia, the procedure still carries significant mortality with many series reporting rates of 40–50% [10]. In either approach, copious irrigation and separation of the new prosthesis or aortic stump from the overlying bowel by interposition of viable tissue may help reduce complications or recurrent fistula. Although some analyses have found improved outcomes with the in situ repair, other reviews have found no statistical difference in long-term outcome between the two approaches.

In patients not hemodynamically stable enough for an open repair or poor candidates due to other co-morbidities, endovascular stent grafting over the fistula site has been done with reasonable success. There are also reports of injecting the fistula tract with *N*-butyl-2-cyanoacrylate, fibrin glue, or coil remobilization of the fistula prior to placing the stent graft. The potential advantages of endovascular repair include rapid control of catastrophic hemorrhage; avoiding operating in an inflamed, hostile field [16, 17]; and avoiding the complications of a prolonged anesthetic and open abdominal procedure.

Complications after repair include graft re-infection, aortic stump blowout, and graft failure. Recurrent ADFs are rare with only scattered case reports in the literature; their outcomes are generally poor [15].

Arteriovenous Malformation

Another unusual entity, arteriovenous malformations (AVMs) of the upper GI tract are an important source of upper GI bleeding. These vascular malformations include lesions described as angiodysplasia, vascular ectasia, vascular dysplasia, and mucosal vascular abnormalities. Although most frequently associated with the colon since the first description in 1956, GI AVMs have been found throughout the GI tract, including the stomach (1.4%), duodenum (2.3%), and pancreas (0.9%) [25]. These upper GI AVMs may account for up to 5–7% of upper GI bleeding [18–21] (Fig. 4). The pathogenesis of AVMs is not well understood. Although the lesions have been found in patients of all ages, symptomatic AVMs are more often found in patients 60–80 years old. Whether these are congenital lesions exacerbated by increased intraluminal pressure over time or acquired lesions of aging as a result of a similar process is unclear [22].

The diagnosis of gastroduodenal AVMs can be made by observing the bright red, fern-like lesions on endoscopy which range in size from 1 to 7 mm. Lesions beyond the duodenal bulb are easily missed via routine endoscopy because the scope is often not advanced far enough. Determining whether an AVM visualized on endoscopy is the actual source of upper GI bleeding may be more of a challenge than finding the lesion. The classic endoscopic criteria for a bleeding AVM are (1) active bleeding from the lesion, (2) clots at the site of the lesion or in the vicinity, and (3) the absence of other potential sources [20, 21]. When blood filling the stomach or prominent mucosal folds complicates identification of the lesions, endoscopic ultrasound has been used in some series to detect abnormal submucosal blood

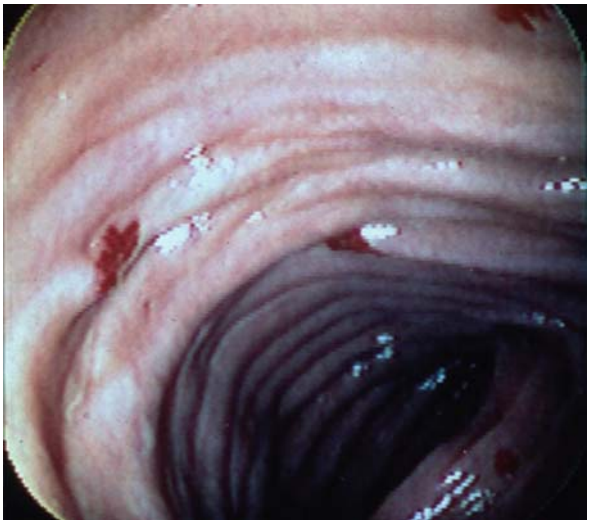

Fig. 4 Small bowel arteriovenous malformations

flow [20]. Angiography and tagged red blood cell scans have limited success in diagnosis [20].

Endoscopy is diagnostic as well as therapeutic for bleeding gastroduodenal AVMs. Electrocoagulation and laser ablation are first-line therapies that have been described and have demonstrated a significant decrease in transfusion requirements in patients with significant upper GI bleeds from AVMs. Recurrences can be managed with repeat endoscopy or hormonal therapy (estrogen–progesterone combination) Although the mechanism of hormonal therapy is not entirely clear, there is some evidence to suggest that hormonal therapy reduces frequency and intensity of bleeding episodes [9, 23, 24]. Surgical resection is rarely needed and should be reserved for treatment failures.

Pancreatic AVMs are a very rare cause of upper GI bleeding, but the bleeding they cause is often catastrophic (Fig. 5a, b). Since their first description in 1968, more than 40 cases have been reported in the literature to date, with the diagnoses increasing as imaging techniques improve. Pancreatic AVMs are either congenital or acquired, resulting from trauma or inflammation. The most frequent symptom associated with pancreatic AVMs is upper GI bleeding, which usually results from the associated portal hypertension. Abdominal pain and jaundice may also be present. Angiography has been the primary diagnostic modality, showing dilated, tortuous feeding arteries with early venous filling and early disappearance of the pancreatic stain [25]; however, non-invasive imaging including Doppler ultrasound and multi-slice CT have recently demonstrated their utility in the diagnosis of pancreatic AVMs [25–27]. The lesions are hypoechoic on ultrasound with a mosaic-like structure on color Doppler. CT findings include a conglomeration of hypervascular spots and early contrast filling of the portal vein on arterial phase.

Anatomic considerations complicate the management of pancreatic AVMs. Embolization has been successful in some reports; however, the multiple feeding

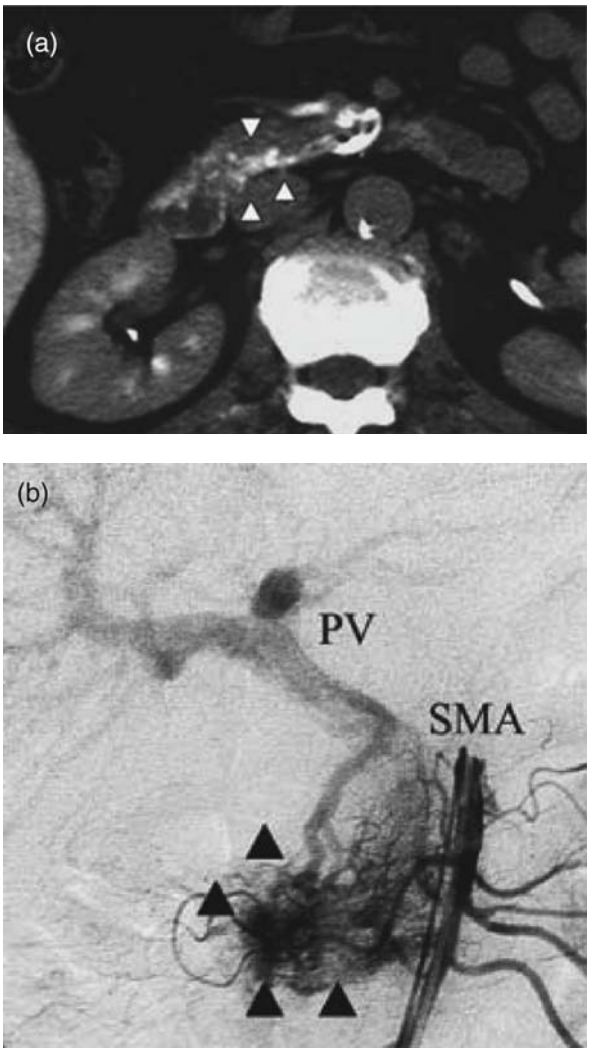

Fig. 5 (**a**) Contrast-enhanced CT of a pancreatic arteriovenous malformation showing the hypervascular lesion. (**b**) Angiography of pancreatic arteriovenous malformation shows vascular proliferation and early filling of the portal vein in the arterial phase. From Uchida et al. [27]

arteries make a complete cessation of blood flow to the AVM difficult. Recurrent bleeding has been reported in over one-third of pancreatic AVMs treated by embolization alone, necessitating repeat embolization or surgical resection [25, 28].

Hemorrhagic Gastritis

Finally, acute hemorrhagic gastritis is the classic term used to describe the superficial, diffuse lesions of the gastric mucosa associated with epithelial cell damage and

regeneration resulting in moderate to massive upper GI bleeding [29]. Acute hemorrhagic gastropathy is the more accurate histological term as the mucosal injury is usually not associated with inflammation (implying *Helicobacter pylori* infection, autoimmune disorders, or hypersensitivity reactions) although rare cases have been reported [30, 31]. Instead, acute hemorrhagic gastritis is more frequently caused by irritants which can directly damage the gastric mucosa, including NSAIDs, bile acid from bile reflux, alcohol, cancer chemotherapy, and accidentally ingested caustic substances, or by mucosal hypoxia induced by trauma, burns, sepsis, or, rarely, long-distance running [29, 32]. In many patients, acute hemorrhagic gastritis is multi-factorial with several of these predisposing gastric insults present [29]. Once compromised, the acids, proteases, and bile acids penetrate the lamina propria causing vascular injury and release of inflammatory mediators.

Recognizing the risk factors in the patient's history and awareness of any recent physiologic stress may lead to the diagnosis of acute hemorrhagic gastritis quickly. Trauma, burn, and severely ill patients in intensive care units are at increased risk for this condition, although recent emphasis on stress ulcer prevention may help decrease the incidence of acute hemorrhagic gastritis among critically ill patients. Bleeding from hemorrhagic gastritis starts suddenly and without other symptoms, although nausea, vomiting, and abdominal pain may develop. The diagnostic modality of choice for acute hemorrhagic gastritis is upper endoscopy, which reveals multiple petechial hemorrhages and small erosions. In acute hemorrhagic gastritis induced by physiologic stress, lesions are often concentrated in the fundus and near the GE junction, while in cases associated with alcohol or NSAID use, they are more widespread [29].

Any discussion of the management of acute hemorrhagic gastritis begins with prevention. In all high-risk patients, including critically ill patients and those on chronic NSAID therapy, prophylactic acid blocking therapy should be given [29, 33–35]. In the severely ill population, aggressive treatment of the underlying disease is crucial in preventing and managing acute hemorrhagic gastritis. Multiple studies have suggested that risk of bleeding from mucosal damage is proportional to the acuity of the underlying illness. Patient prognosis is also more closely associated with disease progression or regression than degree of mucosal injury [29]. Once acute hemorrhagic gastritis has developed, the principles of management are to discontinue any offending agent (NSAIDs, alcohol, etc.), aggressively treat underlying medical problems, correct any coagulation abnormalities, and neutralize gastric acid (with H_2-blocker or proton pump inhibitor therapy). Aggressive medical management leads to improvement in 80% of patients [29].

Patients with massive or persistent hemorrhage can be managed endoscopically with electrocoagulation, laser, or use of sclerosing agents. Arteriography with embolization may be required if endoscopy fails. For most causes of acute hemorrhagic gastritis, surgery is reserved for patients with severe, persistent hemorrhage or perforation and is associated with a high mortality. Although there are no prospective data on the operation of choice for acute hemorrhagic gastritis, vagotomy/pyloroplasty/oversewing areas of bleeding have a higher rate of rebleeding than gastric resection with vagotomy. For patients with bile reflux with a history of

surgically altered anatomy, surgical intervention (typically a Roux-en-Y revision) may be necessary for definitive treatment [29, 31].

Summary

Gastric antral vascular ectasia, aortoduodenal fistula, arteriovenous malformation, and hemorrhagic gastritis are unusual but important causes of upper GI bleeding. Although their incidence is relatively low compared to bleeding peptic ulcers and esophageal varices, these conditions may require quick recognition and intervention, as in the case of ADF, or may be difficult to distinguish from other sources of bleeding. Those caring for patients with an acute GI bleed should be aware of the classic presentation, endoscopic and imaging findings, and management of these conditions and should include unusual sources of GI bleeding on their differential diagnoses.

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Mallory–Weiss Syndrome

Jacob N. Schroder and Malcolm S. Branch

Introduction

Mallory and Weiss first described gastroesophageal tears causing gastrointestinal bleeding in 15 alcoholic patients in 1929 [1]. Since this time, longitudinal mucosal lacerations, associated with forceful retching, has become a well-known cause of upper gastrointestinal bleeding. The prevalence of Mallory–Weiss Syndrome is reported to be approximately 5% of patients suffering acute upper gastrointestinal bleeding, but may be higher [2–4]. The presence of Mallory–Weiss tears without acute bleeding is difficult to quantify and their clinical significance is debatable.

Etiology and Pathogenesis

The pathogenesis of Mallory–Weiss tears is not completely understood, but it is thought that they are most likely caused by a sudden increase in intra-abdominal pressure. This is most likely secondary to forceful emesis, but can be due to straining, lifting, or blunt abdominal trauma. Additionally, Mallory–Weiss tears can be iatrogenic, due to esophageal instrumentation, such as nasogastric tube placement or upper endoscopy, or polyethylene glycol administration. Despite frequent interventions, iatrogenic causes of Mallory–Weiss tears are infrequent [5–7]. Bleeding from Mallory–Weiss tears occurs when the laceration involves either the esophageal arterial or the venous plexus. Most frequently, the tears are single, but may be multiple in up to one-quarter of patients [8, 9].

Alcoholism and hiatal hernias are the two main risk factors identified for the development of Mallory–Weiss tears. Heavy alcohol use associated with emesis has been noted in up to 80% of Mallory–Weiss syndrome [8–10]. Similarly, hiatal hernia is found in almost all patients with bleeding. It has been proposed that a

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higher pressure gradient develops in the intra-thoracic portion of the stomach and G–E junction, thus increasing acute distension and mucosal tears. Although age has been postulated as a risk factor for development of Mallory–Weiss tears, the majority occur in patients in their forties and fifties. It does appear that age may be a predisposing factor for iatrogenic tears after endoscopy, likely due to atrophic mucosa [6].

Presentation

The majority of patients present with hematemesis often associated with epigastric, chest, or back pain. Classically, patients will give a history of antecedent non-bloody emesis or retching but a significant minority will give a history of bleeding with the initial emesis [10]. In the majority of cases, bleeding is self-limited, but life-threatening hemorrhage requiring blood transfusion, hemodynamic support, and endoscopic or operative intervention may be required. A 1997 study identified active bleeding at the time of endoscopy as a risk factor for higher transfusion rate and portal hypertension or coagulopathy as a risk for re-bleeding [11].

Diagnosis

Early endoscopy is the diagnostic modality of choice with Mallory–Weiss tears. Endoscopy is diagnostic and can rule out other causes of upper gastrointestinal bleeding, such as varices, esophageal lesions, esophagitis, or ulcers. Additionally, endoscopy can be therapeutic. Most lesions will heal within 48 h, so delayed esophagoscopy may not be diagnostic. Endoscopically, Mallory–Weiss tears appear as longitudinal lacerations through the mucosa, occasionally exposing the muscular layer of the esophagus (Fig. 1). These tears can be non-bleeding, actively bleeding, or covered in clotted blood.

Treatment

Although up to 70% of patients with Mallory–Weiss syndrome ultimately require blood transfusion, the majority of lacerations heal spontaneously [11]. As with any GIB patient, large-bore intervenous access should be obtained and adequate intervenous fluid resuscitation should be instituted. Coagulopathy should be reversed, with vitamin K or fresh frozen plasma as indicated. Patients should be closely monitored for hemodynamic changes. Most patients are started on proton pump inhibitors, although their effectiveness for Mallory–Weiss tears is doubtful. Additionally, patients should be put on bowel rest during their initial observation.

Early endoscopy is critical in the diagnosis and treatment of patients with Mallory–Weiss tears [12]. If, on endoscopy, active bleeding is not observed, no endoscopic therapy is indicated and the patient should be observed for re-bleeding for 48 h. If bleeding is observed, endoscopic therapy (such as injections, electrocautery, or clipping) is the first-line treatment of patients with on-going bleeding

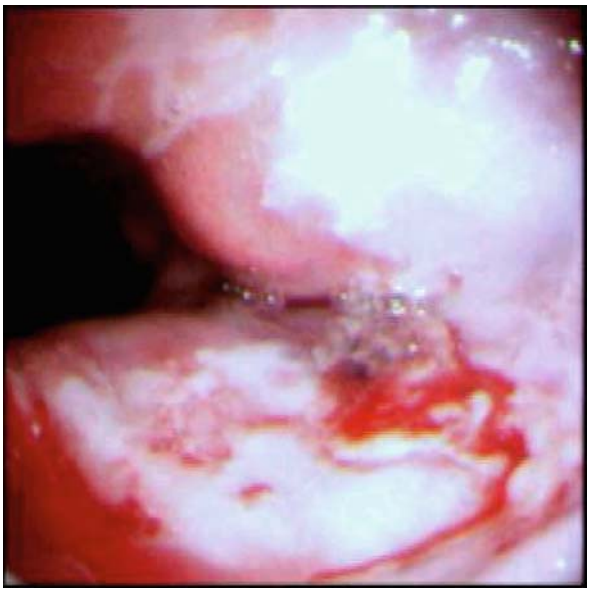

Fig. 1 Endoscopic image of Mallory–Weiss tear

from Mallory–Weiss tears. Injection of epinephrine, ethanol, or other sclerosing agents is the most commonly used treatment (Fig. 2). Epinephrine (1:10,000) with or without an additional sclerosing agent (such as polidocanol) appears to be very effective with an approximately 5% re-bleeding rate [13, 14]. Thermal coagulation

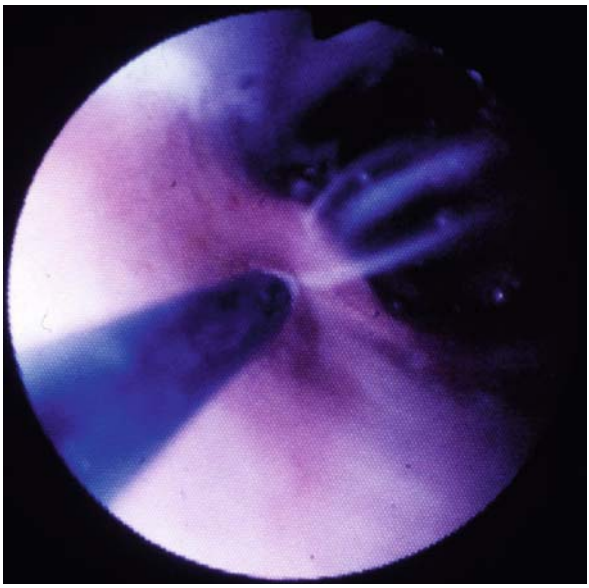

Fig. 2 Injection of epinephrine via needle catheter in esophagus

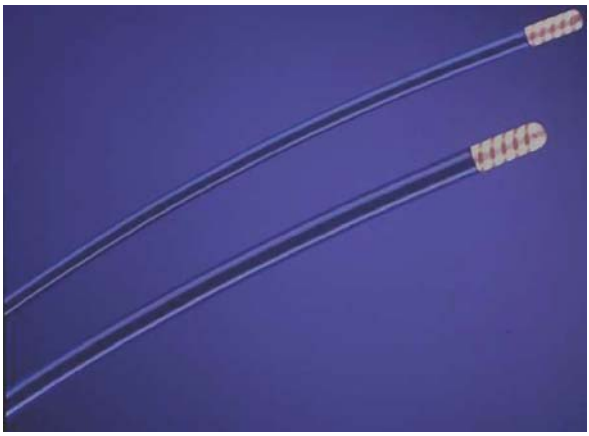

Fig. 3 Multipolar electrocautery catheter (Bicap)

with either bipolar or multipolar electrocautery (Fig. 3) has also been described [15]. Although this treatment modality may be used, caution must be exhibited. The technique of electrocoagulation is similar to that used for bleeding ulcers but usually less tamponade force and lower total energy because of the smaller size area and to avoid perforation (e.g., bipolar probe at 15–18 W, short pulse such as one second and moderate tamponade force often laterally with a stiff probe). Electrocautery should be avoided in patients with portal hypertension and esophageal varices, as this may worsen bleeding and may be life threatening. Additionally, because the esophagus lacks a serosal layer, coagulation may cause full thickness injury and perforation and should be used judiciously. Electrocautery is best indicated in small, limited lesions, where minimal electrocautery can be used.

Multiple small trials have reported excellent results with the application of hemoclips (Figs. 4a, 4b) to Mallory–Weiss tears [16–18]. These studies reported excellent hemostasis and minimal to no re-bleeding. Despite this, a recent meta-analysis of endoscopic clipping for acute non-variceal upper gastrointestinal bleeding reported that clipping alone was not superior to other endoscopic modalities [19]. These results may be slightly skewed due to the fact this analysis contained a majority of patients with lesions other than Mallory–Weiss tears. Variceal banding has been reported for treatment of Mallory–Weiss tears with good results for these patients [18]. Just as with treatment of bleeding ulcers, multiple endoscopic therapeutic techniques have been shown to be effective and the technique used should probably be dependent upon the experience and comfort level of the endoscopist.

Re-bleeding is treated with repeat endoscopic treatment. Patients with refractory bleeding can be treated with angiographic embolization, balloon tamponade, or intervenous infusion of vasopressin. Very rarely, patients with refractory bleeding will require surgical intervention. This usually consists of creating a longitudinal esophagotomy and over-sewing the bleeding vessels. With the improvement of endoscopic therapies, surgery is the last line therapy and is required in a very small

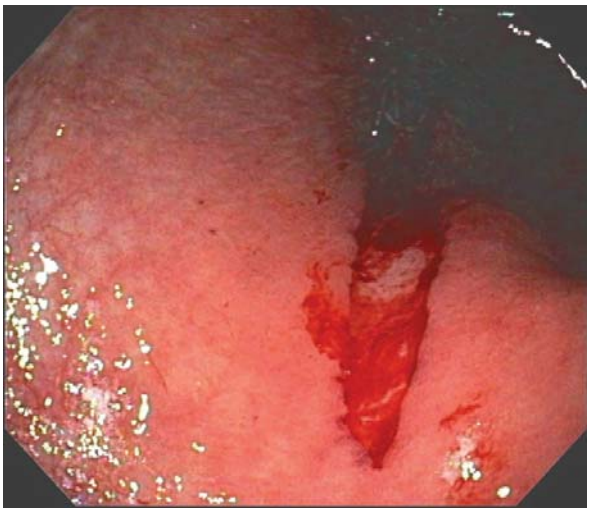

Fig. 4a Mallory–Weiss tear in patient with acute bleeding

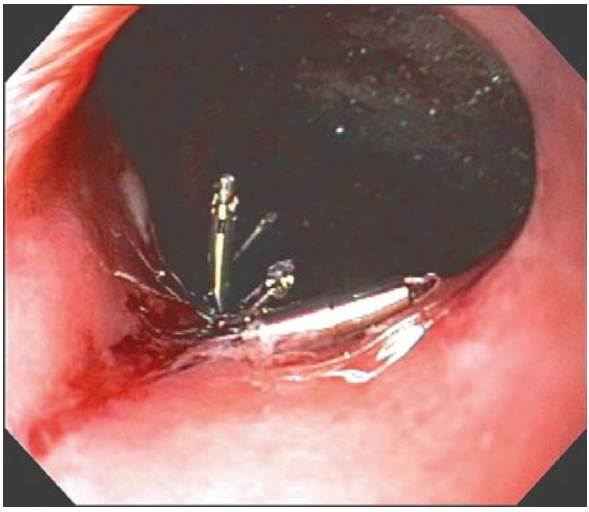

Fig. 4b Multiple endoclips applied to Mallory–Weiss tear

percentage of patients. After successful intervention, the patient should be observed for bleeding for at least 48 h.

Conclusion

Mallory–Weiss syndrome is characterized by bleeding esophageal lacerations most commonly caused by forceful retching. Although up to 70% of patients received

blood transfusions, the majority of bleeding is self-limited and requires no intervention. Early endoscopy is the diagnostic and therapeutic modality of choice. If no bleeding is visualized, the patient can be observed for 48 h. If the laceration is actively bleeding, endoscopic therapies, such as sclerotherapy, electrocautery, or clipping, are highly effective with a re-bleeding rate of approximately 5%.

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Management of Bleeding Small Bowel Tumors

Keri E. Lunsford and Aurora D. Pryor

Introduction

Identification and management of gastrointestinal bleeding originating from the small intestine represents a diagnostic and therapeutic challenge to clinicians. During evaluation of the source of gastrointestinal blood loss, colonoscopy and esophagogastroduodenoscopy (EGD) fail to identify the source of bleeding in approximately 5% of patients. Blood loss stems from small bowel sources in approximately 75% of these patients with obscure GI bleeding (reviewed in [1]). Despite the relative infrequency of small bowel bleeding, understanding and diagnosis of bleeding originating in the small bowel is important. Overall, patients with bleeding originating in their small bowel require more radiologic and endoscopic procedures for diagnosis, a greater number of blood transfusions, and a significantly greater cost for hospital admission than patients with either gastric or colonic bleeding [2].

The diagnostic difficulty of bleeding small bowel lesions stems from the length of the small bowel, its intraperitoneal location, and the variety and nature of lesions affecting the small bowel (Table 1). Vascular lesions are the most common cause of small intestinal bleeding, accounting for 70–80% of cases [3]. Of these, angiodysplasias are most common. Angioectasias, or abnormal thin-walled blood vessels with little to no endothelial lining, occur mostly in older patients (>40 years of age). These lesions are thought to account for 30–60% of cases of small bowel bleeding [4]. Although less common than vascular lesions, tumors of the small bowel, both benign and malignant, represent the second most common cause of GI bleeding originating in the small bowel. Bleeding may also originate from mucosal ulceration of idiopathic origin, secondary to effects of medications such as NSAIDs or secondary to radiation enteritis. Infection of the small bowel with organisms such as tuberculosis and intestinal parasites may also precipitate small bowel bleeding. Finally, conditions such as endometriosis and inflammatory conditions such as IBD

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Table 1 Sources of small bowel bleeding

Vascular lesions	Arteriovenous malformation (AVM) Venous ectasia Angiodysplasia Telangiectasia Varices Dieulafoy's lesion Arterial aneurysm Aortoenteric fistula
Mucosal/structural abnormalities	Mucosal ulcerations (idiopathic, NSAIDs) Meckel's diverticulum Radiation enteritis Diverticulosis Infections (tuberculosis, intestinal parasites) Endometriosis Crohn's disease Celiac sprue
Benign small bowel tumors	Adenoma Lipoma Neurofibroma Brunner's gland hamartoma Hemangioma Cowden disease Ganglioneuromas Schwannomas Nodular lymphoid hyperplasia
Malignant small bowel tumors	Adenocarcinoma Lymphoma Leiomyosarcoma (GIST) Carcinoid
Metastatic small bowel tumors	Melanoma Karposi's sarcoma Lung carcinoma Breast carcinoma Renal cell carcinoma

and celiac sprue may result in bleeding small bowel lesions [5]. The variety of lesions which may cause small bowel bleeding are outlined in Table 1.

The aim of the present chapter is to examine bleeding small bowel tumors. The diagnostic and management approach for the patient with bleeding small bowel tumors will be explored. In addition, a brief review of the types and occurrence of bleeding small bowel tumors with emphasis on the therapeutic approach to each tumor type will be performed.

Epidemiology of Bleeding Small Bowel Tumors

Small bowel tumors represent a small but important source of GI blood loss and are the second most frequent source of obscure GI bleeding. Both benign and

malignant neoplasms of the small bowel have potential for causing GI blood loss; however, malignant lesions of the small bowel are far more likely to be symptomatic and to require surgery. Malignant tumors originating in the small bowel as well as metastatic tumors to the small bowel represent less than 2% of all GI tumors. In contrast to the high frequency of malignancy seen with colonic neoplasms, approximately 75% of small bowel tumors are benign [6], with pathology including adenomas, hamartomas, hemangiomas, and lipomas.

Small bowel neoplasms account for 2–5% of all gastrointestinal malignancy with an overall incidence of 16.8 in 1,000,000 and a prevalence of 0.6% [7, 8]. Of the estimated 1.44 million new cancer cases per annum in the United States, small bowel tumors only account for 5,640 and are estimated to be responsible for 1,090 deaths each year [9]. However, the overall incidence of small bowel cancers has been increasing in recent years, while in comparison, the incidence of both gastric and colorectal cancers is declining [7].

Epidemiologically, small bowel tumors are slightly more common in men than women and in whites than blacks [8]. Geographically, the incidence for small bowel tumors is greatest in North America and western Europe [7]. Tumors are the most common cause of small bowel bleeding in patients younger than 50 years of age, in comparison to other causes of small bowel bleeding such as vascular lesions [1]. However, more than 90% of small bowel malignancies in men and 95% of small bowel malignancies in women occur after the age of 40 [8]. Thus, small bowel tumors must be considered as a possible source of blood loss in patients at any age.

The cause of the relative infrequency of small bowel tumors is unknown. However, several theories have been postulated for the decreased susceptibility of patients to small bowel tumors in comparison to tumors elsewhere in the GI system. (1) The liquid contents transiting through the small bowel cause less mucosal irritation compared to the more solid contents of the large bowel. (2) Rapid transit of contents through the small bowel may result in decreased exposure time of carcinogenic agents to the small bowel mucosa. (3) The small bowel harbors lower bacterial populations in comparison to the large intestines, resulting in decreased bile acid conversion into carcinogens. (4) Small intestinal enterocytes have a rapid turnover, which decreases the potential time for neoplastic transformations. (5) IgA secreted by gut-associated lymphoid tissue (GALT) is present in higher concentrations in the small intestines compared to other areas of the GI tract, allowing for increased immune surveillance. Finally, (6) the large volume of gastric and intestinal secretions allows for dilution of potential carcinogens (reviewed in [6]).

Approach to Patients with Bleeding Small Bowel Neoplasms

Patients with bleeding originating for small intestinal neoplasms may present with a variety of occult or rapid bleeding complaints including iron deficiency anemia, melena, hematemesis (in the case of more proximal small bowel tumors), intermittent dark red or purple hematochezia. Included in the differential work-up for

small bowel neoplasms are more common causes of abdominal pain and bleeding including peptic ulcer disease, irritable bowel syndrome, diverticular disease, endometriosis, as well as colon and gastric cancers. Thus, the diagnosis of a small bowel tumor is often a diagnosis of exclusion after upper gastrointestinal and colonic sources of bleeding have been excluded via endoscopy/colonoscopy. In addition, the diagnosis of a small bowel neoplasm may be delayed due to the insidious and nonspecific nature of symptoms. Small intestinal bleeding is more difficult to localize due to the length and loops of small intestines.

As with any complaint, the work-up of a patient with obscure gastrointestinal blood loss not localized to the stomach or large intestines should begin with a thorough history and physical examination. Patients with small bowel tumors may have history of intermittent obstructive symptoms. History of abdominal pain and weight loss are more common with malignant tumors than other potential causes of small intestinal bleeding. Jaundice in association with melena is suggestive of duodenal and ampullary adenocarcinomas. A history of flushing and diarrhea may suggest carcinoid syndrome in association with carcinoid tumors; however, only 20% of patients with carcinoid tumors in the small intestines exhibit carcinoid syndrome [10]. Fever, diarrhea, and weight loss are common concomitant symptoms with lymphoma [6]. History of primary cancers at extra-intestinal locations, such as breast cancer, lung caner, or melanoma, may be suggestive of secondary metastatic disease to the small bowel. Finally, several medical conditions are associated with particular small bowel tumors (Table 2). History of these conditions may give clue to a small bowel neoplasm as the source of GI bleeding.

The usual work-up for bleeding from gastrointestinal sources will often begin with esophagogastroduodenoscopy (EGD) and colonoscopy. In the case of bleeding from small bowel neoplasms, these tests will often be insensitive unless the source of bleeding is in the proximal duodenum. Negative EGD and colonoscopy should first be repeated to ensure that a bleeding lesion was not missed upon initial evaluation; however, the majority of bleeding not identified by these studies localizes to the small bowel. In these cases, a variety of radiologic and endoscopic techniques are available to further diagnose, evaluate, and characterize bleeding small intestinal lesions. These techniques are reviewed in further detail in other chapters in this book; however, their specific utility for the evaluation of bleeding from the small bowel is reviewed here.

Low-Yield Tools

Small bowel plain films. These are the most widely used studies for small intestine disease and generally include both flat and upright views of the abdomen. Evidence of dilated small bowel loops and the presence of air–fluid levels may suggest an area of obstruction secondary to a tumor. The presence of free air on upright views suggests perforation of a hollow viscous. In addition, a neoplasm may rarely be evident as calcified mass on plain film. Plain films are extremely low yield and

Table 2 Small bowel neoplasms and associated conditions

Small bowel neoplasm	Associated condition	Other manifestations
Adenoma, adenocarcinoma	Familial adenomatous polyposis (FAP)	Polyposis of the colon
	Gardner's syndrome	Multiple colon adenomas, osteomas, thyroid cancer, epidermoid cysts, fibromas, sebaceous cysts, desmoid tumors
GIST	Neurofibromatosis type I (Von Recklinghausen disease)	Café-au-lait spots, axillary or inguinal freckles, cutaneous and subcutaneous neurofibromas, optic nerve tumors, long bone tumors, scoliosis
Hemangioma	Blue rubber bleb syndrome	Cavernous hemangiomas of the skin and GI tract, and other viscera
	Maffucci syndrome	Enchondromas subcutaneous cavernous hemangiomas
	Klippel–Trénaunay–Weber syndrome	Limb hypertrophy, cutaneous hemangiomas, and varicosities
	Peutz–Jeghers syndrome	Benign hamartomatous polyps in the GI tract, hyperpigmented lesions of the mouth, hands, and feet
Nodular lymphoid hyperplasia	IgA deficiency	Recurrent sinopulmonary infections, diarrhea, allergies, autoimmune disorders
Adenocarcinoma	Crohn's disease	Strictures, fistulae, and inflammation of the GI tract, skin rashes, arthritis, and uveitis
Lymphoma, adenocarcinoma	Celiac sprue	Diarrhea, abdominal pain, weight loss, anemia, autoimmune disorders, dermatitis, osteoporosis, type I diabetes
Adenocarcinoma	Cystic fibrosis	Recurrent respiratory infections, diarrhea, pancreatic insufficiency
Adenocarcinoma	Peptic ulcer disease	Gastric ulcers
Kaposi sarcoma	AIDS	Opportunistic infections
Carcinoid tumor	Carcinoid syndrome	Flushing, diarrhea, facial lesions, asthma
Lymphoma	Immunosuppression	
Lymphoma	EBV infection	
Lymphoma	*Helicobacter pylori* infection	

nonspecific in the evaluation of small intestinal neoplasms and are in general not recommended unless evaluating obstructive or peritoneal complaints.

Small bowel follow-through (SBFT). Similar to plain films, SBFT is relatively inexpensive and noninvasive. Contrast tracking through the small bowel may demonstrate the presence of strictures, large masses, large polyps, tumors, and deep ulcerations; however, smaller ulcerations and tumors are more difficult to identify

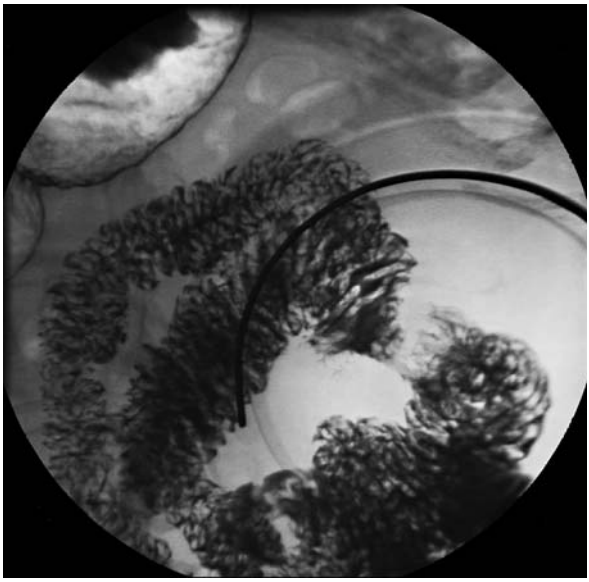

Fig. 1 Upper GI contrast study identifying a jejunal mass

with this method (Fig.1). Overall, the diagnostic yield of SBFT for detecting small bowel tumors is relatively low (0.5–6%) [6]. This may be increased to 10–21% by performing small bowel enterocolysis [5]. In this method, the descending duodenum or jejunum is first intubated with a nasoenteric tube. Using this, barium, sodium diatrizoate, or methylcellulose solutions are infused under pressure into the small bowel. This produces uniform distention of the mesenteric small bowel, and the fluoroscopist may follow the movement of the contrast as it tracts through the small intestines [11]. With small bowel enterocolysis, both mucosal and luminal structures are visualized, and a transient delay in the passage of contrast can identify areas of partial bowel obstruction (for example from a tumor), which are more difficult to identify with other modalities.

Computed tomography (CT) scan. CT scans are often the front-line test performed on patients with abdominal complaints and are the most widely available tests. In general, traditional contrasted CT scan is insensitive at localizing a source of small intestinal bleeding; however, some intestinal neoplasms, especially those with a large extraluminal component, may be detectable. More recently, the introduction of multidetector-row CT technology has allowed for acquisition of thinner slices, faster scans, and multiple contrast phases. Several reports have combined multidetector-row CT scans with neutral contrast enterocolysis to produce uniform dilation of the entire mesenteric small bowel. This technique provides reliable detection of small bowel diseases and neoplasms, but the diagnostic yield of CT enterocolysis for detecting all sources of small bowel bleeding is only 10–36% [12–17].

Angiography. Angiography is a useful, albeit invasive, tool for evaluating active gastrointestinal bleeding sources, and it allows for therapeutic intervention of vascular bleeding sources. Bleeding rates exceeding 0.5 mL/min may be detected with

this technique, although bleeding of 1.0 mL/min is optimal [18]. Diagnostic yield is low in the case of recurrent or intermittent melena or hematochezia. In the case of obscure GI bleeding originating from small bowel tumors, angiography is generally unable to identify specific lesion causing intestinal blood loss [19].

Technetium-labeled nuclear scan. Similar to angiography, technetium-labeled red blood cell scans are most useful in patients who are actively bleeding, and it can detect bleeding rates as low as 0.1 mL/min [20]. While the sensitivity for detecting active bleeding exceeds that of angiography, localization of bleeding within the small bowel is poor. In addition, a positive scan can neither provide the etiology of GI bleeding nor be utilized for therapeutic intervention [19].

Higher Yield Tools

Enteroscopy. Push enteroscopy and double balloon enteroscopy are currently the best endoscopic methods available for evaluation of bleeding lesions in the small bowel. Both methods allow for videographic evaluation of the small bowel mucosal surface, for marking of lesions for localization on later surgical intervention, and for definitive or temporary therapeutic intervention. Push enteroscopy, first described in 1973 by Ogoshi and colleagues [21], involves peroral insertion of a long, thin endoscope (220–250 cm). This allows evaluation of the small bowel within 50–150 cm of the pylorus. The diagnostic yield of this technique ranges between 13 and 78% for diagnosis of obscure GI bleeding; however, the technique allows only limited evaluation of the distal jejunum and ileum. Alternatively, double balloon enteroscopy has more recently become available [22]. This enteroscope consists of 200 cm of working enteroscope length and a flexible overtube of 140 cm in length with a latex balloon at the tip of the enteroscope and the overtube. In addition, this enteroscope can be introduced orally or rectally to facilitate examination of the proximal or distal small bowel, respectively. Recent evaluation of double balloon enteroscopy has shown an improved diagnostic yield (38–91%) over traditional push enteroscopy (reviewed in [23]). Thus, double balloon enteroscopy is quickly replacing push endoscopy as the method of choice for endoscopic evaluation of the small bowel.

Wireless capsule endoscopy. The capsule endoscope is a small 2.6 × 1.1 cm capsule, which is ingested by the patient. Subsequently, the capsule transmits images to a portable recorder via leads tapped to the patient's body. This method provides evaluation of the small bowel and identification of lesions with a diagnostic yield similar to, if not better than, double balloon enteroscopy [24]. The disadvantages of this method, especially in the evaluation of small bowel tumors, are the inability to accurately localize lesions for later therapeutic intervention, increased rate of capsule retention at tumor sites (10–25% compared to 0% in healthy volunteers), and a false negative rate of 1.5–18.9% [25]. Regardless of its disadvantages, capsule endoscopy does allow reliable and relatively noninvasive imaging of the small bowel, and it is quickly becoming a first-line diagnostic tool for evaluation of obscure GI bleeding.

Intraoperative endoscopy. This technique is reserved to facilitate intraoperative localization of presumed small bowel bleeding. One surgeon or gastroenterologist performs an upper GI endoscopy while a second surgeon telescopes the bowel over the endoscope. Alternatively, an endoscope may be inserted via the small enterotomy in the proximal small bowel. The endoscope is then physically maneuvered though the bowel lumen by the surgeon, either laparoscopically or manually using an air-trapping technique. The entire mucosal surface of the small bowel is examined during insertion of the endoscope, as trauma to the small bowel during bowel manipulation may be falsely identified as a bleeding lesion [26]. This technique allows rapid and complete evaluation of the small bowel. It has the distinct advantage of allowing exact localization and immediate management of any lesion identified.

Management of Bleeding Small Bowel Neoplasms

Once a bleeding small bowel tumor has been identified, specific therapeutic intervention must be decided upon. Options are currently limited to endoscopic or surgical approaches. In the case of malignant small bowel tumors, radiation and chemotherapeutic approaches are generally unsuccessful and do not ameliorate blood loss. In all cases, attempts to stabilize and resuscitate the patient with massive bleeding should be performed prior to proceeding to the definitive therapy. Management of the unstable patient with obscure GI bleeding will be discussed in a later chapter; however, the rapidity of blood loss may necessitate more rapid interventions.

Some small bleeding intestinal polyps and adenomas may be successfully removed endoscopically. In addition, endoscopy may be used to quell bleeding originating from small bowel tumors, although rebleeding is a common occurrence following endoscopic therapy. Endoscopic therapeutic options include photocoagulation, injection, mucosectomy, polypectomy, and enucleation [27]. However, endoscopic therapy is not a feasible therapeutic option for the majority of bleeding small bowel neoplasms, especially in the case of malignancy. Thus, surgical intervention remains the mainstay of treatment.

The surgical approach to bleeding small bowel neoplasms depends primarily on the location of the lesion. Resection of duodenal lesions depends on the portion and extent of duodenal involvement, as well as the nature of the tumor. Small and benign lesions may be amenable to duodenotomy with local resection of the tumor. Lesions involving nonampullary portions of the duodenum may be amenable to segmental resection with primary anastomosis. Ampullary lesions, malignant lesions of the duodenum, or diffuse duodenal disease (such as in FAP) generally require a more extensive resection such as a pancreaticoduodenectomy [28–30]. In the case of benign disease, low-grade and early lesions, a less extensive pancreas-preserving duodenectomy or a pancreatic head resection with segmental duodenectomy may be an option [31–35]. Alternatively, laparoscopy-assisted endoluminal resection of

early duodenal neoplasms has been recently described by Franklin et al. This technique employs endoscopy for endoluminal visualization, insufflation, and specimen retrieval in conjunction with intraluminal placement of trocars for surgical manipulation [36]. Such techniques may provide minimally invasive alternatives for management of duodenal tumors in the future.

Resection of small bowel neoplasms in the mesenteric small bowel may be preformed via laparoscopy or via laparotomy. Due to the length of the small bowel, localization of the tumor is often difficult. During laparoscopic exploration, three 5 mm port sites are generally sufficient for initial evaluation (Fig. 2). Following establishment of peritoneal insufflation, the entire peritoneum should be explored for evidence of metastatic disease. To localize the lesion, the entire mesenteric small bowel should be run proximally from the ligament of Treitz distally to the ileocecal valve. Two atraumatic graspers may be used to palpate the small bowel for intraluminal masses (Fig. 3), and visual inspection should be performed to evaluate for stigmata of bleeding and for extraluminal masses. Following identification of the bleeding small bowel tumor, segmental resection of the affected section of bowel should be performed with either intracorporeal or extracorporeal small bowel anastomosis (Fig. 4). The umbilical port may be enlarged to accommodate a larger trocar or wound protector, if necessary for specimen retrieval, and additional port sites may be needed for resection. If laparotomy is required due to adhesions, previous abdominal surgeries, or tumor size, exploration of the abdomen and palpation of the entire bowel should be similarly performed.

Intraoperative enteroscopy may be beneficial for localizing small bowel lesions. As described above, the location of the identified lesion is immediately apparent to the surgeon by transillumination and physical palpation. When combined with intraoperative endoscopy, surgery is able to correctly localize 50–100% of bleeding small bowel lesions [37–39].

Bleeding Small Bowel Neoplasms

With advances in radiologic and endoscopic evaluation, bleeding small bowel tumors are often diagnosed preoperatively. Pathologic diagnosis through tissue biopsy can direct the extent of operative intervention. Specific considerations for the most common types of small bowel neoplasms are discussed below.

Benign Small Bowel Tumors

Adenoma. Small bowel adenomas represent approximately 25% benign small bowel tumors. Similar to adenomas found in the large intestines, they may occasionally cause bleeding. The duodenum, especially the periampullary region, is the most frequent location for adenomas. However, they may occasionally be found throughout the small intestines [6]. Adenomas generally present as singular lesions and

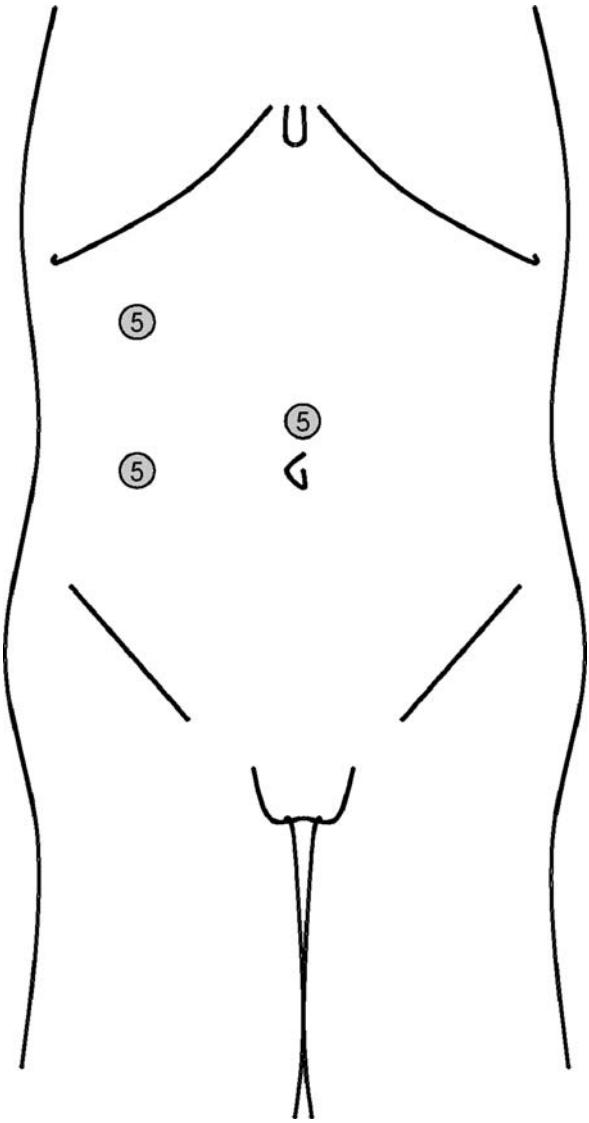

Fig. 2 Laparoscopic set-up for exploration of bleeding small bowel tumor. During initial evaluation, three 5 mm ports are generally sufficient. One port is placed supra-umbilically, one to the right of midline, and one in the right upper quadrant. The supra-umbilical port can later be expanded for placement of a 12 mm port if bowel resection is necessary

may occur sporadically; however, multiple adenomas are common with certain syndromes. For example, in familial adenomatous polyposis (FAP) and Gardner's syndrome, approximately 50–100% of patients harbor small bowel adenomas [40]. These patients are especially at high risk for adenomas in both the duodenum and in the ileum or ilieal pouch following colonic resection with ileal–anal or pouch–pouch anal anastomosis [41]. Adenomas of the small bowel are classified as tubular, villous, and tubulovillous like adenomas localized to the colon. Also

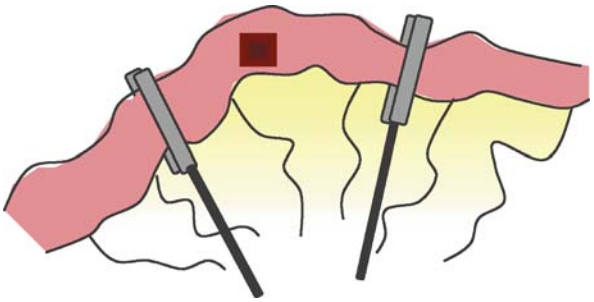

Fig. 3 Laparoscopic localization of bleeding small bowel tumors. To localize a bleeding small bowel lesion, two atraumatic bowel clamps are used to run the bowel and gently palpate for small bowel intraluminal masses. The bowel is visually examined for stigmata for bleeding

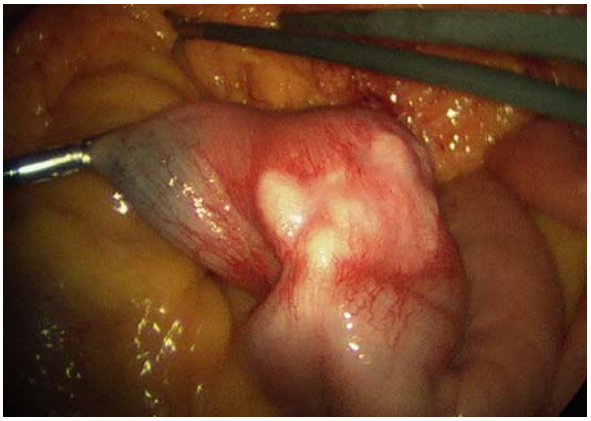

Fig. 4 Identification of a small bowel mass. This jejunal mass was previously tattooed on enteroscopy

similar to their colonic counterparts, small bowel adenomas represent premalignant lesions and may lead to malignant transformation. Especially in the case of villous adenomas, a large proportion progresses to malignancy. In a retrospective analysis of duodenal villous adenomas, 42% were found to posses malignant changes [42]. Due to the propensity for malignant transformation, surgical or endoscopic removal of these tumors is recommended.

Lipoma. Lipomas are the second most common benign tumor of the small bowel with very little malignant potential. These are usually solitary tumors, ranging in size from 1 to 30 cm [43]. More that two-thirds of lipomas are asymptomatic; however, large tumors may be associated with bleeding, as well as small bowel obstruction or intussusception [3]. While lipomas less than 1 cm rarely cause symptoms, 75% of lipomas larger than 4 cm are symptomatic [44]. Most frequently, lipomas are located distally in the small bowel and in the terminal ileum, with the jejunum being the least common location. These tumors usually originate submucosally and tend to form as discrete soft intramural masses covered by intact

mucosa [43]. Their bleeding potential has been postulated to result from ulceration of the mucosa secondary to pressure exerted by extrusion into the lumen or by intussusception [44]. Lipomas are easier to diagnose radiologically than other small bowel tumors because they are well-circumscribed, radiolucent intramural lesions that change shape with compression on barium studies. On CT scan, these tumors appear as homogenous low-density fatty lesions. Endoscopically, the characteristic appearance of lipomas is a yellow-orange submucosal lesion with positive "pillow" sign when touched with biopsy forceps [6]. Surgical resection of lipomas and affected sections of small bowel is required in symptomatic patients.

Brunner's gland hamartoma. Brunner's gland hamartomas, also referred to as Brunner's gland adenoma or Brunneroma, are hyperplasic polyps of Brunner's glands in the duodenum. These are uncommon benign lesions of the proximal duodenum with no malignant potential, which are usually discovered incidentally on endoscopy. Most are asymptomatic; however, they may cause massive bleeding or obstruction when they become large or are associated with mucosal ulcerations. They may present as melena, anemia from chronic blood loss, or massive hematemesis [45]. Although some bleeding Brunneromas may be removed endoscopically, surgical polypectomy or more extensive duodenal resection is necessary if the lesion is large or if endoscopic therapy fails [45–48].

Hemangioma. These rare benign intestinal tumors represent less than 0.05% of all intestinal neoplasms. They are generally present in patients aged 5–25 years. They may become large and cause massive occult bleeding as well as abdominal pain or obstruction. Multiple small bowel hemangiomas have been described in association with blue rubber bleb syndrome, Maffucci syndrome, Klippel–Trénaunay–Weber syndrome, and Peutz–Jeghers syndrome (Table 2) [49]. Bleeding hemangiomas should be treated either endoscopically with photocoagulation or argon laser coagulation or via surgical resection [27].

Nodular lymphoid hyperplasia. It is an obscure benign cause of GI bleeding which has been described primarily in the pediatric and young adult population. Multiple large lymphoid follicles give the appearance of submucosal masses, and these enlarged lymphoid follicles may result in malabsorption and diarrhea. The condition generally affects the distal ileum and jejunum [6]. Patients may present with melena or hematochezia, and rarely massive GI bleeding. Treatment involves resection of the involved segments of bowel [50].

Malignant Small Bowel Tumors

Gastrointestinal stromal tumors (GIST). Gastrointestinal stromal tumors are the second most common tumor of the small bowel; however, precipitous or occult GI bleeding is the most common presentation of GIST tumors (33% of cases) [51]. They can be either benign or malignant; this diagnosis is finalized postoperatively. The high propensity for bleeding of gastrointestinal stromal tumors is a result of the highly vascular nature of the tumor and the presence of central ulcerations (up to

50% of tumors) [6]. GISTs comprise a large number of tumors previously diagnosed as leiomyomas, leiomyosarcomas, leiomyoblastomas, neurofibromas, and schwannomas. These are spectrum mesenchymal tumors that contain mutations of KIT (CD117) or mutations of the closely related platelet-derived growth factor-alpha receptor [52]. GISTs may occur throughout the GI tract including the omentum and mesentery; however, they most commonly originate in the tubular portions of the GI tract. Twenty-five percent of these tumors localize to the small intestines. Within the small bowel, GISTs are most common in the jejunum (25%) and the ileum (22%), with approximately 15% found in the duodenum [7]. Growth pattern may be intraluminal, intramural, extraluminal, or dumbbell shaped. Between 40 and 50% of small intestinal GISTs are clinically malignant. In the absence of symptoms such as bleeding or obstruction, GISTs may grow quite large prior to diagnosis, and as many as half of patients with malignant GISTs have distant metastases at the time of presentation. GISTs are most likely to metastasize to the liver or peritoneum, with extraperitoneal and lymph node involvement being rare [52, 53].

If a GIST is suspected or detected during the evaluation of a patient with GI bleeding, preoperative evaluation should include CT scan of the chest, abdomen, and pelvis in order to both plan the operative strategy and evaluate for metastatic disease. On CT scan, GIST tumors classically appear as well-defined masses with heterogeneous soft tissue rims, often with a central fluid collection [53]. Endoscopy with or without endoscopic ultrasound may be of benefit if not previously performed, and biopsy of the mass may allow for risk stratification of the patient [54]. Endoscopically, GISTs appear as single, firm, grey-white masses, often with a central ulceration [6]. Surgical resection is the preferred and only potentially curative management for all GIST tumors. During resection, exploration of the peritoneum and liver for possible metastases should be performed. Care should also be taken to prevent tumor rupture to avoid dissemination of the tumor. If possible, complete tumor resection with intact pseudocapsule and negative margin should be performed. Lymph node resection is not necessary if the diagnosis of GIST is made prior to surgery due to the low propensity of GISTs to metastasize to lymphoid depots. Multiple recent clinical trials evaluating adjuvant or neoadjuvant (in the case of unresectable disease) chemotherapy with imatinib mesylate (Gleevac®) or sunitinib malate (Sutent®) demonstrate definitive survival benefits for patients with GISTs, and these therapies should be considered in patients bearing GISTs [53].

Adenocarcinoma. Adenocarcinoma is the most common malignant tumor of the small bowel, accounting for 30–50% of cases. Massive GI bleeding is uncommon with adenocarcinoma; however, they commonly present with overt or occult bleeding. Other presenting symptoms may include jaundice, weight loss, or intestinal obstruction. Highest incidence of adenocarcinoma occurs in the duodenum (54%), especially in the periampullary region. The incidence decreases distally with 28% of adenocarcinomas found in the jejunum and 18% found in the ileum [8]. The exception to this is Crohn's disease in which adenocarcinomas are most commonly found in the distal jejunum and ileum [55]. The peak incidence of small bowel adenocarcinoma is in the seventh decade of life, and it more commonly affects males

than females [7]. Alcohol (but not tobacco use), certain occupations, Crohn's disease, celiac disease, neurofibromatosis, and urinary diversion procedures predispose patients to the development of small bowel adenocarcinoma, but the most important risk factor is the presence of pre-existing small bowel adenoma [6].

Unfortunately, in contrast to colonic adenocarcinomas, the majority of small bowel adenocarcinomas are metastatic at the time of detection. This is likely due in part to the large amount of gut-associated lymphatic tissue (GALT) present in the small bowel villi near the luminal surface, allowing for earlier lymphatic invasion and spread. The liquid stream in the small intestine is also less likely to obstruct. Thus, if small bowel adenocarcinoma is suspected or detected, patient work-up should include chest, abdomen, and pelvis CT scans to evaluate for metastatic disease. In addition, MRI, EUS, and angiography may also be useful for evaluation of metastases in some cases. Five-year disease-free survival is 30.5% with median survival of 19.7 months for small bowel adenocarcinoma [6]. While endoscopy, polypectomy, or mucosectomy may be appropriate for small, especially polypoid, lesions confined to the mucosa or submucosa, the treatment of choice for adenocarcinoma is small bowel resection with wide margins and associated mesentery. This currently represents the only therapeutic modality with curative potential as neither chemotherapy nor radiation therapy alone has any proven benefit in the treatment of small bowel adenocarcinoma. However, recent studies suggest that patients with small bowel adenocarcinoma may benefit from adjuvant chemotherapy with newer platinum-based compounds [56, 57].

Lymphoma. The GI tract is the most common site of extranodal non-Hodgkin's lymphoma, accounting for 5–20% of all non-Hodgkin's lymphoma. Although more than two-thirds originate in the stomach, approximately one-sixth of these tumors originate in the small bowel. Lymphoma is the third most common malignant SB tumor, accounting for 15–20% of malignant small bowel tumors. The majority of small bowel lymphomas localize to the ileum (53%), while 35% occur in the jejunum and 12% occur in the duodenum. In addition, the incidence of small bowel lymphoma at all sites is higher in men than in women [8] and is higher in whites than in blacks [7]. Bleeding is less common with lymphoma than with other small bowel tumors, and lymphomas are more commonly associated with occult GI bleeding and with anemia rather than with overt bleeding. Other common presenting symptoms include fever, weight loss, fatigue, diarrhea, and intermittent abdominal pain [6]. Surgical resection of intestinal lymphomas remains the mainstay of treatment, and segmental resection with concurrent lymphadenectomy is important for local control. Adjuvant chemo- and radiation therapy are of definite survival benefit to patients with non-Hodgkin's lymphoma, and these therapeutic options should be pursued postoperatively [58].

Carcinoid tumors. Carcinoid tumors account for approximately 25–30% of small bowel tumors; however, they are a rare cause of small bowel bleeding [6]. These tumors arise from the enterochromaffin cell of the gut and, in the small bowel, most commonly localize to the ileum (52%) [7]. If detected in the evaluation of a bleeding small bowel tumor, a careful evaluation of the entire small bowel is necessary to exclude the presence of multiple synchronous carcinoid nodules [59].

Metastatic tumors to the small bowel. The small intestine is more frequently involved in secondary and metastatic tumor involvement than as the site of primary neoplastic disease. Tumors may spread to the small intestines by direct extension, by intraperitoneal seeding (colon, ovary, uterus, and stomach neoplasms), or by hematogenous metastasis (melanoma, lung, breast, and renal cell carcinoma) [6]. These metastases have the potential to cause occult or overt bleeding from the small bowel, and secondary involvement of the small bowel should be considered in patients with history of malignancy presenting with GI bleeding. Depending on the extent of disease and degree of bleeding, endoscopic therapy or segmental resection may be necessary to alleviate symptoms.

Summary

Although an uncommon cause of gastrointestinal bleeding, bleeding small bowel tumors represent an important source of obscure GI blood loss. Timely identification and therapeutic intervention of these tumors is of utmost importance, as delay in diagnosis may affect patient outcomes. Concurrent symptoms such as weight loss, intermittent obstruction, and fever may give clues to diagnosis. In addition, specific attention must be paid to patients presenting with small bowel bleeding who have conditions that may predispose them to the development of small bowel neoplasms. A variety of diagnostic tools facilitate diagnosis of bleeding tumors of the small bowel. These tools, including double balloon enteroscopy and capsule endoscopy, should be employed after ruling out more common causes of GI bleeding through EGD and colonoscopy. Once identified, the bleeding small bowel tumors should be resected surgically or endoscopically, if appropriate.

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Management of Bleeding from the Bile Duct

Carlos E. Marroquin and Bridget M. Marroquin

Bleeding from the gallbladder or biliary tree ("hemobilia") is not seen frequently in clinical practice. Historically, hemobilia was predominantly observed in the trauma setting. Both penetrating and blunt trauma have been recognized as a common source of hemobilia since the review by Sandblom [1]. Currently, trauma is believed to represent only 1–3% of cases of hemobilia [2, 3]. In recent years, there has been a dramatic increase in both diagnostic and therapeutic hepatobiliary procedures. This has resulted in a dramatic increase in the incidence of iatrogenic hemobilia [4] which is becoming important in clinical practice. The etiology of iatrogenic hemobilia is diverse. It may be observed, for example, after endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiograms, percutaneous biliary drainage, preoperative portal vein embolization, radiofrequency ablation, and liver biopsies. Hemobilia may also be associated with hepatic artery aneurysms, inflammatory, and infectious conditions as well as neoplastia [1, 2].

Presentation and Differential Diagnosis

Bleeding from the biliary tree may present with the classic triad of upper GI bleeding (hematemesis or melena), jaundice, and right upper quadrant abdominal pain. However, this triad is only seen in approximately one-third of patients [2, 4]. While the majority of patients who develop hemobilia remain asymptomatic, hemobilia can be lethal [5, 10]. Depending on the etiology and nature of the bleeding, hemobilia may present acutely or it may have an insidious and seemingly obscure presentation. When biliary tract bleeding evolves after a diagnostic or therapeutic intervention, the presentation may be subtle but the diagnosis is generally obvious

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given the concomitant development of jaundice and/or GI tract bleeding following the procedure.

Liver injury with late hemobilia that develops after blunt trauma can often be missed. Therefore, when hemobilia occurs after trauma, one must have a higher index of suspicion. Particularly, if one has decided to proceed with non-operative management after blunt hepatic trauma. Subtle clues may involve rising bilirubin or evolving anemia or both. The presentation of hemobilia following trauma may be as early as 4 days after the injury but can also occur as late as a month following the event [3]. Occasionally, the symptoms may involve pain and hematemesis after decompression of an intrahepatic hematoma into the biliary system.

In some cases, hemobilia may present as "obscure gastrointestinal bleeding." This is defined by the American Gastroenterological Association (AGA), as GI bleeding that persists or recurs without an obvious etiology after standard endoscopic examination (routine upper endoscopy and colonoscopy) [6]. The etiology of obscure GI bleeding can be difficult to identify and includes hemosuccus pancreaticus, hemobilia, aortoenteric fistula, Dieulafoy's lesion, Meckel's diverticulum, and extraesophageal varices (gastric, small bowel, colonic) [7].

Pathophysiology and Etiology

The portal triad consists of the hepatic artery, portal vein, and bile duct. These structures ramify as one unit throughout the liver giving rise to the segmental anatomy of the liver [8]. As such, concomitant injuries can occur to two or more of these structures at once during a traumatic or iatrogenic misadventure. Patients commonly develop pain and jaundice as a result of biliary obstruction by thrombus formation. Blood loss through the ampulla of vater may result in melena, hematemesis, and hypotension with shock in the extreme. When the hemobilia occurs from a mild venous bleed, the blood loss and hemodynamic instability is relatively minor. However, when the resultant hemobilia is associated with significant venous or arterial bleed, the blood loss can be major and associated hemorrhagic shock can ensue. Sometimes injury to intra-parenchymal branches of the hepatic artery or portal vein may result in development of an arterio-biliary fistula, porto-biliary fistula, or arterio-portal fistula with subsequent hemobilia (Fig. 1a, b).

Development of hemobilia has been associated with multiple etiologies with penetrating and blunt hepatic trauma providing the early descriptions. Complications that result from hepatic trauma such as intra-parenchymal hematoma, pseudoaneurysm, bile lake, and abscess formation are capable of decompressing into the biliary tree resulting in upper GI tract bleeding. A variety of procedures, both diagnostic and therapeutic, may be associated with development of hemobilia. These include transjugular liver biopies [9, 10], sphincterotomy [11], percutaneous liver biopsies, placement of percutaneous hepatic drains, placement of transjugular intrahepatic portosystemic shunts (TIPS), percutaneous transhepatic cholangiograms (PTC), and percutaneous biliary drainage (PBD) procedures.

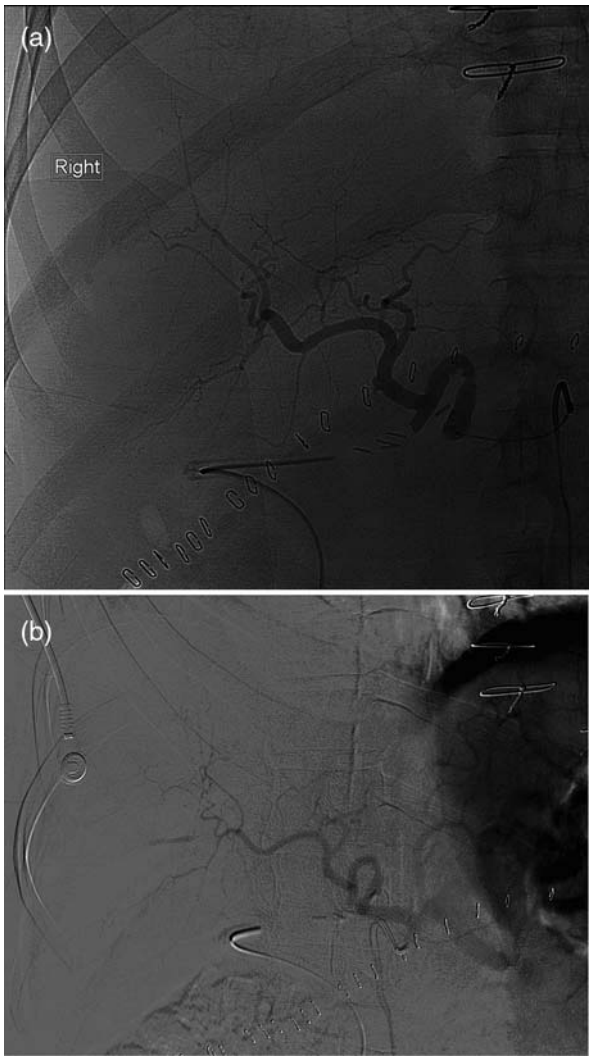

Fig. 1 (**a**) Early phase of selective angiogram of right hepatic artery. (**b**) Late phase of selective angiogram demonstrating arterio-portal fistula

PTC is a relatively safe procedure with a less than 1% rate of hemobilia formation. Hemobilia following TIPS occurs less than 5% of the time. In contrast, PBD placement is associated with an 8% hemobilia rate [12]. Hemobilia may result from therapeutic hepatobiliary procedures as well. In our own experience, we have seen a case of bleeding into the gallbladder after a laparoscopic radiofrequency ablation of a liver mass (Fig. 2).

Hemobilia can also result from vascular etiologies. While hepatic artery aneurysms (HAA) represent approximately 20% of all visceral aneurysms, HAA were the number one visceral artery aneurysm reported during the decade between

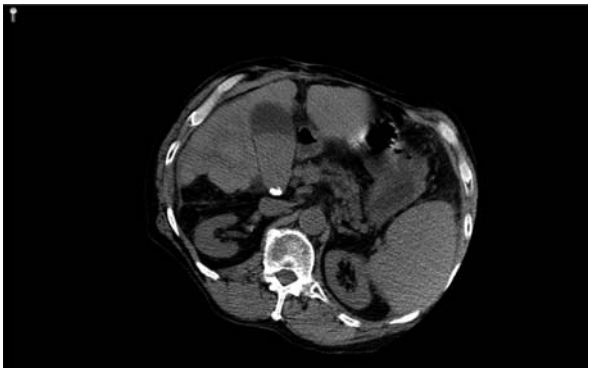

Fig. 2 Completion CT scan after satisfactory RFA demonstrates an interval development of a high-density fluid level within the gallbladder, consistent with acute blood

1985 and 1995 [13]. Similar to the increasing trend in hemobilia that results from iatrogenic sources, this increased incidence in HAA is also the result of an increase in diagnostic and therapeutic hepatobiliary procedures. Biliary tree hemorrhage has been described with rupture of hepatic artery aneurysm [14, 15] and can be universally fatal owing to the lack of pre-morbid diagnosis. It has also been described with cystic and hepatic artery pseudo-aneurysms.

The gallbladder is another source of biliary tract bleeding that may result secondary to severe cholecystitis producing both jaundice and hemobilia [1, 2, 16]. While the vast majority of these cases are associated with cholelithiasis, there are reports of biliary tract bleeding from acalculous cholecystitis [17]. Blood may even accumulate in the gallbladder in cases of hemorrhagic cholecystitis. Potential mechanisms of hemorrhagic cholecystitis include the development of necrosis with erosion of the cystic artery into the gallbladder lumen [18]. Biliary tract bleeding has also been described following liver transplantation, liver resections, and Roux-en-Y biliary reconstructions in patients with neoplastic conditions (malignant hepatic and biliary tumors) [2, 4].

Hemobilia may be seen infrequently in patients with bleeding diathesis such as patients with von Willebrand disease [19], patients with liver failure and coagulopathy, or patients with prolonged bleeding time as in Bernard–Soulier Syndrome [20]. Finally, hemobilia has also been described after treatment with anticoagulants, such as Coumadin [21], and following interactions with other medications [22]. It can develop in association with inflammatory conditions (acute pancreatitis) and infectious conditions such as ascariasis as well as cytomegalovirus [23].

Diagnostic Work-Up

An index of suspicion is critical to the prompt diagnosis of hemobilia. This suspicion should be corroborated with laboratory studies, abdominal imaging, angiography, and/or endoscopy. The laboratory findings in a patient with hemobilia include

evidence of biliary obstruction with increasing direct bilirubin and/or evidence of upper GI bleeding with anemia. In cases of hepatic trauma, an initial CT scan may demonstrate a hepatic hematoma, laceration, or even a missile's trajectory [24]. The development of concomitant jaundice and anemia after hepatic trauma or following a diagnostic or therapeutic hepatobiliary procedure should prompt a celiac artery angiogram. If an arterio-biliary fistula is the cause of this clinical picture, the angiogram will reveal the fistula. When evidence of GI bleeding following traumatic or iatrogenic hepatic injury has been pursued with endoscopy to no avail, repeating the endoscopy is usually unrevealing. Consequently, a known history of hepatic injury in the setting of GI bleeding mandates a celiac artery angiogram [3]. When hemobilia is due to a porto-biliary or arterio-portal fistulae, the angiogram may still demonstrate the fistula during the late portal vein phases of the angiogram (Fig. 1a, b).

Another group of patients may be diagnosed with a GI bleed which is subsequently localized to an upper GI source and eventually to the biliary tree. In these cases, an upper endoscopy with ERCP may reveal a filling defect within the bile duct with associated dilatation. However, the bleeding may be intermittent resulting in a non-diagnostic endoscopy. In these cases, the utility of the endoscopy is that it effectively rules out other sources of upper GI tract bleeding. These cases should be followed with an angiogram which will provide the diagnosis of hemobilia.

Therapy

The majority of contemporary cases of hemobilia result from iatrogenic sources such as diagnostic or therapeutic procedures [4]. The initial morbidity from these procedures is relatively minor and permits expectant management. In fact, it is reasonable to assume that a number of these cases never come to clinical significance. During the course of expectant management, one should aggressively correct any degree of coagulopathy with fresh frozen plasma, cryoprecipitate, and vitamin K as necessary. If the patient is thrombocytopenic or has uremia that may predispose to platelet dysfunction, then platelets should be infused to correct the thrombocytopenia and adjuncts like DDAVP and premarin should be used to increase platelet adherence. If bleeding persists after conservative management, some intervention will be necessary. In cases following a PTC, exchanging smaller tubes with larger tubes may tamponade the bleeding in cases of venous-biliary fistulae, and embolization is effective in the vast majority of cases of arterio-biliary fistulae [4, 12, 25].

When hemobilia results form penetrating or blunt trauma, the diagnostic suspicion is usually confirmed by angiography. This is particularly useful in these cases since the diagnostic technique also serves as a therapeutic intervention. Angiography will commonly demonstrate a hepatic artery aneurysm or pseudoaneurysm that can be embolized with steel coils, gelfoam, or acrylate [2, 4]. Selective arterial embolization is the standard of care for treatment of intrahepatic hemobilia and is better than 80% effective and as high as 97% successful [4, 25]. In

some centers, one may not have access to embolization, but the hepatic injury clearly resides within the right or left lobe. One alternative in these circumstances is direct ligation of the feeding hepatic artery [26]. Occasionally, hemobilia will be associated with a large intrahepatic defect. While radical surgical approaches have been employed in the treatment of hemobilia [27, 28], they are rarely indicated. The optimal treatment in cases with large defects is hepatic resection incorporating the defect and pseudo-aneurysm within the resection zone [3]. Since the portal triad gives rise to the successive branching pattern that forms the basis of hepatic anatomy, and since these injuries usually involve adjacent biliary and vascular structures, segmental resections should adequately control the hemorrhage while preserving hepatic parenchyma during urgent operative intervention.

In patients with no underlying liver disease and failed transcatheter embolization of pseudo-aneurysms with persistent bleeding, surgical management is effective in the treatment of refractory hemobilia [2, 4, 25, 28, 29]. Some causes of extrahepatic bleeding may lend themselves to surgical correction such as bile duct tumors or ampullary lesions.

A relatively common finding after failure of conservative management and selective arterial embolization is hemocholecystitis. These cases have been managed with cholecystectomy with no additional sequelae [29]. Similarly, if hemobilia results from cholecystitis, cholecystectomy is curative. In cases of hemobilia that are associated with a hepatic artery aneurysm, depending on the location of the aneurysm, these can be treated with embolization or surgical ligation or resection. Given the significant morbidity associated with an exploratory laparotomy and ligation or resection, one should entertain embolization as a first-line therapy. Particularly when the vascular lesion is located within the hepatic parenchyma. In the rare instance of an extrahepatic arterial aneurysm producing biliary hemorrhage from rupture into the biliary tree, a surgical approach is more fitting with ligation or resection of the involved branch or lobe. Since hepatic artery reconstruction is not a straightforward procedure and since it may not be an option in a patient in extremis, ligation is an attractive alternative. Ligation of the extrahepatic artery without restoration of the arterial continuity is an effective technique, particularly if the liver and adjacent organs are fed through collateral circuits [26]. Cases of bilioportal fistulae also appear to be amenable to surgical interventions [30]. Independent of the surgical procedure, some authors advocate the placement of biliary drains after hemostasis has been obtained. External drains allow lavage of retained thrombi and facilitate clearing thrombus formation in cases of re-bleeding [29] and allow the subsequent fibrinolytic effects of bile to clear the duct. However, these drains are large by necessity and need to be placed centrally to be effective, and both their size and central placement are associated, potentially, with further injury. Therefore, if additional decompression is necessary, an ERCP with sphincterotomy and stent placement or subsequent nasobiliary stenting will facilitate biliary flow (Fig. 3).

Since patients who develop biliary tract hemorrhage may also have underlying liver disease that prompted the insult in the first place, a thorough evaluation of the patient with hemobilia is necessary before embarking on a surgical intervention. Patients with decompensated liver disease who required a percutaneous or

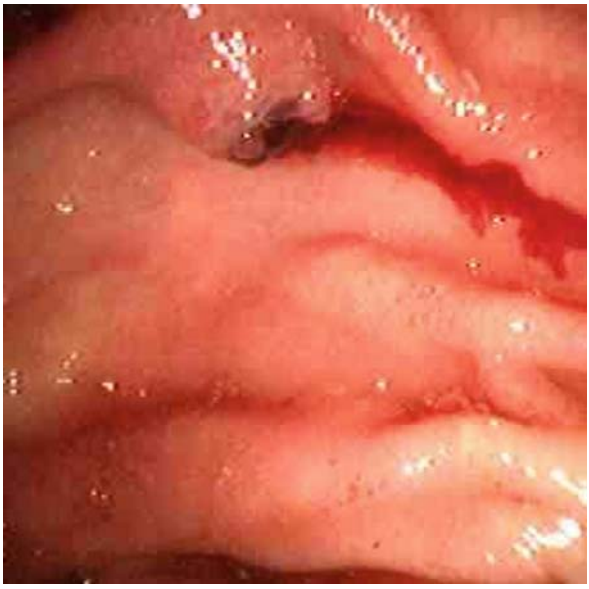

Fig. 3 Post-cholecystectomy ERCP revealed persistent bleeding after cholecystectomy. The entire main bile duct, left main hepatic duct, and right main hepatic duct contained filling defects thought to be a large clot. As the sphincterotomy was being performed, a large clot came out of the ampulla. The biliary tree was swept with a balloon starting at the bifurcation with delivery of large clots

transjugular liver biopsy, a transhepatic embolization of a liver mass, or radiofrequency ablation are likely poor operative candidates. In patients with known underlying liver disease who are prohibitive operative candidates, every effort at non-operative therapy should be exhausted. Aggressive platelet and factor replacement and the use of adjuncts like recombinant factor VII should be attempted. Fortunately, as the majority patients with hemobilia will stop bleeding with conservative management.

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Management of Bleeding from the Pancreas

Eugene P. Ceppa and Dana Portenier

Introduction

Acute hemorrhage originating from the pancreas is the least common form of upper gastrointestinal bleed [1, 2]. Specifically, hemorrhage from the pancreatic duct through the papilla of Vater is rare with approximately 100 cases having been reported in the literature. The first report by Lower and Farrell in 1931 identified a splenic artery aneurysm as the cause [3]. This phenomenon has been described in various terms including *wirsungorrhagia* and *hemowirsungia*, highlighting the identification of hemorrhage from the pancreatic duct into the duodenum [4, 5]. *Hemosuccus pancreaticus* was first proposed by Sandblom in 1970 signifying emission of blood from the pancreatic ducts through the ampulla of Vater [6]. Longmire proposed *hemoductal pancreatitis* as another synonymous term [7].

Surgical Anatomy

The pancreas was first described by Eristratos in 300 BC. The origin of the word pancreas is Greek for *pan* meaning all and *kreas* defined as meat/flesh. The pancreas is a retroperitoneal organ situated at the level of the L2 vertebrae. The pancreas is commonly divided into segments consisting of the head, uncinate process, neck, body, and tail. The head of the pancreas lies nestled in the c-loop of the duodenum and the uncinate process is the portion of the head that extends posterior to the superior mesenteric vessels. The neck overlies the superior mesenteric vessels. The body begins at the level of the superior mesenteric vessels and the tail extends into the splenic hilum.

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The duct of Wirsung (main pancreatic duct) was first described in 1642 and the duct of Santorini (accessory duct) in 1734. These are the two main ducts that drain exocrine secretions into the duodenum. The duct of Wirsung drains most of the head, body, and tail of the pancreas, while the duct of Santorini drains the superior portion of the head. Most possess branching that connects these two major ducts. Vater described the common bile duct and ampulla in 1720. However, it was not until 1919 that a pathologist from Johns Hopkins by the name of Oddi described the common duct theory where the common bile duct and main pancreatic duct joined together to drain via the ampulla of Vater into the duodenum. Of note, the accessory duct empties directly into the duodenum (minor papilla) several centimeters proximal to the ampulla of Vater.

The arterial blood supply of the pancreas is both redundant and profound. The celiac axis provides the common hepatic artery which in turn supplies the gastroduodenal artery as the origin of the superior branches of the pancreaticoduodenal artery. The pancreaticoduodenal branches supply the head of the pancreas. In addition the splenic artery provides the dorsal pancreatic, the great pancreatic, and the caudal pancreatic arteries as it travels toward the splenic hilum. These branches supply the body and tail of the pancreas. The superior mesenteric artery supplies the inferior branches of the pancreaticoduodenal artery as well as the inferior pancreatic artery. The venous anatomy parallels the arterial supply. Specifically, the superior pancreaticoduodenal veins drain into the portal vein, meanwhile the inferior pancreaticoduodenal veins unite to form the Henle trunk just proximal to the superior mesenteric vein. The veins from the body and tail drain directly into the splenic vein.

Clinical Presentation

Hemosuccus pancreaticus (HP) is a rare cause of upper gastrointestinal hemorrhage seen predominantly in men (sex ratio 7:1) [8]. Most of these cases are related to chronic consumption of alcohol. Frayssinet et al. reported the mean age of onset as 50 or 60 years when the site of pathology was the pancreatic parenchyma or the pancreatic arterial supply, respectively [9]. HP can present with an abrupt onset of epigastric abdominal pain to be later followed by acute gastrointestinal hemorrhage. The epigastric pain begins and radiates posteriorly [10] due to increased intraductal pressure by the presence of blood in the main pancreatic duct [11]. Within 48 h, gastrointestinal hemorrhage ensues as either hematemesis or melena; the onset of hemorrhage is usually associated with improvement of the abdominal pain. The amelioration of the abdominal pain is considered pathognomonic for HP. In addition, the intermittent nature of hemorrhage is specific for HP as a result of the cyclic balance between clot formation and dissolution within the pancreatic duct [1, 5]. Other possible associated symptoms include jaundice, weight loss, and a palpable pulsatile, epigastric mass with a systolic thrill.

Diagnostic Studies

The diagnosis of HP is a clinical dilemma due to the nature of intermittent hemorrhage from a source that is difficult to detect by common diagnostic studies. Upper gastrointestinal endoscopy can visualize active hemorrhage from the papilla in 30% of patients [1] (Figs. 1 and 2). This confirms either HP or hemobilia, while blood seen in the second portion of the duodenum provides evidence suggestive of these diagnoses. Endoscopy can also disclude other causes of upper gastrointestinal hemorrhage, such as gastritis, ulcers, and varices. Endoscopic retrograde cholangiopancreatography (ERCP) can also sort through HP as a cause of hemorrhage; pancreatic duct filling defects can represent the presence of blood clot or opacification of pseudocysts and/or communicating arterial aneurysms can identify the etiology of HP. Abdominal CT angiography rarely provides direct evidence of HP. However, pseudocysts and aneurysms are sometimes visible which can lead to a diagnosis with correlating symptoms. Technetium 99m-labeled red cell scintigraphy can identify a zone when active hemorrhage is present, yet the intermittent nature of HP makes this test unlikely to yield any helpful data [11].

Selective mesenteric arteriography provides the best opportunity for diagnosis of HP. This modality is capable of providing definitive proof by opacification of the main pancreatic duct [4]; arteriography has a 96% sensitivity in diagnosis of HP. However, identifying a direct vascular communication with the pancreatic duct is rare [12, 13]. Pseudoaneurysms of the common hepatic, gastroduodenal, or splenic arteries seen by arteriography in the setting of gastrointestinal hemorrhage are suggestive of HP.

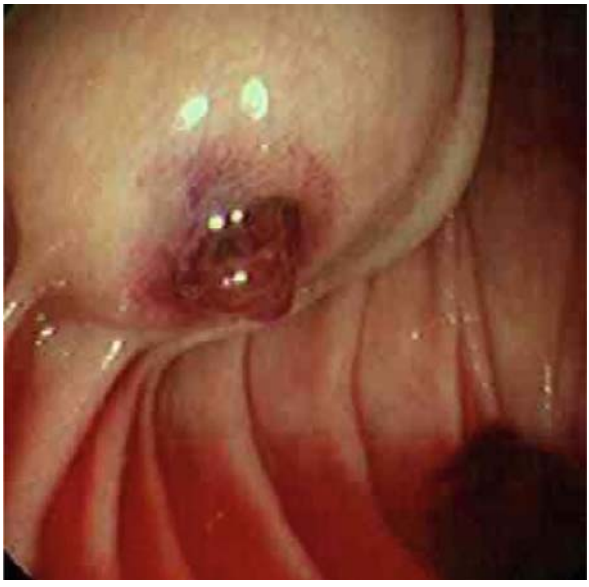

Fig. 1 Hemobilia visualized at the ampulla of Vater on endoscopic exam

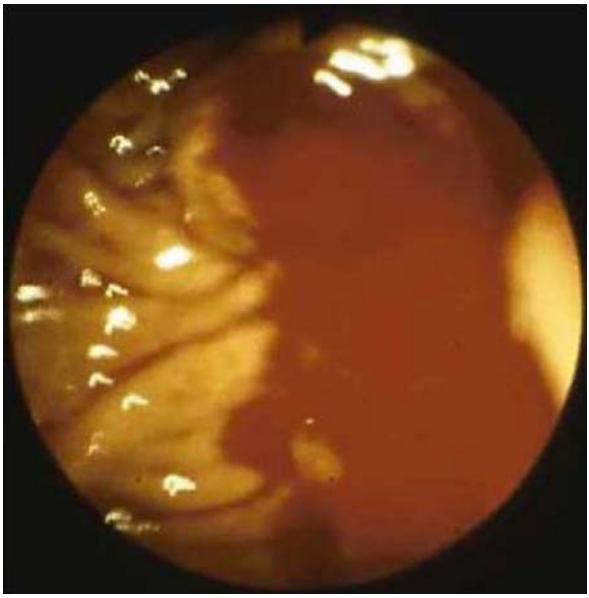

Fig. 2 Substantial hemobilia is more difficult to localize

Pathophysiology

There are various etiologies to HP. Pseudoaneurysms of the common hepatic, gastroduodenal, pancreaticoduodenal, or splenic arteries have been reported [14–17]. Acute or chronic pancreatitis is the most common cause of pseudoaneurysm formation [18]. Pseudoaneurysms occur due to exocrine enzyme autodigestion and erosion into peripancreatic vessels [14, 18]. The most common cause of hemorrhage is due to a rupture of the splenic artery (60–65%) followed by gastroduodenal (20–25%), pancreaticoduodenal (10–15%), and hepatic artery (5–10%) [17, 19–21]. Ruptured pseudoaneurysms portend a poor prognosis with a reported mortality of 12–57% [17]. Other uncommon causes include pancreatic pseudocysts and pancreaticolithiasis [22, 23].

Management

Upon confirmation of HP, intervention generally consists of a combination of endovascular control of arterial hemorrhage and subsequent operative intervention. Hemodynamically stable patients can be temporized with endovascular techniques for control of hemorrhage. Interventional radiographic methods provide the optimal first line of treatment. Transcatheter balloon occlusion, coil embolization, and vascular stent deployment are several distinct methods for treatment. Balloon occlusion obstructs the artery prior to surgery, limiting blood loss and shortening operative times [1]. Coil embolization induces thrombus formation within the diseased vessel

inducing complete obliteration of the artery [24, 25]. Thus embolization of the celiac axis, common hepatic artery, and superior mesenteric artery are contraindicated. Nevertheless, embolization of hemorrhage secondary to pancreatitis or pseudocysts has been shown to be very effective [25–27]. Some argue that coil embolization can be used as a definitive therapy as an alternative to operative intervention [26, 27]. Stent deployment allows for exclusion of a pathologic segment of an artery with continued distal perfusion of vital organs. Overall success of endovascular techniques for treatment of visceral aneurysms or pseudoaneurysms is 75–80% [8, 28]. There is a reported 17–37% recurrence rate associated following coil embo lization [29].

Surgery is considered the definitive treatment and first-line therapy for hemodynamically unstable patients. Surgical management can include management of pancreatic parenchymal disease by drainage of pseudocysts, arterial disease by ligation of bleeding arterial disease, or a combination of drainage procedure and arterial ligation. The risk of recurrent bleeding, infection, and necrosis is possible after these procedures [30, 31]. A more aggressive and preferable approach is pancreatic resection which would address both problems [32]. Disease involving the pancreaticoduodenal arteries requires ligation of arterial bleeding, resection of the head, and drainage of the distal pancreas. Splenic artery etiologies require distal pancreatectomy. Nevertheless, surgical management of HP is technically difficult with a 70–85% success rate and associated 20–25% mortality [17, 19, 21, 26].

Conclusion

HP is a rare cause of upper gastrointestinal hemorrhage. Diagnosis is often delayed due to intermittent hemorrhage and the limitations of diagnostic studies to identify active hemorrhage. Most patients have previously suffered from acute or chronic pancreatitis, thus these patients should have a higher index of suspicion for HP as the cause of gastrointestinal hemorrhage. Endovascular techniques have increased the available therapeutic options with less invasive alternatives; these serve well as first-line therapies in hemodynamically stable patients. Endovascular techniques can also be used as a bridge to more definitive surgical treatment. Surgical drainage of pancreatic disease, arterial ligation of peripancreatic vessels, and pancreatic resection are all valid options. Ideally, anatomic pancreatic resections have the best outcomes but are still associated with a significant mortality.

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Part II
Lower GI Bleeding

Urgent Workup of Lower GI Bleeding

Dawn M. Emick and Leila Mureebe

Introduction

Lower gastrointestinal bleeding (LGIB) is defined as bleeding originating from bowel distal to the ligament of Treitz. LGIB presents as either melena or hematochezia, depending on the source and the rapidity of hemorrhage. The most common cause of blood per rectum is actually upper gastrointestinal bleeding where blood has traveled antegrade through the intestinal tract. Only about 20% of all gastrointestinal hemorrhages arise from the lower GI tract, and the vast majority of these bleeds arise from the colon. A significant minority originates in the jejunum or ileum. The annual incidence of LGIB is 20–27 cases per 100,000 population in Western countries. The overall mortality rate is reported as 3.8%, which is similar to upper GI bleeding, but in some studies has been reported to be as high as 20%. Negative prognostic factors include advanced age, high transfusion requirements, comorbid factors, and hospitalization at the onset of the bleeding episode [1]. As in upper GI bleeding, approximately 80% of LGIB spontaneously cease. This chapter addresses the urgent management of those 20% that do not.

The etiology of LGIB varies widely by age, and the epidemiology of the disease must be considered in arriving at the correct diagnosis (Table 1). The most common cause of LGIB is colonic diverticulosis, which accounts for up to 60% of all LGIB. In children, however, Meckel's diverticulum, a congenital anomaly of the small bowel, and intussusception are common sources of LGIB [2]. In adults older than 60 years of age, angiodysplasia may be slightly more common than diverticular disease. Other frequent causes of lower GI bleeding are colitis from inflammatory bowel disease, infection or ischemia, neoplasms, polyps, anorectal disease such as hemorrhoids or anal fissures, and mesenteric ischemia. Causes may be iatrogenic in the instance of post-polypectomy hemorrhage or post-radiation proctitis after treatment for prostate cancer. Rare causes include aortoenteric (or graft-enteric) fistula

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Table 1 Common etiologies of LGIB by age (Edelman and Sugawa [1]; Elta [9]; Leung and Wong [2]; Zuckerman and Prakash [3])

Infants/toddlers	Children/teenagers	Adults	Older adults
Milk allergy	Anal fissures	Diverticulosis	Angiodysplasia
Necrotizing enterocolitis	Polyps	Upper GI source	Diverticulosis
Volvulus	Inflammatory bowel disease	Neoplasm/polyps	Neoplasm/polyps
Anal fissure	Intussusception	Inflammatory bowel disease	Upper GI source
Intussusception	Infectious colitis	Anorectal disease	Anorectal disease
Hirschsprung disease	Meckel diverticulum	Iatrogenic (radiation proctitis, post-polypectomy)	Iatrogenic (radiation proctitis, post-polypectomy)
Meckel diverticulum	Angiodysplasia Henoch–Schoenlein purpura Hemolytic uremic syndrome	Angiodysplasia	Mesenteric ischemia Inflammatory bowel disease

after aortic surgery, anorectal varices, solitary rectal ulcer syndrome, and Dieulafoy lesions [3].

Diverticular disease of the colon is the most common overall cause of LGIB in adults. Diverticula are outpouchings of colonic mucosa through the muscularis and serosa, most commonly found on the mesenteric side of the colon at the site of penetrating blood vessels (vasa recta), where the colonic wall is weakest. A Western diet, which is low in fiber and high in saturated fats, contributes to the pathophysiology of this disease, and it has been estimated that over 50% of adults over the age of 60 in the United States have diverticular disease, most commonly in the sigmoid colon. Diverticula can become inflamed and painful leading to diverticulitis. Alternatively, diverticula can bleed, and up to 17% of people with diverticula experience bleeding at some point, ranging from mild to severe [1]. Painless bleeding per rectum in an adult under the age of 65 is most commonly diverticulosis.

With aging, the presence of angiodysplasia (or arteriovenous malformations – AVM) increases. By the age of 65, AVM may be the most common source of colonic bleeding. AVM are vascular anomalies of the gastrointestinal tract characterized by dilated and tortuous submucosal vessels. AVM may be congenital, but more often these develop over time, possibly from chronic venous obstruction, chronic mucosal ischemia, or as a complication of other comorbidities such as cardiac, vascular, or pulmonary disease. There is an association between AVM and aortic stenosis; however, a causal role has not been revealed [4]. In contrast to diverticular disease, colonic AVM are most often located in the right colon.

Inflammatory bowel disease, both ulcerative colitis (UC) and Crohn's disease (CD), leads to LGIB. UC affects primarily the colon, and bloody diarrhea is a

common symptom. Up to 50% of patients with UC experience mild-to-moderate LGIB. CD can affect the entire gastrointestinal tract, and bleeding is less common, although when it occurs it is more likely to be severe than UC [3]. Other inflammatory conditions affecting the colon include post-radiation therapy colitis, most commonly after treatment for prostate cancer, and infectious colitis, which rarely leads to significant hemorrhage.

Neoplasm must always be on the differential when considering a source of blood loss per rectum. Colorectal cancer is the second leading cause of cancer death in the United States, and with aggressive screening programs, mortality can be greatly reduced [5]. Cancers or polyps may bleed from surface erosions or ulcerations. Significant bleeding immediately after endoscopic polypectomy can be attributed to inadequate coagulation. Delayed bleeding days to weeks after polypectomy can also occur [6]. Overall rates of post-polypectomy bleeding vary from 0.3 to 6%. Endoscopists typically inject saline submucosally prior to polyp removal to ensure complete resection, and it was thought that using diluted epinephrine instead of saline might reduce the incidence of post-polypectomy hemorrhage. This was found to be true in several small trials. However, the most recent large, randomized controlled trial of dilute epinephrine vs. saline injections prior to endoscopic polypectomy found no difference in early or late bleeding events [7].

Bright red blood per rectum can often be attributed to diseases of the rectum or anus. When blood travels a great distance through the bowel, hematin becomes oxidized and turns black, mixes with intestinal contents, and emerges as melena. When red blood exits the rectum, it is because of either fast transit time (brisk bleed) or short transit distance (distal source). Hemorrhoids are a common problem and can range in severity from a minor inconvenience to a source of massive hemorrhage. Internal hemorrhoids are painless and bleeding is often the only symptom. External hemorrhoids can also bleed, but are more likely to present with pain or itching. Hemorrhoids are common, and their presence should not exclude a more complete workup in the case of rectal bleeding. In fact, because they are so common and often minor, they are often considered distinct from LGIB. Chronic constipation can lead to anal fissures, a painful and often recurrent problem that can be a bleeding source.

Mesenteric ischemia and ischemic colitis can be a cause of LGIB, but bleeding is often a late and ominous finding. In general, ischemia occurs when the oxygen demand of an organ exceeds supply. Mesenteric ischemia can be a chronic disease caused by atherosclerosis of the mesenteric arteries. It can be difficult to diagnose and requires a low threshold for suspicion. Symptoms include post-prandial pain, weight loss, “food fear,” and diarrhea in older adults. Mesenteric ischemia can also be acute, most often caused by an embolus to the superior mesenteric artery. In critically ill patients, acute mesenteric ischemia can be a result of shock and a low-flow state to the intestine. Treatment for embolic ischemia is surgical or percutaneous thrombectomy, while treatment for ischemic colitis and hypotensive acute mesenteric ischemia is supportive unless there is evidence of perforation or necrosis.

Resuscitation and Stabilization for Massive LGIB

A massive, acute LGIB is a life-threatening situation and is defined by a transfusion requirement of more than 4 units of blood in a 24-h period. Massively hemorrhaging patients present with hemodynamic instability and shock, a drop in hemoglobin levels and immediate transfusion requirements. Bleeds that do not spontaneously resolve in <3 days or that bleed after initial stabilization are also considered significant LGIB. Fortunately, most cases of LGIB are mild to moderate, but this chapter will focus on the approach to and management strategies for this group of patients requiring urgent diagnosis and therapy.

The approach to any patient with a large amount of red or dark blood per rectum begins with a history, while simultaneously addressing vital sign abnormalities and immediate resuscitation. Important historical information includes use of aspirin, NSAIDs, warfarin, or other anticoagulation medications, personal or family history of clotting disorders, previous surgeries, history of GI bleeding, and recent procedures. For a patient with a large amount of blood or melena and/or hemodynamic instability, two large-bore intravenous lines should be placed in antecubital veins and resuscitation begun with warmed crystalloid fluids. The patient should be placed on continuous hemodynamic monitoring and a urinary catheter should be inserted. Since the most common cause of blood per rectum is upper GI bleeding, a nasogastric tube must be placed and the stomach lavaged. If bloody or coffee ground material is aspirated, the diagnostic pathway to follow is for upper GI bleeding. If bilious material is aspirated, the patient is presumed to have bleeding distal to the ligament of Treitz; aspiration of clear fluid favors a more distal source but does not completely rule out upper GI bleeding. Necessary laboratory investigations include a complete blood count, arterial blood gas, electrolytes, coagulation tests, and type and cross-match. The patient should be admitted to a monitored unit, potentially intensive care if conditions warrant. If the patients' hemodynamic instability does not respond appropriately with fluid resuscitation, blood transfusion with O negative unmatched blood may be necessary while waiting for the cross-matched blood. Physical exam should include digital rectal exam and anoscopy or rigid proctoscopy when feasible.

Once the diagnosis of LGIB is suspected, there are three urgent diagnostic modalities from which to choose, and considerable disagreement still exists among experts (Fig. 1). Without convincing evidence for a clear preferred initial study, the choice between colonoscopy, arteriography, and radionucleotide scintigraphy depends on the individual patient and the rate of bleeding. Urgent colonoscopy is probably less useful immediately in cases of massive hemorrhage, because the volume of blood in the colon will obscure imaging. Alternatively, angiography is less useful in slower bleeding because it can only detect bleeding at a relatively brisk rate (0.5–1.0 cc/min). Nuclear medicine studies have a wide range of reported sensitivities and have fairly poor resolution. The sensitivity of nuclear medicine bleeding studies is significantly lower than angiography and is on the order of 0.1 cc/min, and localization is imperfect and is regional, at best. Other modalities such as wireless capsule endoscopy have no role in the immediate period for a patient with ongoing LGIB, but will be discussed elsewhere.

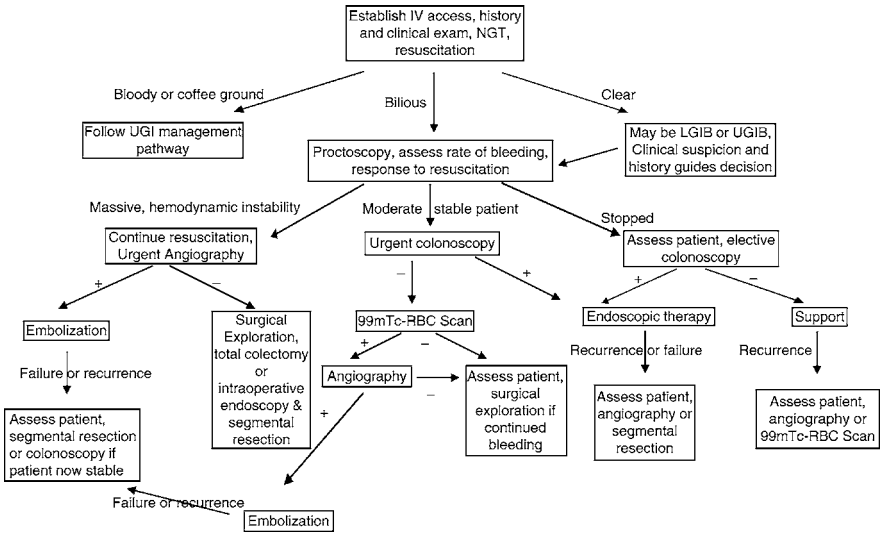

Fig. 1 Suggested workup and treatment algorithm for lower gastrointestinal bleeding

Urgent Colonoscopy

All patients with LGIB that has resolved spontaneously should have a semi-elective colonoscopy after thorough preparation of the bowel. In the 20% of patients where bleeding does not cease, or in patients where bleeding recurs early, urgent colonoscopy after a rapid bowel preparation should be considered. Historically, colonoscopy was thought to be of little yield in a briskly bleeding patient with an unprepared colon because of inadequate visualization. This argument still holds true in the massively bleeding patient requiring ongoing blood transfusions. However, a recent review reveals that early colonoscopy (within 12–48 h of admission) has a higher diagnostic yield and lower complication rate than arteriography, results in shorter length of stay, and avoids further surgical intervention in those patients who respond appropriately to initial resuscitation efforts [8].

Colonoscopy is both a diagnostic and a therapeutic tool. It provides direct visualization of the colonic mucosa and simultaneous treatment of bleeding via endoscopic epinephrine injection, thermal therapy, or other hemostatic techniques. Bowel preparation for urgent colonoscopy is best achieved with polyethylene glycol-based solutions, such as Golytely or Colyte. Patients generally have to ingest 1 L of solution every 30–45 min, and a median dose of 5.5 L is reported for adequate preparation [9]. This large volume may be quite challenging for patients to ingest and may be better accomplished by administering via the previously placed nasogastric tube.

There are no randomized controlled trials comparing diagnostic or treatment modalities in LGIB, but a single study comparing a cohort of patients with active diverticular bleeding against historic controls provides the best evidence in favor

of urgent colonoscopy for diagnosis and treatment in these patients. Several other case series, though small, add credence to this recommendation. In the Jensen trial, consecutive patients with LGIB and diverticulosis all underwent colonoscopy after bowel preparation. In the historic control group, 17 of the 73 patients had endoscopic evidence of active or recent bleeding and were treated medically; no endoscopic hemostatic treatment techniques were utilized. Nine (53%) of those patients had recurrent bleeding; six went on to require hemicolectomy. Of the 48 patients in the intervention cohort, 10 had evidence of active or recent hemorrhage and were treated endoscopically. None of these patients had recurrent bleeding [10].

Once a bleeding source is identified, several treatment modalities have been found to be effective. For bleeding diverticula, heat probe, bipolar or multipolar coagulation, or epinephrine injections can be used independently or concurrently. Endoscopic metallic clip placement is an alternative, but requires visualization of a vessel. It is actually uncommon to easily identify a bleeding vessel or stigmata of recent bleeding, such as adherent clot. More often, there is a presumed area of concern that can be treated (Fig. 2). For AVMs, both thermal and epinephrine injections are quite successful. In November 2005, the American Society for Gastrointestinal Endoscopy issued guidelines for LGIB recommending early colonoscopy and reviewed the different treatment modalities [11].

Colonoscopy is an invasive study that is not without risk. Perforation occurs in 1 in 1,000 colonoscopies and requires surgical resection. The usefulness of colonoscopy is also somewhat user dependent, and at inconvenient times, it may

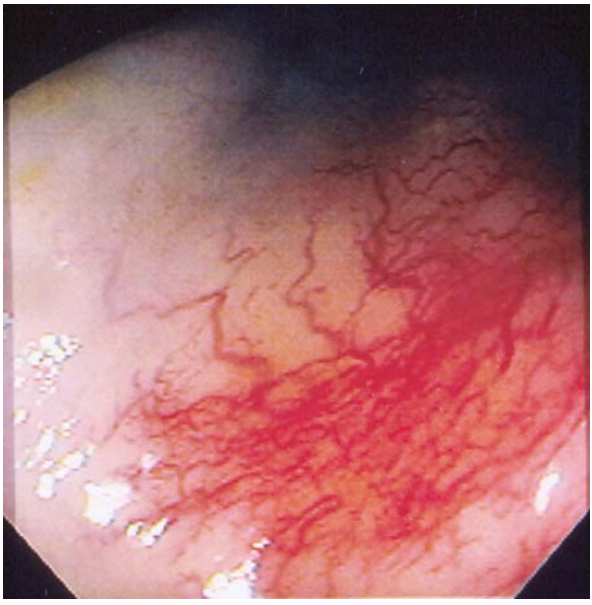

Fig. 2 Arteriovenous malformation, no signs of active or recent stigmata of bleeding (Courtesy of John Migaly, M.D., Duke University Medical Center, Durham, NC)

be difficult to get a skilled endoscopist to perform the procedure on an urgent basis. In cases where endoscopic intervention is not effective in stopping the hemorrhage, the area of bleeding can be marked or tattooed for surgical intervention. It may always be prudent to tattoo the area of concern in case of recurrent hemorrhage. If colonoscopy reveals a bleeding mass, biopsies should be taken of the mass for pathologic diagnosis, and a full oncologic workup is indicated. Further disadvantages to colonoscopy include poor diagnostic yield in brisk bleeds due to poor visualization and inability to detect small bowel sources. In massive ongoing bleeding, arteriography and prompt surgical consultation is probably more appropriate.

Urgent Arteriography

Arteriography is both diagnostic and potentially therapeutic and, in contrast to colonoscopy, is only useful in the urgent setting and in cases of brisk bleeding. In hemodynamically unstable patients who have high transfusion requirements of >5 units of blood, urgent arteriography is preferred over colonoscopy [12]. For a bleeding vessel to be detectible during a normal, non-provocative angiography, it must be bleeding at a rate of at least 0.5 mL/min. Slower bleeds or bleeds that have stopped, even temporarily, will not be seen on a normal angiogram. There are provocative maneuvers that can be done during angiography to search for more occult bleeding that will be discussed in a future chapter.

A second appropriate use of arteriography is in patients who experience LGIB, have a colonoscopy that localizes the area of hemorrhage, but rebleed despite endoscopic treatment. A second colonoscopy with repeat endoscopic treatment may be useful, but it is potentially more effective to employ a second treatment modality such as arteriography before proceeding to surgical intervention for these difficult cases [12].

Once a bleeding vessel or AVM is identified through angiography, there are different options for treatment (Fig. 3). Traditionally, embolization was used in upper GI bleeding sources but avoided in lower GI bleeds because of the high rate of bowel infarction. However, over the past 10–15 years, smaller catheter and interventional platforms have become available (from 0.035″ systems to 0.018″ and 0.014″). With the newer technology and increasing skill with the technology, embolization has proven safe and is preferred over the previous recommended therapy of vasopressin infusion for LGIB [13]. Vasopressin infusion is effective in stopping a LGIB (59–90%), but requires long-term catheter placement, and potential complications from having a catheter in place in the femoral artery for 1–2 days. Embolization is also successful (73–100%) in controlling hemorrhage from a lower GI source, but is technically slightly more challenging and difficult in cases of tortuous vessels or arterial spasms (Fig. 4).

Arteriography is also an invasive procedure that carries some real risks, including contrast-induced nephropathy. It requires arterial access (usually via the femoral artery) and there are risks of arteriovenous fistula formation, pseudoaneurysm creation, thrombosis of the access site, or distal embolic complications. There is always

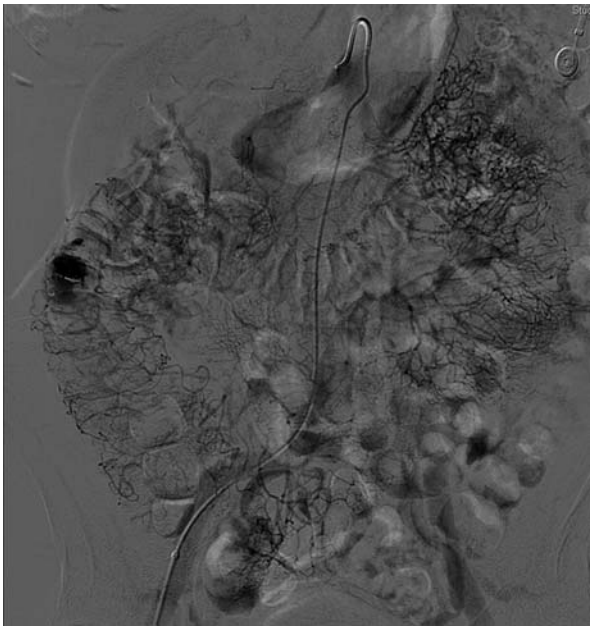

Fig. 3 Superior mesenteric angiography positive for right colonic bleeding

a bleeding risk with percutaneous vascular procedures, and the success of both diagnosis and therapy can also be operator dependent. In cases where therapy is not effective in stopping the bleeding, angiography provides a more detailed location of the hemorrhage for surgical intervention. Unlike colonoscopy, angiography can detect bleeding sources in the small bowel. However, angiography is not as effective as colonoscopy about differentiating causes of bleeding. Through a colonoscope, one can easily see the difference between a bleeding diverticula, an angiodysplasia, and a mass (Fig. 5). Interpretation of an angiogram is less straightforward, and further workup with computed tomography or even follow-up colonoscopy may be required to make the definitive diagnosis.

Urgent Tagged Red Blood Cell Scan

The most controversial of the three modalities in the urgent setting is radionucleotide scintigraphy. Technetium 99m-labeled erythrocyte scintigraphy is the most widely available, used and preferred because of its long half-life and its usefulness in delayed images. Alternate molecules have been used for scintigraphy, such as sulfur colloid and albumin. Technetium 99m-sulfur colloid is unavailable in many areas; the sulfur colloid molecule is rapidly cleared from the vasculature into bone marrow, liver, and spleen. This test is only useful if a patient is bleeding at the moment

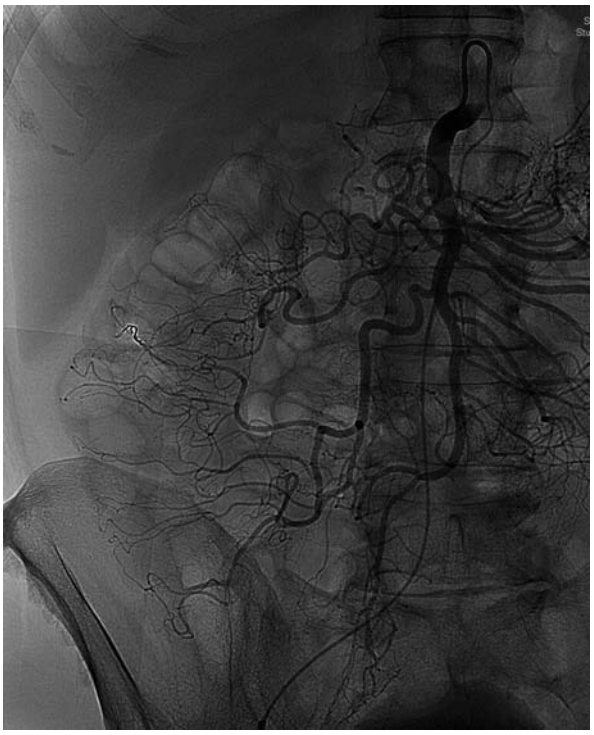

Fig. 4 Superior mesenteric angiography for the same patient in Fig. 3 after embolization with coils

of injection, because delayed images of the colonic flexures are obscured by high uptake in the liver and spleen [14].

Briefly, this test is performed by drawing 1–3 mL of blood from the patient, labeling the erythrocytes with 99mTc using a commercially available kit, and returning the blood to the patient at the time of the scan. Alternatively, in vivo labeling injection kits are also available. The labeled red blood cells are resident for roughly 24 h, and repeat scanning is possible and injection does not have to occur during a period of active hemorrhage. Delayed images are taken at 1-h intervals and can detect blood pooling from an obscure bleed not initially detected. The radiation exposure to the patient is low, less than for one abdominal CT scan [15].

Technetium 99m-labeled erythrocyte scintigraphy may be able to detect hemorrhage at rates as low as 0.1 mL/min, thus can be more sensitive than angiography in slower bleeds. The published sensitivity is incredibly variable and ranges from 26 to 82%. False-positive studies may lead to inappropriate surgery, and false negatives lead to diagnostic delays. Of the positive scans (Fig. 6), location of bleeding is inaccurate 20–25% of the time, which can also lead to inappropriate surgeries [14]. Because published studies enroll a wide variation of patients, interpretation of results is operator dependent, bleeding can be intermittent, and studies are

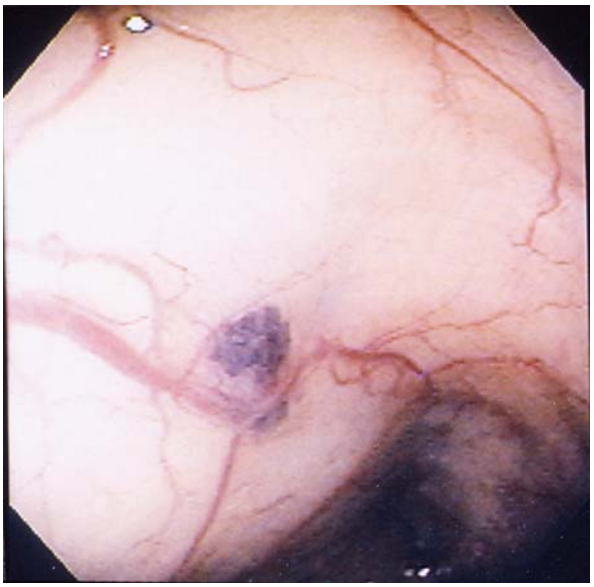

Fig. 5 Venous ectasia (Courtesy of John Migaly, M.D., Duke University Medical Center, Durham, NC)

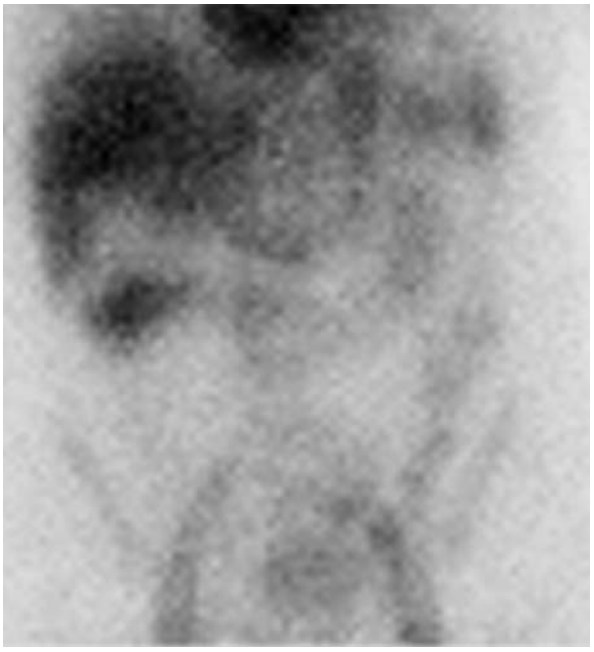

Fig. 6 Technetium 99m-labeled erythrocyte scintigraphy positive for bleeding in the area of the hepatic flexure

designed with different end points, it is difficult to compare studies and the debate about the proper use and timing of this modality continues. For most surgeons, rarely is an operation planned solely on the results of 99mTc-labeled erythrocyte scintigraphy [16].

Recent studies have focused on techniques to improve the diagnostic sensitivity and specificity of 99mTc-labeled erythrocyte scintigraphy. Subtraction scintigraphy is a technique where the first image obtained represents a background image and is subtracted from each subsequent image. An Australian group recently proposed that this technique does lead to greater diagnostic accuracy, reducing the false-positive rate from 9.6 to 3.6%. This was done in a small sample of 49 images, only 7 of which were true positives in the post hoc analysis and had a wide range of interobserver agreement [17]. One recent Italian study using single-photon emission computed tomography/computed tomography (SPECT/CT) in conjunction with scintigraphy showed greater diagnostic accuracy, as well as more precise localization of bleeding [18]. Again, results of this study should be interpreted cautiously in light of its small study size (19 patients), but there are other interesting studies on various contrast-enhanced CT techniques that may lead to better non-invasive diagnostic techniques in the near future.

This nuclear medicine study is often chosen because it is non-invasive and without the risks of angiography or colonoscopy. However, it is rarely sufficient for definitive diagnosis and often leads to either colonoscopy or angiography. There is no therapeutic component to scintigraphy, as it is a strictly diagnostic modality. Because of its low resolution, it can be difficult to pinpoint the location of the bleeding, and it is generally not recommended that segmental resection be performed solely on the basis of scintigraphy results. Its use, therefore, is limited in the urgent setting and should be implemented based on clinical judgment for an individual patient who may not be a suitable candidate for either colonoscopy or angiography.

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Bleeding Hemorrhoids

Kelley A. Hutcheson and Danny O. Jacobs

Introduction

Hemorrhoids are formed when fibromuscular cushions normally lining the anal canal become pathologically engorged leading to symptoms of bleeding, pruritis, and pain. These cushions serve to aid with control of continence and evacuation of formed stool without mucosal injury [1]. They are classically located in three positions: right anterior, right posterior, and left lateral [2]. There are two classes of hemorrhoids that can cause significant symptoms: internal and external, divided based on their position relative to the dentate line (Fig. 1). Internal hemorrhoids form when the anal cushions normally located proximal to the dentate line and held in place by connective tissue bands become dislodged and enlarged. They then become symptomatic by degrees which defines how urgently they require intervention. Bleeding is the symptom most commonly prompting intervention. First-degree hemorrhoids remain inside the anal opening but cause a sensation of fullness upon defecation and can cause localized pain and bleeding. Second-degree hemorrhoids prolapse outside of the anal opening with the increased pressure of Valsalva that is required for passage of feces, then spontaneously internalize once again. Third-degree hemorrhoids prolapse with Valsalva and remain outside the anal opening unless manually replaced in their anatomic position above the dentate line. Fourth-degree hemorrhoids prolapse with increased pressure and remain externalized, unable to be even manually reduced. External hemorrhoids are formed when peri-anal venous structures become engorged and thrombose causing pain ([3], Fig. 2).

Diagnosis

Evaluation of rectal bleeding begins with a thorough patient history and physical examination. Careful attention should be paid to historical findings including specifics of patient diet, pattern of regular fluid intake, presence of constipation,

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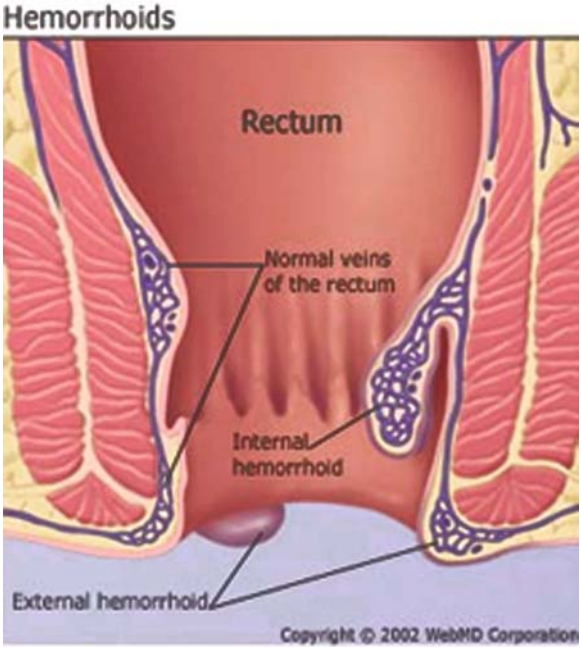

Fig. 1 Drawing of internal/external hemorrhoids

liver disease, coagulopathies, portal hypertension, pregnancy, medications (particularly narcotics, iron supplements, or other drugs known to cause constipation), family history of colorectal disorders, or personal prior history of colorectal disorders or interventions. A carefully detailed history of bleeding episodes must be obtained including frequency, amount, appearance (melena or hematochezia), and persistence. If bloody stools, anemia, or bleeding not typical of hemorrhoids is present, or if the patient is of sufficient age to warrant screening for colorectal cancer, colonoscopy should be performed to exclude other serious causes of bleeding regardless of whether hemorrhoids are present [4].

Presence of hemorrhoids is initially diagnosed at the bedside with inspection and a thorough digital rectal examination (DRE). The DRE is a crucial initial step in the evaluation of patient complaint of melena or hematochezia. During this examination, careful attention should be paid to the presence of external hemorrhoids, the integrity of the sphincters, the presence of internal hemorrhoids, and the character of stool in the rectal vault. Note should also be made of extreme pain on DRE which may signal the presence of thrombosed hemorrhoids or other causes of rectal bleeding including fissures, fistulae, or masses. If thrombosed or fourth-degree prolapsed hemorrhoids are identified, urgent intervention must be undertaken. If DRE is not sufficient to clarify what type of disorder is present, anoscopy, proctoscopy, or even colonoscopy should be undertaken [5].

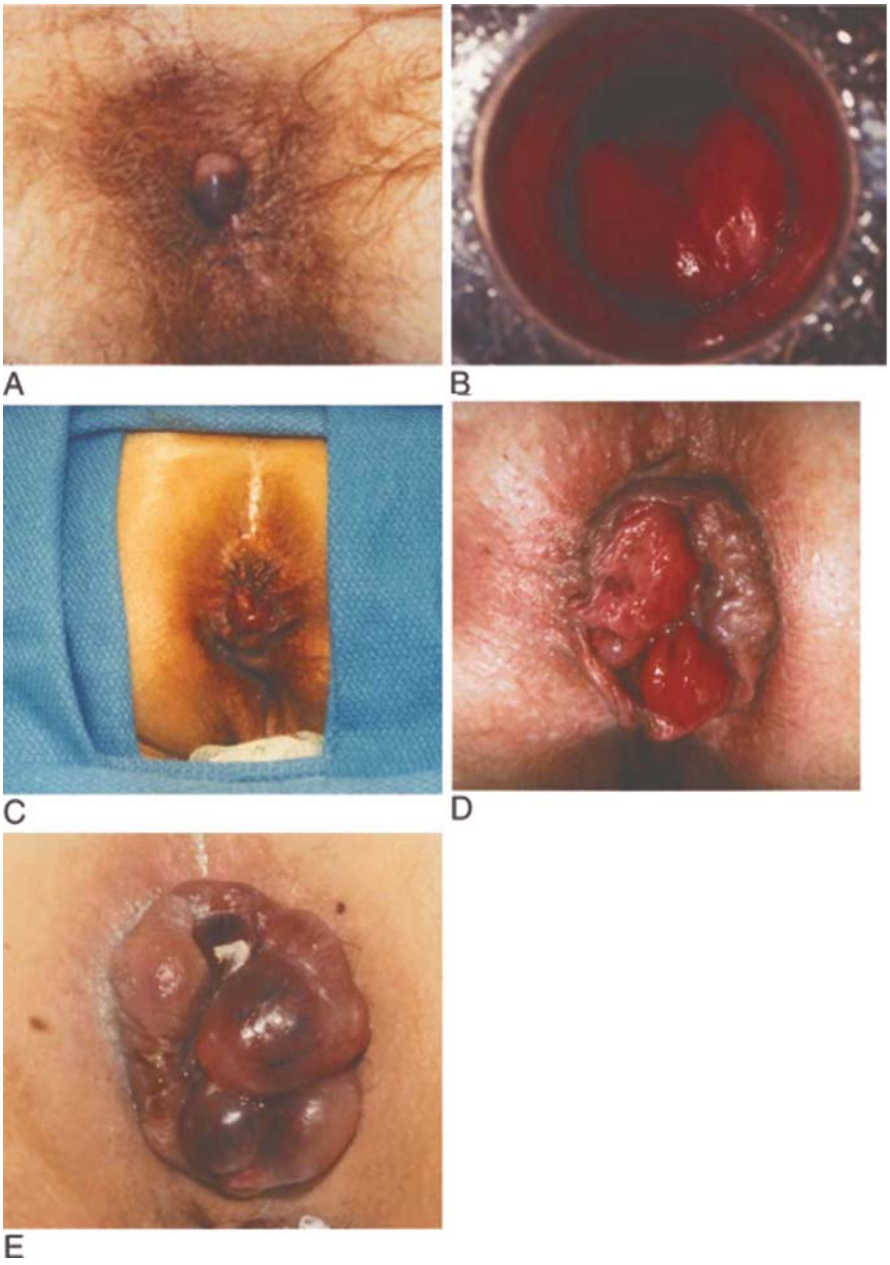

Fig. 2 Photos of hemorrhoid grades. **(a)** Thrombosed external. **(b)** First-degree internal viewed through anoscope. **(c)** Second-degree internal prolapsed, reduced spontaneously. **(d)** Third-degree internal prolapsed, requiring manual reduction. **(e)** Fourth-degree strangulated internal and thrombosed external. *(by permission of Mayo Foundation)*. Nelson [3]

Treatment

In the emergency department or office, acute hemorrhoidal hemorrhage can be tamponaded by direct application of pressure with packing (Gelfoam, etc.). If this is unsuccessful, control of hemorrhage can be achieved by placing a large-bore Foley catheter in the rectum, filling the balloon with at least 25 mL of fluid, and pulling the balloon tight against the top of the anal ring. If this method fails, epinephrine can be injected at the bleeding site. Finally, if the above methods fail to control an acute bleed, a suture ligature may be required to stop the bleeding and such may require an urgent trip to the operating room for treatment under anesthesia. Once local control is obtained, laboratory values including type and screen, hemoglobin and hematocrit, platelet count, and coagulation studies should be measured. Medication history, particularly all forms of anticoagulation, should be assessed. Then, volume resuscitation including administration of fresh frozen plasma and platelets as needed should be instituted, along with medical reversal agents such as vitamin K. Once any coagulopathy is corrected and local control is achieved, further evaluation and treatment of hemorrhoids can proceed [6].

Once bleeding hemorrhoids are identified, there are several options for treatment depending on the location of the hemorrhoids, the amount of bleeding present, and patient history/comorbidities (Fig. 3). The options range from lifestyle modifications to minimally invasive incision and drainage of thrombosed external hemorrhoids to rubber-band ligation to stapled or open hemorrhoidectomy for internal disease. First-degree and second-degree hemorrhoids are largely managed conservatively with measures including stool softeners, increased dietary

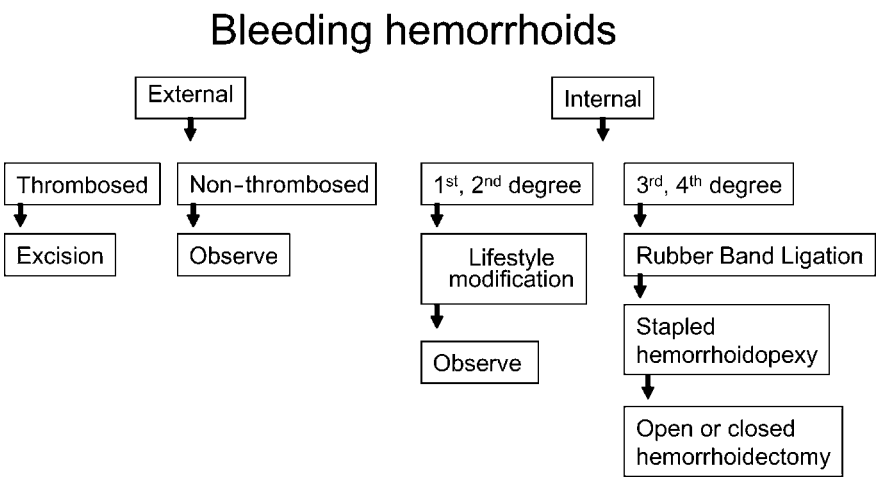

Fig. 3 Treatment algorithm. Mayo Clinic Staff. Hemmorrhoids. Mayo Foundation for Medical Education and Research, Mayoclinic.com; December 24, 2008. © 1998–2009 Mayo Foundation for Medical Education and Research (MFMER). All rights reserved

fiber consumption, increased fluid intake daily, decreased time spent on the toilet/decreased straining, and improved personal hygiene [5]. Eighty percent of these hemorrhoids respond to conservative measures not requiring further intervention [7]. Hemorrhoids that result from self-limited conditions such as pregnancy often resolve without requiring definitive intervention.

Third-degree hemorrhoids, however, do not typically respond to conservative measures and require further intervention. The most universally applied initial management is rubber-band ligation where rubber bands are applied via a proctoscope with success rates of 86–95% [8, 9]. There are proctoscopes that can deliver multiple bands during a single session [10], but limited banding is recommended due to the increased risk of infection and post-procedural discomfort with multiple bands in a single session [11, 12]. Complications of which to be aware include anal pain (2–5%), urinary retention (2–5%), band slippage (1–2%), development of post-banding ulcer (1%), hemorrhage (1%), or severe pelvic infection (<0.5%). Anal pain can be avoided by uniformly placing the band at least 2 cm proximal to the dentate line to avoid serious pain complications associated with banding in the sensate portion of the anoderm [13]. This procedure should not be performed in seriously immunocompromised patients due to an unacceptably high risk of pelvic sepsis or death ([3], Fig. 4).

Another alternative is infrared coagulation therapy where infrared radiation is applied to hemorrhoids in short bursts lasting 1–1.5 s to decrease blood flow to the region [14]. This treatment has recently fallen out of favor due to increased post-procedural pain syndromes. Sclerotherapy is another alternative method in which a sclerosing agent is injected locally into the apex of hemorrhoidal clusters. Agents include phenol in oil, sodium morrhuate, sodium tetradecyl sulfate, and quinine urea. Dangers of this technique include significant peri-anal infection or fibrosis if injectant is applied improperly [3]. Cryotherapy to relieve symptoms has been attempted with 90% success rates but unacceptably high rates of post-procedural pain as well as foul-smelling discharge [15]. Ligation under vision is another technique which has been described in a small series from Israel. Bronstein performed this technique as an outpatient procedure in 32 patients with grade II and III hemorrhoids. The procedure consists of suture ligation of hemorrhoids under direct vision without additional instrumentation and took an average of 22 min to perform. At median follow-up of 21 months, 12.5% of patients (4 of 32) continued to suffer from symptomatic bleeding with 8% suffering return of prolapse. Overall, 90.5% of patients considered the procedural result to be good or excellent [16]. This technique can be particularly useful when applied in addition to correction of other more complex anal pathology. Finally, another minimally invasive technique useful for managing bleeding is Doppler-guided hemorrhoidal artery ligation where a Doppler device attached to the end of a proctoscope is used to guide identification of hemorrhoidal tissue to be ligated [17]. Though it controls bleeding, this method is not effective in treatment of hemorrhoidal prolapse with recurrent prolapse occurring in 64% of patients [18].

Fourth-degree hemorrhoids as well as some third-degree hemorrhoids require operative intervention to either resect the involved tissue or replace it into its

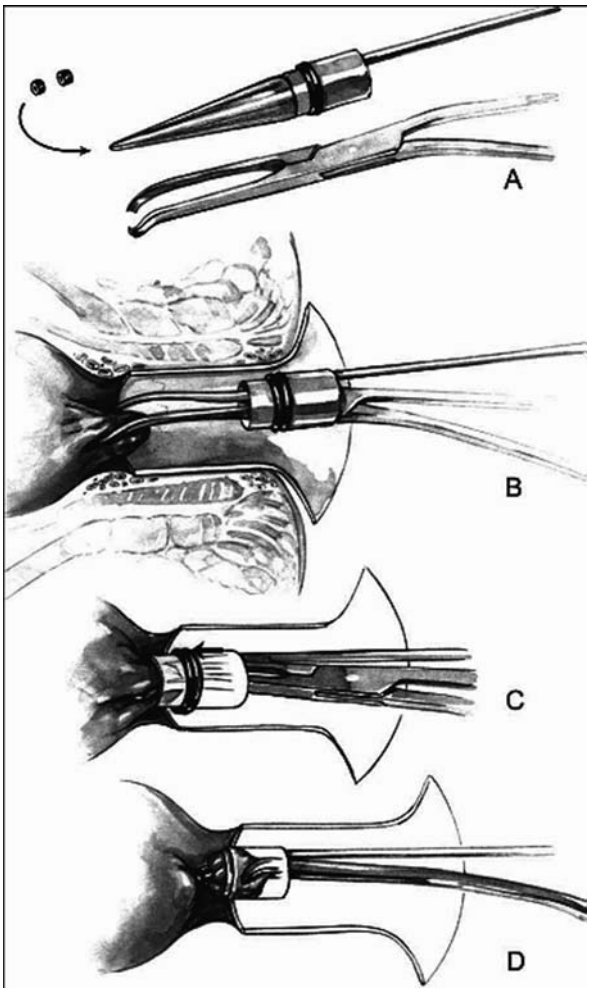

Fig. 4 Diagram of rubber-band ligation. The technique of rubber band ligation. **(a)** Two bands are placed on the McGivney hemorrhoid ligator. **(b)** Hemorrhoidal tissue is localized and grasped with the forceps. **(c)** The ligating instrument is advanced above the dentate line and fired. **(d)** The hemorrhoid ligator is removed. (Reprinted from Gearhart, SL. Advances in Surgery 2004;38:167–182.)

anatomic position proximal to the dentate line. The choice of which procedure to pursue should be based on overall patient health, cost, operative time, hospital length of stay, post-procedural pain, time until return to daily activities, and patient preference. Traditional operative management includes either open or closed hemorrhoidectomy. A newer technique gaining widespread acceptance is the stapled hemorrhoidopexy.

Open hemorrhoidectomy, or the Milligan–Morgan technique, involves ligation of hemorrhoids followed by excision of the involved tissues leaving the wound open to close by secondary intention [19]. This technique has been a mainstay of surgical therapy for hemorrhoids since its introduction in 1937 with good results. In 1959, Ferguson introduced an alternative procedure in which the resultant anal

skin is closed. Closed hemorrhoidectomy, or the Ferguson technique, involves ligation of hemorrhoids followed by excision of the involved tissue with closure of the wound (20, Fig. 5). Historically, both of these operative techniques involved hospital stays of 3–4 days, although many are now performed as ambulatory procedures. Significant postoperative pain, however, remains the complication most feared by patients. Other known complications include postoperative bleeding, urinary retention, fecal impaction, wound complications, anal stricture, flatus incontinence, anal fistula, anal fissure, mucosal ectropion, and abscess [21]. Arbman et al. also described a recurrence rate of symptomatic hemorrhoids of greater than 10% in patients treated by either the open or the closed technique [22]. Guenin et al.

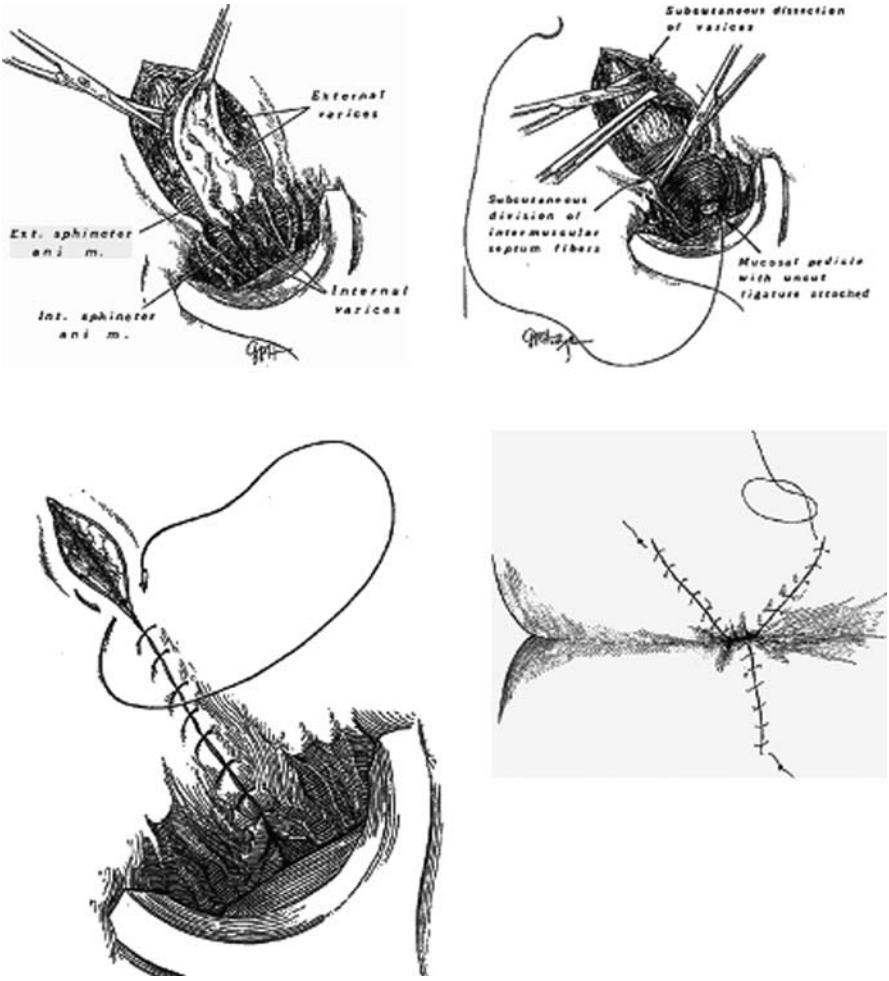

Fig. 5 Diagram of Ferguson technique (Ferguson [20])

examined operative results and patient satisfaction with Ferguson hemorrhoidectomy 4.7 years after operation. Only 0.4% of patients had to undergo reoperation for hemorrhage. There was no mortality in the study. Sixty-seven percent of patients reported relief of the leading symptom prompting intervention with an additional 27.2% reporting improvement in symptoms. Patients evaluated the surgical result as excellent 70.5% of the time, good 21.4% of the time, and bad in only 1.9% of patients [23].

Wang et al. described a modified Ferguson technique for treating circumferential prolapsed grade III or IV hemorrhoids in 738 patients. They radically resected hemorrhoidal tissues and redundant anoderm before anchoring the residual anoderm and mucosa to the internal sphincter above the dentate line in a tension-free manner. Mean operative time was 27 min and hospital stay was 3.4 days. Their complication rates, including anal stenosis and incontinence, were comparable to other radical techniques. Their incidence of hemorrhoidal recurrence and postoperative pain was less than with other radical techniques making this a reasonable alternative to consider [24].

Stapled hemorrhoidopexy, also known as the procedure for prolapsing hemorrhoids (PPH), has been gaining popularity since its introduction in the late 1990s. Longo first described the technique in 1998 whereby a specially designed circumferential stapler is carefully applied via a proctoscope [25] and used to secure the anal cushions back in their anatomic position (Fig. 6). Early results from clinical trials

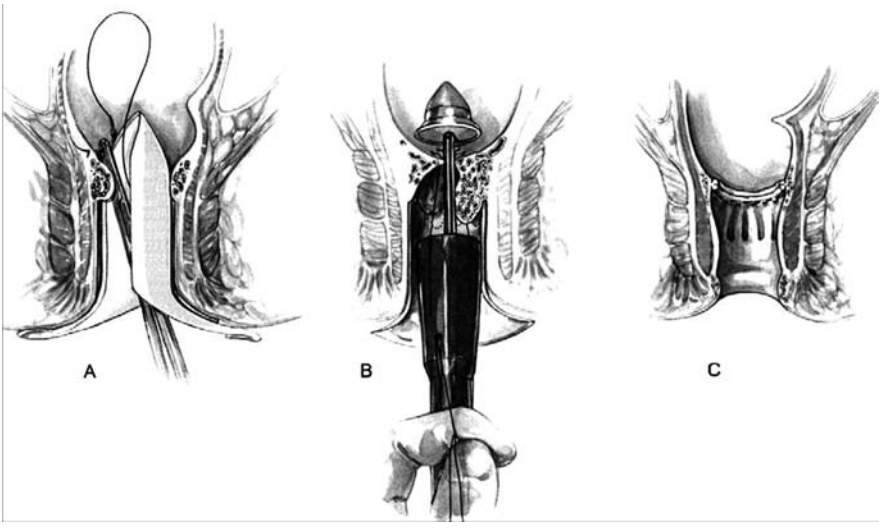

Fig. 6 Diagram of stapled technique. **(a)** A purse-string suture is placed approximately 2–4 cm from the dentate line. **(b)** The purse-string suture is secured around the stapling device. At this point, in female patients, the vagina should be examined for the presence of a stitch or pulling before firing the stapling device. **(c)** The hemorrhoid complexes have been resuspended and an intact staple line is present. (Reprinted from Gearhart, SL. Advances in Surgery 2004;38: 167–182.)

suggest that this technique is as effective as closed Ferguson or open Milligan–Morgan techniques [26] and results in reduced postoperative pain syndromes and shorter hospital stays [27]. Recurrence rates are approximately 18% and recurrences tend to be of lesser severity. If repeat intervention is required for recurrent hemorrhoids, minimally invasive techniques are usually sufficient. Care must be paid to prevent serious complications using this technique. If performed on a woman, operative procedure must include concomitant vaginal exploration to prevent inclusion of vaginal tissue in the staple line [28]. Similarly, attention must be paid to prevent complete occlusion of the anal opening with the stapler. Devastating complications have been rarely reported including retroperitoneal sepsis [29, 30]. Care must also be paid to proper placement of the staple line sufficiently above the dentate line to prevent serious post-procedural pain syndromes inherent in stapling the sensitized anoderm. Finally, cost is also a consideration with stapled hemorrhoidopexy being more expensive than traditional techniques due to cost of the stapling device [31].

The Association of Coloproctology of Great Britain and Ireland conducted a national audit in 2005 which included 695 patients undergoing stapled hemorrhoidopexy for bleeding or prolapsed hemorrhoids. This audit concluded that it is a safe and effective procedure with good short-term outcomes and requires longer-term follow-up [26].

Ceci evaluated stapled hemorrhoidopexy outcomes for grade III and IV hemorrhoids at mean follow-up of 73 months, finding that there were no symptoms related to hemorrhoids in 65.3% of patients, moderate symptoms in 25.4%, and severe symptoms in 9.3% of patients. Hemorrhoids recurred in 18.2% of patients. Postoperative bleeding was the most common complication affecting 4.8% of patients. Incontinence of stool was reported in 1.4% of patients. Patient satisfaction with the procedure was 89.7% overall [32]. Stolfi compared stapled hemorrhoidopexy with the conventional Milligan–Morgan technique in 171 patients with third-degree and fourth-degree hemorrhoids and found that early postoperative pain was not different between them but that pain was significantly reduced in the stapled group between postoperative days 3 and 8. Unfortunately, the incidence of anal fissure was significantly higher in the stapled group (6.3 vs. 0%) but the incidence of other postoperative complications was similar between the two [33].

Finally, a meta-analysis comparing stapled hemorrhoidopexy with conventional operative techniques including 29 randomized trials of 2,056 patients demonstrated that the stapled technique was less painful, required a shorter inpatient hospital stay, could be performed more quickly, and allowed patients to return to normal activities sooner. Complication rates were not significantly different. Unfortunately, the stapled technique resulted in a higher rate of recurrent disease (relative risk 2.29). It was also noted that the learning curve to perform the stapled procedure independently is at least 10 cases [27].

Treatment of the other class of hemorrhoids, external hemorrhoids, is much simpler and is required only when they become thrombosed causing local pain or an uncomfortable mass effect. External hemorrhoids rarely present with bleeding as a significant complaint but instead with painful thrombosis. If present for

less than 72 h, treatment consists of complete surgical incision and decompression of the thrombosed hemorrhoid to prevent recurrent thrombosis ([34], Fig. 7). If present for more than 72 h, the condition is often self-limited and can be managed conservatively with resolution.

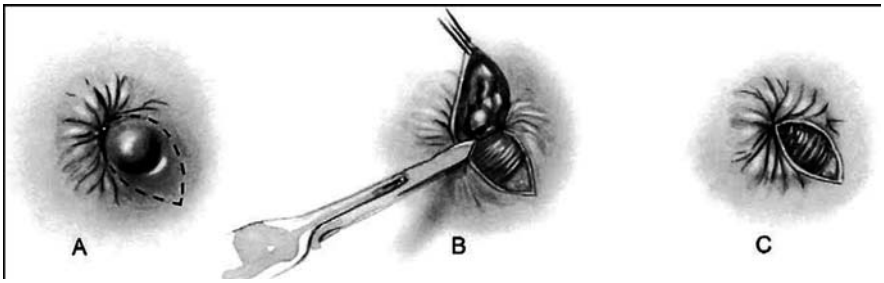

Fig. 7 Diagram of external hemorrhoid excision. **(a)** An elliptical excision that fully encompasses the thrombosed hemorrhoid should be made. **(b)** The excision should completely remove the hemorrhoid complex. **(c)** The excision site is left open to heal. (Reprinted from Gearhart, SL. Advances in Surgery 2004;38:167–182.)

Overall, bleeding hemorrhoids are a significant clinical problem affecting more than 10 million Americans and require safe, effective treatment [35]. Fortunately, there are many diverse options available allowing for differences in severity of symptoms, patient demographics, and patient preference. As biotechnology improves, advances continue to be sought in this field including design of new equipment that combines classic operative techniques with modern technology to achieve superior results in the modern era [36, 37]. Once hemorrhoids have been identified as the cause of rectal bleeding, all of the above information can be applied in selecting the optimum treatment strategy for a given patient.

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Management of Bleeding Colitis and Colonic Diverticular Disease

Sebastian G. de la Fuente, Hardeep S. Ahluwalia, Alex Perez, and John Migaly

Bleeding Colitis

Inflammatory bowel disease, infectious, or ischemic colitis can all present with lower gastrointestinal (GI) bleeding. Overall, colitis contributes to approximately 20% of all causes of lower GI bleed [1]. Bleeding from colitis is usually intermittent, self-limiting, and commonly associated with other symptoms such as diarrhea, fevers, abdominal pain.

By definition, colitis refers to inflammation of the mucosa and can be associated with inflammation of other segments of the GI tract (e.g., ileitis) or be limited to the colon. Proctitis refers to inflammation limited to the rectal mucosa.

Classification of colitis (Table 1) depends on the etiology of the offending factor, but in general, the clinical presentation and endoscopic appearance are similar in different types of colitis. Endoscopic examination usually reveals a friable mucosa with edema, erythema, and tendency to bleed upon manipulation.

The diagnosis of colitis is established with a complete history and physical examination, evaluation of stool in case an infectious source is suspected, and ultimately by colonoscopy. Findings of mucosal inflammation can also be detected by computer tomography and barium enema in some cases. In patients that remain hemodynamically stable, treatment is aimed at the source of the inflammation. If hemodynamic stability is compromised or if bleeding is severe enough to require multiple transfusions, angiography or emergent surgery is indicated.

Infectious and Antibiotic-Associated Colitis

The most common pathogens of infectious colitis in immunocompetent patients in the United States are Salmonella, Campylobacter, Shigella, *Escherichia coli* (enterohemorrhagic *E. coli* [EHEC], enteroinvasive *E. coli* [EIEC]), and

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Table 1 Causes of colitis

• Inflammatory bowel disease *Ulcerative colitis, Crohn's disease, indeterminate colitis*
• Ischemic colitis
• Infectious colitis
• Radiation-induced colitis
• Medication-related colitis
• Neonatal necrotizing enterocolitis

species of Yersinia. Immunocompromised patients can experience colitis from Cytomegalovirus, Campylobacter infections, Cryptosporidiosis, etc.

Various antibiotics may alter the balance of normal colonic flora allowing the overgrowth of Clostridium species. *Clostridium difficile* is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhea and colitis. *C. difficile* produces two toxins. Toxin A is a cytotoxin and creates the colonic inflammation that allows Toxin B to enter the colonic mucosal cells. Toxin B is extremely toxic to colonic cells. Diarrhea and colitis are caused by toxins produced by pathogenic strains of this bacteria. Clinical manifestations may range from simply loose stools to active colitis with bloody diarrhea, pain, fever, leukocytosis, and protein-losing enteropathy. Diagnosis is suspected when there is a history of diarrhea after antibiotic use. Most cases involve the distal colon and flexible sigmoidoscopy usually detects the disease. In those cases with distal sparing a complete colonoscopy is required. Endoscopically, pseudomembranes appear as multiple raised, white/yellow adherent plaques. Diagnosis can also be confirmed by detection of *C. difficile* toxin in the stool. Most cases will resolve with metronidazole or oral vancomycin therapy. Intractable or fulminant disease may require hospitalization for supportive measures including blood transfusion according to the same principles for the management of ulcerative colitis, and even emergent colectomy if deterioration continues. The operation of choice in fulminant pseudomembranous colitis is a total abdominal colectomy with end-ileostomy; other operations such as loop ileostomy, segmental resection, or "blowhole" stoma carry a significantly higher mortality in comparison to total colectomy with end-ileostomy [2–4].

Ulcerative Colitis

Ulcerative colitis is a chronic mucosal inflammatory process of the colon. The mildest form of this disease, ulcerative proctitis, only affects the rectum (Fig. 1), but this may progress and involve the more proximal colon. Bleeding is the most common local complication of ulcerative colitis. History and stool examination usually permit a presumptive diagnosis that must be confirmed with colonoscopy and biopsy. This also provides a measure of disease activity.

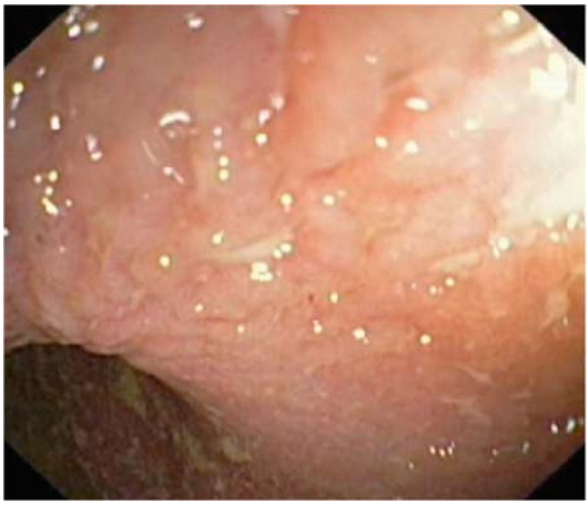


Fig. 1 Endoscopic appearance of ulcerative colitis showing erythema, edema, and granularity of the colonic mucosa

Bleeding from mild disease confined to the rectum and sigmoid colon can be treated topically, thus systemic treatment is not always necessary. Hydrocortisone or 5-ASA enemas can be quite effective in the treatment of left-sided disease.

Severe disease, manifested by >10 bloody bowel movements per day, tachycardia, high fever, or severe abdominal pain, requires hospitalization. If the patient had been receiving oral corticosteroid treatment $\geq$30 days prior to admission, hydrocortisone 300 mg/day should be given as a continuous IV infusion. In patients who have not received recent corticosteroids then ACTH 75–120 U/day by continuous drip should be initiated. Treatment is given for 7–10 days and response is monitored by noting the nature and frequency of the bowel movements. An initial radiographic imaging should be obtained to assess colonic involvement and the patient must be followed closely for the development of toxic megacolon. Oral prednisone 60 mg/day may be substituted after remission has been achieved and after a course of parenteral treatment. Stability on an oral regimen can be followed by hospital discharge with close home monitoring.

Emergency colectomy is indicated for massive hemorrhage, fulminant toxic colitis, or perforation. Subtotal colectomy with ileostomy and rectosigmoid closure is usually the procedure of choice because most critically ill patients cannot tolerate total proctocolectomy. The rectosigmoid stump may be removed at another setting since it may represent a site for disease reactivation.

Cyclosporine has been used as a final therapeutic measure prior to colectomy in patients with bleeding refractory to high-dose intravenous steroids; however, it may take up to a week for patients to have a significant improvement in symptomatology. Cyclosporine is also nephrotoxic and may not be a therapeutic measure that is of much benefit overall since most patients receiving cyclosporine eventually progress to requiring a colectomy within a year. Therefore, the risks and

benefits of cyclosporine therapy clearly favor colectomy over prolonging medical treatment [5].

Ischemic Colitis

Intestinal ischemia occurs most commonly in the colon and results from low-flow and/or small vessel occlusion (Fig. 2). Signs and symptoms of ischemic colitis reflect the extent of bowel involvement and may begin suddenly with severe left lower abdominal pain followed by bloody diarrhea. Diagnosis can be made by colonoscopy and treatment depends on clinical severity. Endoscopically, mild ischemic colitis can appear as long segment strip of ischemic mucosa on the antimesenteric surface of the colonic lumen, where the blood flow is most tenuous. More progressive ischemia will appear confluent on colonoscopy. Roughly 80% will recover with bowel rest, hydration, and broad-spectrum antibiotics. Hemodynamic parameters must be optimized especially in the setting of hypotension and suspected low-flow states. This process may progress to bowel necrosis, perforation, and peritonitis. Colonoscopy should be performed after recovery to evaluate for strictures and to rule out other pathology. Failure to improve with continued bloody bowel movements after 2–3 days of therapy is an indication for resection of necrotic tissue.

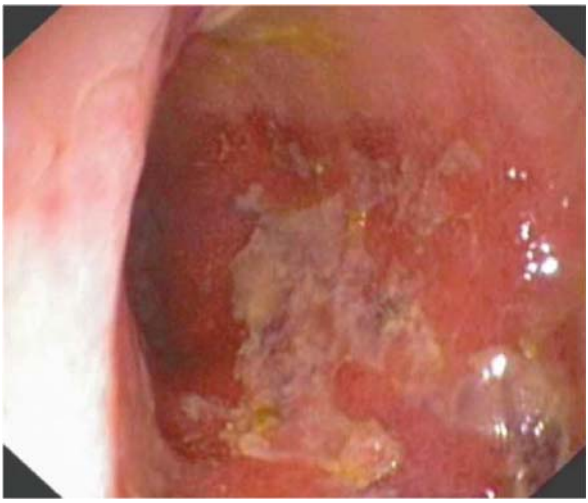


Fig. 2 Colonoscopy of a patient with ischemic colitis showing necrosis of the mucosa, erythema, and areas of petechia

Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is common cause of colitis in newborns that affects premature patients. NEC presents with gas accumulation in the bowel wall and progresses to necrosis that can lead to perforation, peritonitis, and sepsis. Treatment of NEC depends on the overall condition of the patient. Even though bloody stools

are a common presentation of NEC, transfusions are rarely needed. Treatment is aimed at resting the bowel, hemodynamic support, and broad-spectrum antibiotics. Surgery is reserved for cases of free perforation, obstruction, failure of conservative treatment, or sepsis.

Diverticular Disease

Colonic diverticular disease refers to the presence of multiple pouches or herniations of the colonic wall. Colonic pseudodiverticula or outpouchings consisting of only mucosa and submucosa occurs in areas of weakness of the colonic wall such as where the bowel wall is penetrated by its vasculature. Most cases of diverticulosis are acquired but congenital cases have been described in the literature. Although not fully understood, the etiology of acquired colonic diverticular disease has been attributed to a variety of factors such as colonic aging, dysmotility, transient increases in colonic intraluminal pressures, and environmental conditions such as a lack of fiber in the diet. Diverticuli are most commonly located in the sigmoid (95–98%); however, diverticulosis can also involve the descending, ascending, and transverse colon as well as the jejunum, ileum, and duodenum. Overall, about half of all Americans age 60–80 have colonic diverticulosis and almost everyone over the age of 80 has some degree of the disease [6].

Even though the presence of diverticular disease can remain asymptomatic for decades, the two most common complications of diverticulosis include diverticulitis or inflammation of the pouch and bleeding. Indeed, approximately 10–20% of patients with colonic diverticula will have a complication during their lifetime. While diverticulosis affects all races equally, right-sided diverticula, which are usually congenital, occur most commonly in Asians.

Most commonly, lower GI bleeding from diverticular disease occurs in the form of bright red-colored stools but bleeding can also be sudden and massive compromising the hemodynamic state of the patient. These patients typically require intensive care admission with transfusion of blood and correction of any coagulopathy that might co-exist. In patients in whom the bleeding is not too significant, hemorrhage will cease in about 90% of the time. The recurrence rate over time after the first episode of bleeding is 9% at 1 year, 10% at 2 years, and 90% at 3 years [7].

Diagnosis and Therapeutic Options

Establishing the diagnosis of colonic diverticular disease starts with a complete history and physical examination. The presence of any associated comorbidity, family history of bleeding disorders, cancer, medications, and date of last colonoscopic examination should be investigated. Physical examination can demonstrate tachycardia, hypotension, and postural changes based on the amount of blood lost. Stool usually is guaiac positive but negative guaiac stools can be found since bleeding may

be intermittent. Basic laboratory data should be obtained including a CBC count, coagulation parameters, and serum iron levels. The diagnosis of diverticulosis can be established with imaging studies such as barium enema or computer tomography; however, colonoscopy remains the most common method of establishing the diagnosis when the patient present with lower GI bleeding.

Colonoscopy

The stigmata of bleeding on endoscopy such as active bleeding or adherent clots is used to identified the bleeding source in upper endoscopies (Fig. 3a); however, most endoscopists do not perform urgent colonoscopy to identify stigmata of bleeding from lower gastrointestinal lesions, but rather perform elective colonoscopy when the patient has had a chance to undergo a colonic purge that would facilitate visualization.

A major problem in patients with active bleeding is the low detection rate of bleeding lesions, thus not allowing endoscopic hemostasis. Some authors, however, have found colonoscopy to be useful in the emergency setting. Jensen and colleagues investigated the role of urgent colonoscopy in the diagnosis and treatment of 121 patients with severe hematochezia and diverticulosis who underwent a colonoscopy within 6–12 h after hospitalization or the diagnosis of hematochezia [8]. In this study, at least one-fifth of patients were confirmed to have diverticular disease as the source of bleeding and colonoscopic treatment of such patients with epinephrine injections, bipolar coagulation, or both allowed prevention of recurrent bleeding and decreased the need for surgery. In a more recent study at our institution, 100 consecutive patients presenting with lower GI bleeding without upper or anorectal bleeding sources were randomized to urgent purge preparation followed immediately by colonoscopy or a standard care algorithm based on angiographic intervention and expectant colonoscopy [9]. In this study, a definite source of bleeding was found more often in urgent colonoscopy patients than in the standard care group. When outcomes were studied, however, there was no difference between the two groups in mortality, length of hospital stay, ICU stay, transfusion requirements, early and late rebleeding rates, or the need for surgery. Other studies investigating urgent colonoscopy have found this approach to yield a definite bleeding site in 7–100% of patients [10–12]. The wide discrepancy reported in the literature is likely reflective of a number of factors such as differences in equipment used between studies, timing, and quality of the preparation among studies, experience of the endoscopist.

Colonoscopy allows not only the diagnosis of diverticular disease but also treatment in some cases. Endoscopic treatment can be accomplished by a variety of methods including heater probe or argon plasma coagulation, injection of vasoactive substances, or application of clips (Fig. 3b, c). Although there have been widespread practical experience to support the efficacy of these approaches in upper GI bleeding, there are much fewer such data for lower GI bleeding. In the study by Jensen

[8], urgent colonoscopic treatment reduced the number of patients requiring surgery and reduced rebleeding rates. This statement, however, has not been proven true in large randomized trials. The difficulties in controlling bleeding endoscopically reside not only in the need for large-dual channel endoscopes, not widely available, but also in the endoscopic characteristics of the diverticulum (i.e., the bleeding vessel may originate from deep inside the diverticulum as well as from the rim) making endoscopic therapy especially difficult. Most experts agree that severe or ongoing recurrent bleeding mandates management by radiologic embolization or urgent surgery.

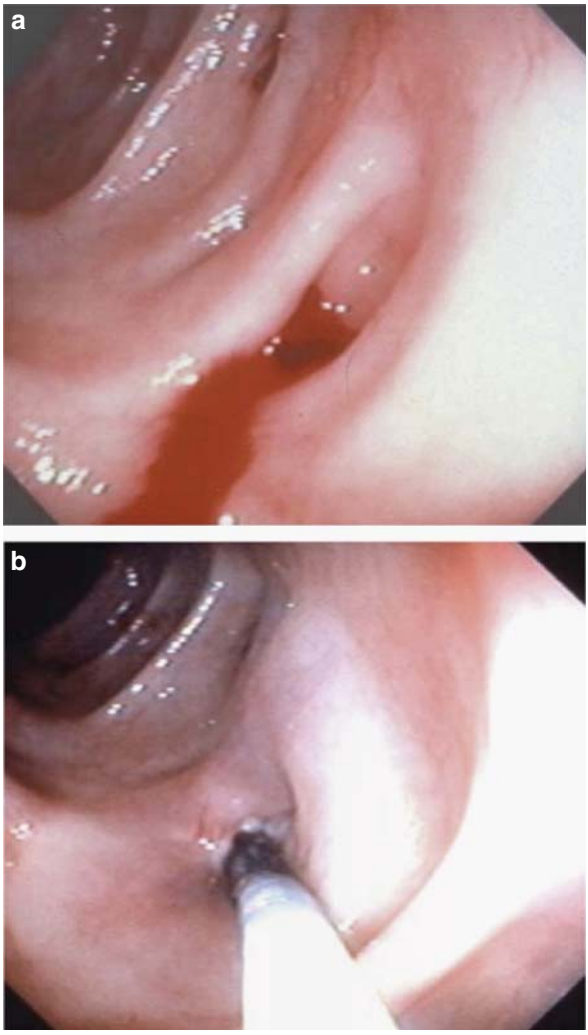
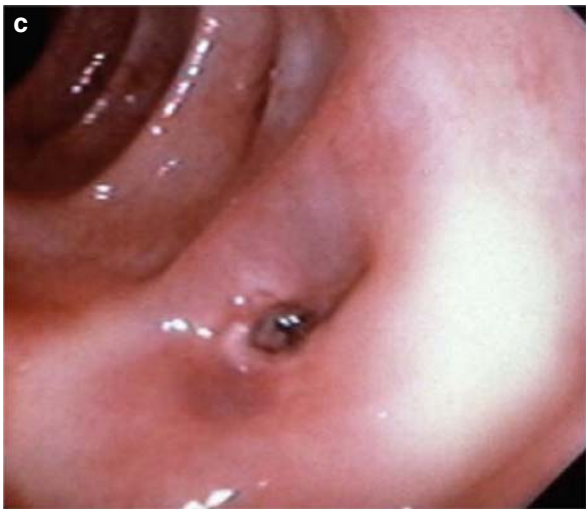


Fig. 3 Bleeding colonic diverticula (a) treated endoscopically with a heating probe (b). Resolution of bleeding following treatment (c). Other alternatives include argon plasma coagulation, injection of vasoactive substances, or application of clips

Fig. 3 (continued)



Angiography

Angiography remains an excellent means for the diagnosis and treatment of bleeding diverticular disease. The overall sensitivity of angiography ranges from 58 to 86% and detection of bleeding depends on the rate of bleeding (as low as 0.5 mL/min) and localization. Selective mesenteric angiography should be reserved for those patients in whom colonoscopy is not appropriate [1] or in patients who are actively bleeding.

Selected infusions of vasopressin by angiography has proven effective in 36–90% of cases with ongoing bleeding [13, 14]. The recurrent bleeding rate after infusion of vasopressin is in the 22–71% range. Vasopressin infusion during angiography can control bleeding, but potential complications including bowel infarction and perforation, arterial vasospasm, and lower extremity ischemia can occur. Selective embolization, on the other hand, has a success rate of 71–90% with a rebleeding rate of 15–20%. Even with highly selective transcatheter embolization, the rate of significant intestinal ischemia can be as high as 20%.

Other Tests

Radionuclide scanning using technetium ^{99m}Tc-labeled red blood cells or ^{99m}Tc sulfur colloid is helpful in detecting active bleeding. The advantage of Technetium scintigraphy is that it can detect bleeding at a rate of 0.05–0.1 mL/min [15]. Furthermore, the tracer persists in the blood stream long after injection, which is particularly useful if the bleeding is intermittent in nature. The patients can be successfully scanned without repeat injection as much as 24 h after the original

injection. There is significant reflux of contrast back and forth in the colon particularly toward dependent areas, such as the flexures, which can sometimes make localization of the bleeding sites difficult and there can be a false localization rate as high as 25%. Therefore segmental resections should be avoided if they are based purely on radionuclide scanning; in these cases supplemental information should be sought if possible or total colectomy should be considered.

Surgical Approach

If previous endoscopic and angiographic attempts have failed, surgery provides the definitive treatment for ongoing or recurrent diverticular disease bleeding. Indications for surgery include patients that require more than 4 units of blood in a 24-h period to remain hemodynamically stable, those in whom bleeding has not stopped after 72 h, or those who experience rebleeding within 1 week after an initial episode.

Surgical options include segmental resections or more extended operations depending upon the location of the disease and overall state of the patient. Patients that would not tolerate a prolonged operation might be much better off with limited control of the bleeding with the understanding that leaving disease behind can be associated with recurrent bleeding. In general, control of bleeding can be obtained in most patients and the need for transfusions decreases significantly after surgery. Finally, blind segmental resection is discouraged if preoperative imaging has failed to identify localization of the bleeding source. Partial colectomy with unidentified bleeding source has been linked with rebleeding rates of approximately 75% and high mortality [16]. In these cases, intraoperative localization options include upper endoscopy, colonoscopy, or small bowel endoscopy assisted by hand manipulation of the small bowel by the operating surgeon.

In patients where localization of chronic, ongoing bleeding has proven difficult, such as in situations where arteriogram and Technetium scans have both been nondiagnostic, the choice of procedure is sometimes difficult. If pandiverticulosis has been documented, and upper gastrointestinal/obscure sources of bleeding have been ruled out via upper endoscopy and/or capsule endoscopy, total abdominal colectomy with or without ileoproctostomy is an acceptable option in the face of ongoing bleeding.

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Colonic Arteriovenous Malformations

Sebastian G. de la Fuente and Christopher R. Mantyh

Introduction

Arteriovenous malformations (also known as angiodysplasias, vascular ectasias, or angiomas) are defined as degenerative lesions of the gastrointestinal tract that result from chronic obstruction of the submucosal veins. Even though the etiology of these lesions is not well understood, a leading hypothesis is that peristaltic contractions of the muscular layers lead to chronic partial obstruction of submucosal veins of the intestinal wall and with time these veins become dilated and tortuous. Ultimately, the precapillary sphincters become incompetent and arteriovenous communications develop [1].

Colonic arteriovenous malformations (AVM) are a relatively common cause of lower gastrointestinal bleeding, especially in the elderly. In some reports, hemorrhage secondary to AVM accounts for up to 40% of all lower intestinal bleeding [2]; however, more recent evidence shows that the real incidence is lower than that [3]. In the review done by Vernava et al. [4], AVM accounted for only 1–4% of cases depending on the diagnostic method used, and Sebastian–Domingo reported an incidence of approximately 2% on 2,750 colonoscopies [5]. Among healthy asymptomatic people these lesions are exceptionally uncommon and generally benign with a low risk of bleeding [6].

There is an equal distribution of AVM between genders. In terms of anatomic location, AVM are most common in the cecum and proximal ascending colon (54%), followed by the sigmoid colon (18%) and rectum (14%) and about 15% are limited to the jejunum and ileum [7]. Most commonly colonic AVM present as multiple vascular lesions but can also manifest as an isolated finding. Unlike congenital or neoplastic vascular malformations, this lesion is not associated with angiomatous lesions of the skin or other viscera.

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Arteriovenous malformations have been associated with aortic stenosis. Heyde first reported this association in 1958, describing the *Heyde syndrome* as the combination of aortic stenosis and GI bleeding due to colonic AVM. These lesions are also notably associated with renal failure, especially in elderly patients, and patients with von Willebrand disease have an increased incidence of gastrointestinal bleeding from colonic AVM.

The classic clinical presentation of colonic AVM is characterized by low-grade, intermittent bleeding in the forms of maroon-colored stool, melena, or hematochezia. Even though bleeding stops spontaneously in most patients [8], recurrence occurs in about half of patients within 5 years from the original presentation. Approximately 15% of patients with colonic AVM present with massive bleeding [9].

Initial Work-Up and Diagnosis

The initial examination of the patient should include a complete physical exam and assessment of medical and surgical history. Patients should be thoroughly questioned about associated comorbidities, family history of bleeding disorders, cancer, medications, and last colonoscopic examination. Physical examination can demonstrate tachycardia, hypotension, and postural changes based on the amount of blood loss. Stool usually is guaiac positive but negative guaiac stools can be found since bleeding may be intermittent. Basic laboratory data should be obtained including a CBC count, coagulation parameters, and serum iron levels. A microcytic hypochromic anemia, reflecting iron deficiency, is observed in 10–15% of cases.

Imaging Studies

Imaging studies are cornerstone in the diagnosis of colonic AVM. What type of imaging study is needed to diagnose AVM, however, depends on a variety of different factors including patient cooperation, ability to obtain bowel preparation, and more importantly, hemodynamic stability. If the patient remains hemodynamically stable and bowel preparation can be done safely, colonoscopic examination is indicated. Endoscopic examination allows not only diagnosis but also treatment of small AVM bleeds. If the patient is unstable and bleeding is massive, selective mesenteric angiography is preferred. Radionuclide scanning using technetium ^{99m}Tc-labeled red blood cells or ^{99m}Tc sulfur colloid is helpful in detecting active bleeding but with the caveat that this technique can be limited by the intermittent bleeding nature of AVM. It also fails in most cases to localize the source of the bleeding and should be avoided if the test will delay definitive diagnosis and treatment. There is evidence that patients with delayed blush or negative scans on radionuclide testing have low angiographic yields and should proceed to colonoscopy for definitive treatment [10].

Colonoscopy

Colonoscopy is a sensitive method in diagnosing colonic AVM. Lesions are typically described as red, flat consisting of ectatic blood vessels that appear to radiate from a central feeding vessel; they may have a diameter of 2–10 mm [11, 12] (Fig. 1). If bowel preparation was performed correctly, the sensitivity of colonoscopy for detecting AVM exceeds 80% [13].

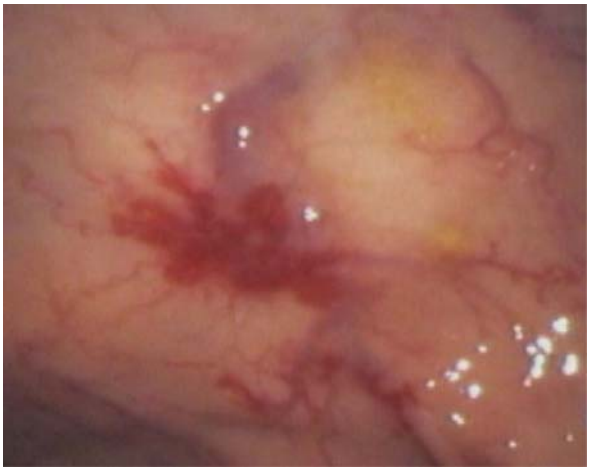

Fig. 1 Endoscopic view of colonic AVM

Inadequate bowel preparation may lead to incomplete evaluation of the colonic mucosa. Colonoscopy may be also ineffective in the face of active bleeding and insufflation of air may obliterate the lesions. In addition, blood pressure and volume status can alter the colonoscopic appearance of vascular lesions as it is the use of narcotic medications for sedation and analgesia. Studies have shown that administration of intravenous naloxone enhances the appearance of AVM during colonoscopy in patients who have received meperidine for sedation [14].

In general, endoscopic forceps biopsy is not indicated in benign looking lesions because of the risk of provoking bleeding. Endoscopic biopsy has revealed characteristic histopathological features of AVM in only 31–60% of specimens.

It has been widely reported that urgent colonoscopy is safe and yields a specific diagnosis in a high proportion of cases [15–17]. As opposed to upper endoscopies, colonoscopy is often performed after the bleeding has stopped and the patient adequately prepared [18]. Some nonrandomized studies, however, have failed to demonstrate improvement in outcomes after urgent colonoscopy for lower GI bleeding [19, 20]. In a recent study done at our institution, a total of 100 patients presenting with lower GI bleeding without upper or anorectal bleeding sources were randomized to urgent purge preparation followed immediately by colonoscopy or a standard care algorithm based on angiographic intervention and expectant colonoscopy. This study showed that urgent colonoscopy identifies a definite source

of lower gastrointestinal hemorrhage more often than a standard care algorithm that utilizes elective colonoscopy. However, urgent colonoscopy did not significantly improve important outcomes such as either early or late re-bleeding [21].

Angiography

Despite recent advances in endoscopic techniques and equipment, angiography remains the gold standard for the diagnosis of colonic AVM. Selective mesenteric angiography is especially indicated in patients with massive bleeding in whom a colonoscopic diagnosis is difficult. The overall sensitivity of angiography ranges from 58 to 86% and detection of bleeding depends on the rate of bleeding (as low as 0.5 mL/min). Following injection of contrast, AVM are seen as ectatic slowly emptying veins, vascular tufts, or small veins with early filling. Vasopressin infusion during angiography can control bleeding, but potential complications including bowel infarction and perforation, arterial vasospasm, and lower extremity ischemia can occur.

Other Tests

Other less invasive methods of diagnosing colonic AVM are available and their indications depend of the status of the patient, timing since last bleeding episode, and previous failed attempts at diagnosis using colonoscopy and/or angiography. Radionuclide scanning using technetium ^{99m}Tc-labeled red blood cells or ^{99m}Tc sulfur colloid is a helpful method when there is active bleeding at a rate of as low as 0.1 mL/min [22]. Helical CT angiography (CTA) can detect extravasation from AVM and is a noninvasive test in patients with obscure bleeding sites. Junquera has shown that sensitivity, specificity, and positive predictive values of CTA for detection of colonic AVM can be as high as 70, 100, and 100%, respectively [23]. Capsule endoscopy has been reported to detect cecal AVM in selected cases, but its role as a diagnostic test for the colon is still under investigation [24, 25]

Treatment

Non-surgical Approach

The first step in the management of patients with lower GI bleeding from AVM is to correct any coagulopathic condition. Aggressive volume resuscitation is sometimes required. In general, a conservative approach to patients who are hemodynamically stable is recommended because most bleeding AVM will cease spontaneously. Treatment is not advocated in asymptomatic patients with incidental AVM finings on routine colonoscopy.

Endoscopic therapy is the treatment of choice in patients with colonic AVM. Endoscopic sclerotherapy has been a very useful method for controlling bleeding from these lesions [26]. Submucosal injection can be done with a variety of different substances including normal saline, epinephrine, ethanolamine, etc [27, 28]. Endoscopic therapy of AVMs also can be achieved by obliteration of the lesion with a heater probe or multipolar electrocoagulation. Endoscopic laser photocoagulation can also be used [29, 30] but complications can occur in up to 15% of patients. Colonoscopic tattooing of bleeding lesions can help delineate any further surgical intervention needed should these less invasive methods fail.

In those patients that remain hemodynamically unstable or in whom previous endoscopic attempts have failed, angiography is indicated. Angiography is also indicated in debilitated patients that would not tolerate surgical exploration. Selective angiography offers a relatively less invasive approach than surgery and can be reattempted should the first effort fails. In general, the use of superselective mesenteric embolization for the treatment of lower GI bleeding is highly successful and relatively safe. The most significant risks of transcatheter embolization are intestinal ischemia and infarction, the latter occurring in a range between 0 and 20% [31–33]. Immediate hemostasis is normally achieved and the prevalence of recurrent hemorrhage requiring surgery is 10–20%.

Infusion of vasopressin into the bleeding vessels is also used to control bleeding. Once localization of the bleeding site has been identified angiographically, infusion is initiated at 0.2 U/min and can be increased to a rate of 0.4 U/min. The site is then checked again: if bleeding is controlled, the catheter is left in place and vasopressin is continuously infused for 6–12 h. If the bleeding continues to be controlled, infusion is continued for an additional 6–12 h at 50% of the previous rate [34, 35].

Surgical Treatment

If previous endoscopic and angiographic attempts have failed, surgery provides the definitive treatment. Surgery is limited to acute, uncontrollable, or recurrent forms of GI bleeding from colonic AVM. Most patients that require more than 4 units of blood in a 24-h period to remain hemodynamically stable, those in whom bleeding has not stopped after 72 h, or who experience re-bleeding within 1 week after an initial episode should undergo surgery [1].

Segmental resection is usually recommended after identification of the lesion or subtotal resection is performed depending on the location of the AVM. Direct segmental resection is associated with re-bleeding rates ranging from 0 to 14% and mortality rates ranging from 0 to 13% [36, 37]. In general, bleeding control can be obtained in most patients and the need for transfusions decreases significantly after surgery.

Finally, blind segmental resection should not be performed if preoperative imaging has failed to identify localization of the bleeding AVM. Partial colectomy with

unidentified bleeding source has been linked with re-bleeding rates of approximately 75% and high mortality [38]. In these cases, intraoperative localization options include upper endoscopy, colonoscopy, or small bowel endoscopy assisted by hand manipulation of the small bowel by the operating surgeon.

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Bleeding Colonic Tumors

Vanessa A. Olcese and Christopher R. Mantyh

Introduction

Bleeding colonic tumors represent one of many causes of lower gastrointestinal bleeding (LGIB) and may present acutely or chronically. The evaluation and management LGIB as a whole is discussed elsewhere in this text. This chapter will focus on the etiology, work-up, and treatment of bleeding colonic tumors.

Overview

To briefly review, by definition the source of LGIB arises distal to the ligament of Treitz [1]. In 80% of cases, bleeding spontaneously resolves, however, re-bleeding can occur in 25% of patients [2–4]; the probability of a third bleeding episode increases to over 50% after the initial recurrence [2, 5]. Depending on the patient acuity level and briskness of bleeding, emergent intervention may be required. In fact, patients require surgery more frequently when GIB is from a lower GI source versus an upper GI source [3, 6]. LGIB most commonly presents as hematochezia, although melena, hemodynamic abnormalities, and anemia are other presentations [3, 6]. In only 15% of cases does fulminant hematochezia originate from the upper GI tract [3]. The differential diagnosis of LGIB is broad and includes diverticular disease, angiodysplasia, neoplasms, and inflammatory bowel disease. Specifically, with respect to neoplasms, bleeding colorectal neoplasia accounts for 7–33% of cases of severe LGIB [2, 3, 7, 8].

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Etiology

Although bleeding colonic tumors may have the insidious presentation of a chronic anemia, they can also present acutely. In the latter setting, the hemorrhage is secondary to tumor erosions on the luminal surface and as noted above, the incidence varies with the series. In one series, of 311 patients with massive colonic bleeding that underwent emergent colonoscopy, carcinoma was the cause in 21% [9]. In another series, urgent colonoscopies performed for severe bleeding identified colorectal carcinoma and polyps as the etiology in 11% of patients [10]. Another study using emergency angiography found carcinoma as the cause of massive bleeding in 10% of 55 patients [11]. Polyps, although more common than colorectal neoplasia, are less commonly a cause of massive lower GI bleeding, with an incidence ranging from 2 to 10% [10, 11, 9]. Postpolypectomy hemorrhage is a possible culprit, with an incidence of 1–6%, and is felt to be secondary to inadequate cauterization of the biopsy site at the time of polypectomy [3, 12–14]. There have also been reports of metallic stents used as palliative therapy for near-obstructing coloinic tumors inciting mucosal ulceration at the stent borders leading to LGIB [15].

Evaluation

The evaluation undertaken for LGIB is detailed elsewhere in this text. The notable points center around localization of the bleeding source. Given the increasing probability of re-bleeding following recurrence, expeditious definitive surgical intervention is recommended after the source is localized. It should be remembered that upper gastrointestinal tract hemorrhage is the origin of 80% of all GIB [2]. If a lower source is suspected, ergot an upper source has been ruled out, endoscopy may be attempted first. With brisk bleeding, however, this may prove to be difficult as blood and feces present in the LGI system can obscure visualization of the source. In experienced hands, endoscopy leads to localization of the site of bleeding in 72–86% of cases of moderate active hemorrhage [2, 16, 6, 17].

If bleeding is suspected to be severe, angiography has proved to be a more sensitive method to localize the bleeding source in the setting of massive active hemorrhage compared to colonoscopy [2]. Angiography detects bleeding greater than 0.5–2 mL/min with a sensitivity of 40–86% and a specificity of 100% [2]. The intermittent nature of LGIB accounts for the false-negative results, as active bleeding is required for a positive result during angiography. Provocative maneuvers can be employed during angiography if the diagnostic portion of the study is negative. Such maneuvers include specific, catheter-directed application of anticoagulants during the angiogram. This strategy for bleeding site localization is usually employed in more protracted clinical situations where bleeding is recurrent and an exhaustive work-up has already been unrevealing [2, 18].

Nuclear scintigraphy is another option for source identification and has a detection threshold of 0.1 mL/min, making its sensitivity superior to that of angiography [19, 2]. Increasing background radiation makes reliable localization impossible after

4–24 h and hence delayed scans are not reliable for localization. The interpretation of these studies is difficult and accuracy for source localization is poor. This in combination with poor correlation with subsequent angiogram results limits the usefulness of nuclear scans. It is not recommended to perform segmental resections based on a positive nuclear scan alone [3, 20–23].

With continued advances seen in computed tomography (CT) technology, including CT angiography (CTA), this minimally invasive technique can detect bleeding rates of approximately 0.4 mL/min. Reports have been published indicating that CTA has a higher sensitivity with respect to the detection of colonic angiodysplasia compared with conventional angiography [2, 24–27]. CT also has general applicability as a screening test in that it may both localize GIB and provide a visual clue as to its etiology. In the case of colonic tumors, invaluable additional information relevant to staging may be simultaneously obtained.

Barium enema may play a role in the evaluation of a suspected colonic tumor, but really plays no role in the assessment of severe hematochezia. It fails to identify the hemorrhagic source in up to 30% of cases [3, 28]. Even when positive, there is no guarantee that the visualized lesion is also the bleeding culprit. Finally, the barium itself interferes significantly with future evaluations, such as colonoscopy or angiography.

Treatment

Approximately 90% of the time, the source of GI hemorrhage is localized and in 70% of cases, bleeding can be successfully treated or temporized by endoscopic or angiographic intervention (Figs. 1, 2, 3, and 4) Improvements in these techniques have allowed upfront damage control surgery to become the exception rather than the rule for patients with acute GIB. For patient outcomes, this represents a huge impact in that “blind” segmental resections based on suspicion alone are associated not only with high rates of recurrent hemorrhage but also with high rates of morbidity and mortality [2, 16, 29–31].

Therapeutic options during endoscopy include contact coagulation, epinephrine injection, hemoclipping, fibrin sealant application, or a combination thereof [32, 33, 2, 34, 35]. With respect to postpolypectomy hemorrhage, this is best prevented with the injection of epinephrine at the time of polypectomy, but can be managed with endoscopic clips (Figs. 5 and 6). During angiography, superselective microembolization can be performed with microcoils, gelfoam, or polyvinyl alcohol [36, 2, 37–39]. Selective vasopressin infusion is also part of the armamentarium, but is associated with high recurrence rates and chances for concomitant cardiovascular complications [2]. With embolization strategies, postembolic ischemia is a concern, with a reported incidence of 0–22%. It is lowest if the most distal vascular site is chosen for embolization [40, 38,39,41–46].

Surgery is indicated as definitive therapy after patient stabilization, source localization, and additional patient evaluation, including clinical staging and assessment of operative risk. If initial attempts at source localization are unsuccessful and the

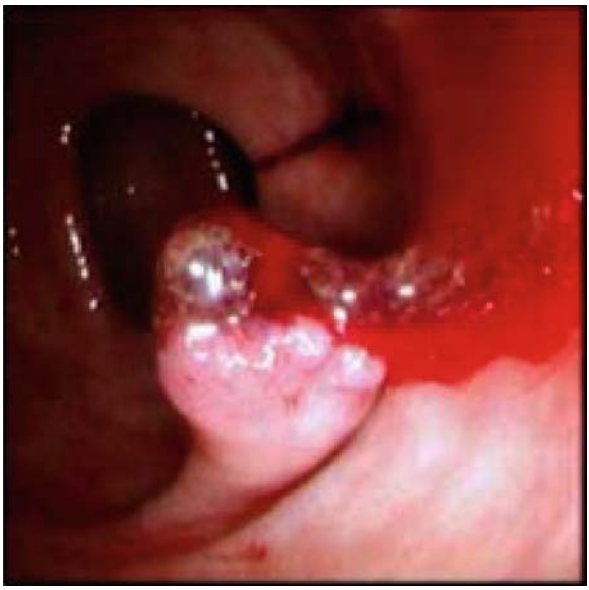

Fig. 1 Bleeding polyp localized at endoscopy

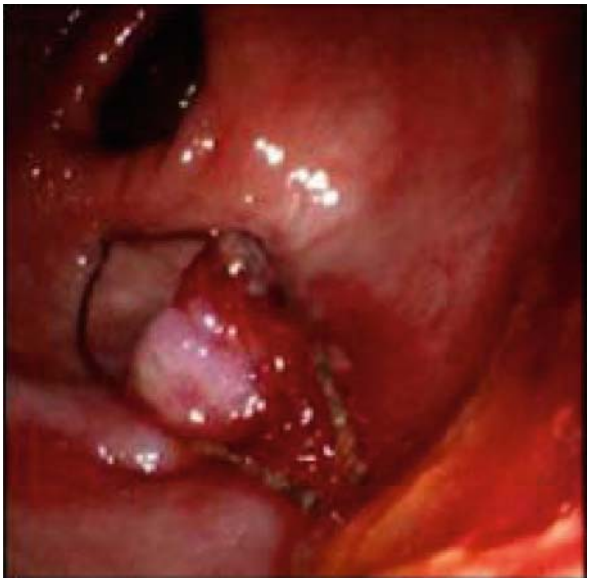

Fig. 2 Snare polypectomy to control bleeding

patient is suffering from unabated hemorrhage, surgery is indicated as a last resort. Segmental resection after source identification is associated with recurrent bleeding in 0–14% of cases, with the lowest recurrent bleeding rate of <5% being observed after subtotal colectomy [19, 2, 11, 47]. Notably, blind subtotal colectomies are

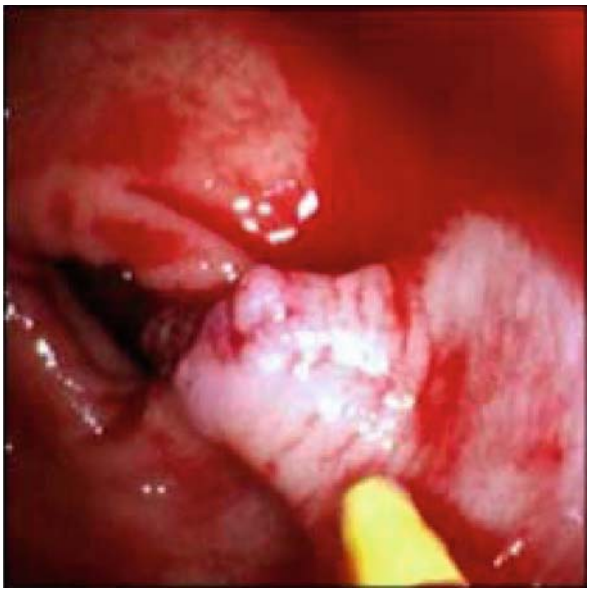

Fig. 3 Epinephrine injection

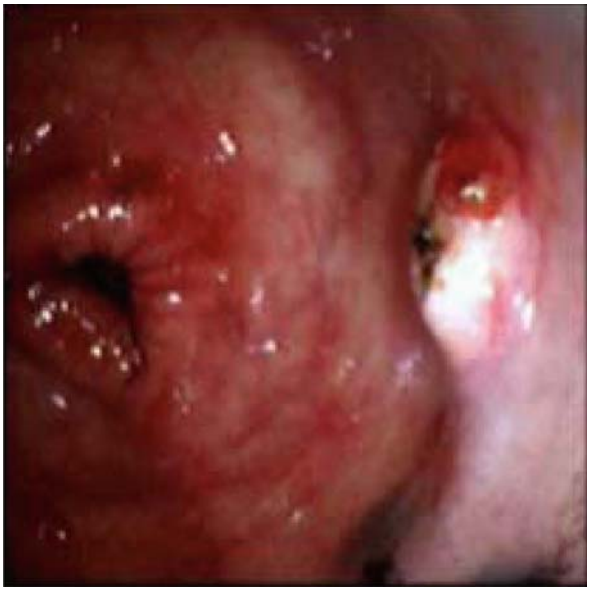

Fig. 4 Hemostatic control

associated with a mortality rate of up to 30% [48–50]. Specifically with respect to colonic tumors, the chances that the tumor would not be apparent at laparotomy but anatomically significant enough to induce massive hemorrhage are remote.

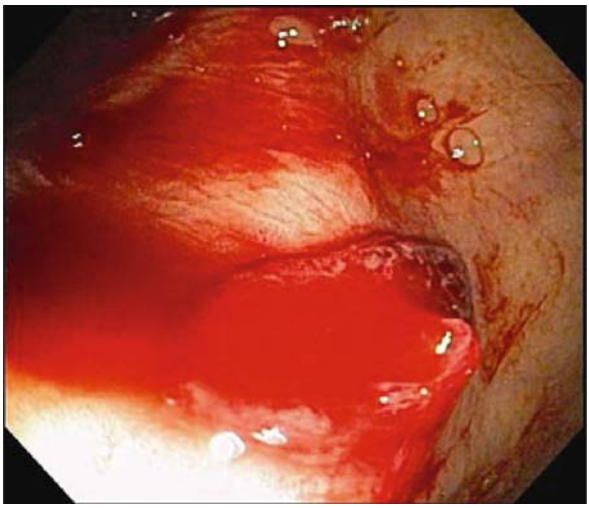

Fig. 5 Postpolypectomy bleeding

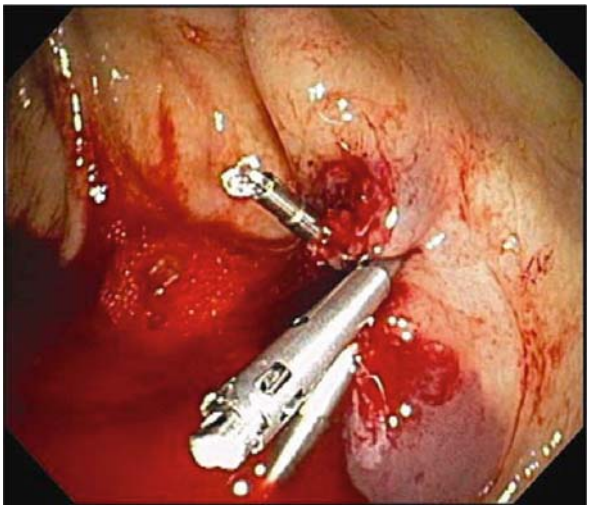

Fig. 6 Clips used successfully to control postpolypectomy bleeding

Summary of Management: Key Points

Principles of the evaluation and management of bleeding colonic tumors are no different from those for the entity of GIB as a whole. Key points specific to acute colonic bleeding are shown in the flowchart below (Fig. 7).

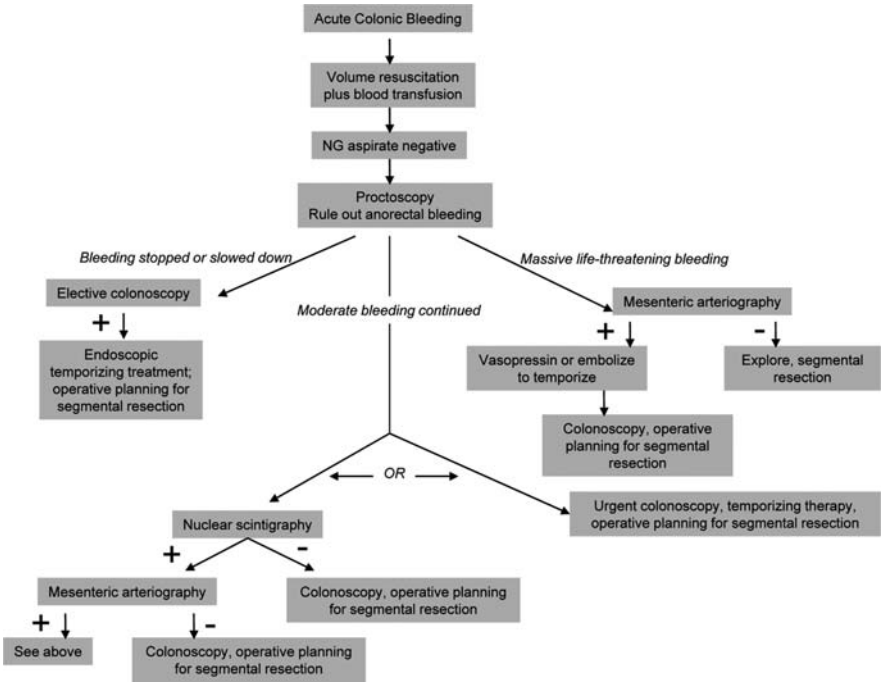

Fig. 7 Algorithm for management of colonic bleeding (Adapted from [8])

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Part III
GI Bleeding from an Unknown Source

Evaluation of the Guaiac Positive Patient

Rebecca Burbridge and Melissa Teitelman

Introduction

One of the more common encounters a physician must deal with is the presence of occult gastrointestinal blood loss. The prevalence may reach up to 1 in 20 adults. The detection of occult blood is important because a person may lose up to 150 ml of blood from the proximal gastrointestinal tract before producing overt melena [1]. Before proceeding further, an important distinction must be made between *occult* gastrointestinal blood loss and *obscure* gastrointestinal bleeding. The following definitions were derived from the 2007 American Gastroenterological Association (AGA) Institute position statement on obscure gastrointestinal bleeding [2]:

Occult bleeding: initial presentation of a positive fecal occult blood test (FOBT) results and/or iron-deficiency anemia, when there is no evidence of visible blood to the patient or physician.

Obscure bleeding: bleeding from the gastrointestinal tract that persists or recurs without an obvious etiology after upper endoscopy, colonoscopy, and radiological evaluation of the small bowel (such as by small bowel follow through or enteroclysis).

As stated in the above definition, occult gastrointestinal blood loss is most commonly brought to the physician's attention by a positive fecal occult blood test or iron-deficiency anemia if the blood loss has been chronic. This chapter will primarily focus on the differential diagnosis and systemic approach to the evaluation of the guaiac positive patient.

Fecal Occult Blood

The main focus of testing for fecal occult blood has been in the screening for colorectal cancer. Annual testing has been recommended by the American Cancer

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Society, World Health Organization, and the United States Preventative Services Task Force. A positive test is often followed up with endoscopic or radiological evaluation of the gastrointestinal tract. The cumulative effect of this testing method has been shown to reduce mortality rates from colorectal cancer to up to 33% [3]. However, anywhere from 2 to 16% of people who are tested for fecal occult blood will have a positive result [4, 5]. The high rate of false-positive results often leads to unnecessary health-care expenses.

Gastrointestinal blood loss must exceed 10 ml/day (normal <2 ml/day) to produce a positive fecal occult blood test. This degree of bleeding (10 ml/day) will produce a positive test only 50% of the time by most testing methods [6]. Multiple factors determine the likelihood of detecting fecal occult blood. These factors include the sensitivity of the particular test which is being used, the anatomic level of bleeding, the frequency and rate at which the causative lesion bleeds, and bowel motility. All of these factors influence the intraluminal metabolism of hemoglobin.

Commercially Available Fecal Occult Blood Tests

There are three main categories of fecal occult blood testing methods commercially available: guaiac based, heme–porphyrin based, and immunochemical based. Depending on the particular testing method used, occult blood loss can be detected from any location in the gastrointestinal tract.

Guaiac-Based Tests

Guaiac-based fecal occult blood testing is the most commonly used testing method because of its simplicity. Guaiac is a colorless compound that turns blue on exposure to hemoglobin. Guaiac tests are more sensitive for the detection of bleeding from the lower gastrointestinal tract than from the upper gastrointestinal tract because hemoglobin is degraded as it travels down the gastrointestinal tract [7]. The likelihood that a guaiac test will detect fecal occult blood is related to the quantity of hemoglobin in the stool, which in turn is affected by the size and location of the bleeding lesion [8].

A drawback of guaiac-based testing is the high rate of false-positive results (Table 1). For this reason, patients are often asked to avoid certain peroxidase-containing foods and red meats for 3 days prior to stool testing. Nonsteroidal anti-inflammatory drugs and aspirin (if taking greater than one adult aspirin per day) should be avoided for 7 days prior to testing unless the patient is on a cardioprotective regimen. Oral iron was once believed to cause false-positive guaiac results. This line of thinking was thought to be secondary to the fact that oral iron gives the stool a dark green/black appearance which may be confused with the blue color of a positive guaiac reaction. However, even in large amounts, oral iron does

Table 1 Substances causing false-positive and false-negative guaiac testing results

False positives	False negatives
Radishes	Vitamin C
Turnips	Antacids
Cantaloupe	Heat
Bean sprouts	Acid pH
Cauliflower	Impaired bowel motility
Broccoli	"Dry stools"
Grapes	
Artichokes	
Mushrooms	
Horseradish	
Oranges	
Bananas	
Red meats	
NSAIDS/ASA	
Sucralfate	
Cimetidine	
Halogens	
Toilet bowel sanitizer	

not cause guaiac to react positively [9]. Like iron, bismuth also gives the stool a dark color, but has no effect on the results of guaiac testing.

Heme–Porphyrin-Based Tests

The heme–porphyrin test is the most sensitive test to detect fecal occult blood loss, but its use is limited by a high false-positive rate. The test utilizes a fluorometric assay to quantify heme and heme-derived porphyrin in stool. Unlike the guaiac-based tests, vegetable peroxidases do not affect the result. However, the presence of myoglobin in red meats will artificially raise the amount of heme–porphyrin in the sampled stool, thus creating a false-positive result. The test is useful for detecting occult bleeding in any part of the gastrointestinal tract, but one major drawback is the inability to perform this test at the bedside as the stool samples must be sent to a reference laboratory for processing.

Immunochemical-Based Tests

The principal behind immunochemical tests is the use of antibodies directed against human globin epitopes to detect colonic blood [10]. Because globin molecules are degraded in the upper gastrointestinal tract, this test is useful only in the evaluation of lower gastrointestinal bleeding. The test is highly sensitive for the detection of colonic blood [11], however, it is quite cumbersome for the physician to perform. Room temperature storing of the sample must be avoided as loss of hemoglobin antigenicity may occur. The sample cannot be processed in the physician's office, instead needing to go to a special laboratory for processing.

Differential Diagnosis

Although the focus of fecal occult blood testing is in the screening of colorectal cancer, there are many other causes of occult gastrointestinal bleeding. A detailed history and physical examination often provide the first clues to the etiology. An important component of the history to ascertain is an updated medication list. In particular, nonsteroidal anti-inflammatory drugs [12], potassium chloride, and alendronate all have the potential to injure the gastrointestinal mucosa. The use of anticoagulants may increase the rate of blood loss from preexisting lesions, thereby increasing the incidence of occult bleeding. Some familial conditions may predispose to a patient to bleeding tendencies (i.e., hereditary hemorrhagic telangiectasia or von Willebrand's disease).

In general, any GI lesion from the mouth to the anus may cause occult GI bleeding. It is important to recognize that lesions in the upper GI tract have the potential to cause occult GI bleeding. These lesions may include epistaxis, bleeding gums, esophagitis, peptic ulcers, esophageal and gastric malignancies, hemobilia, and angiodysplasias to name a few. Traditional colonic sources of occult blood loss include large colon polyps, colon adenocarcinoma, inflammatory bowel disease, ischemic bowel, hemorrhoids, and anal fissures.

Iron-Deficiency Anemia

Iron-deficiency anemia is the most common form of anemia worldwide. The anemia is reflective of a chronic blood loss, typically in excess of 5–10 ml/day over many weeks. In the United States, the prevalence of iron-deficiency anemia reaches 1–2% of the adult population [13]. Iron deficiency without anemia is much more common, presenting in up to 11% of women and 4% of men. In women, the anemia is most often identified in the premenopausal years because of menstrual and pregnancy-associated iron losses. In all other age groups, the primary cause of iron-deficiency anemia is chronic blood loss from the gastrointestinal tract. Therefore, investigation of the gastrointestinal tract is essential in the evaluation of iron-deficiency anemia [7].

Differential Diagnosis

The differential diagnosis of iron-deficiency anemia encompasses many of the same disorders that can cause occult GI blood loss. Although GI blood loss is the most common etiology for iron-deficiency anemia, reduced gastrointestinal absorption of iron and dietary deficiency can also cause iron-deficiency anemia [14]. Diseases associated with generalized malabsorption and/or achlorhydria can predispose to iron-deficiency anemia. Celiac disease has been shown to be present in up to 8.5% of patients with iron deficiency unresponsive to conventional iron supplementation

[15]. Other causes of iron-deficiency anemia that are not associated with blood loss include intravascular hemolysis and gastric bypass for morbid obesity (Table 2).

Table 2 Possible causes of occult gastrointestinal bleeding

Infectious causes	Tumors and neoplasms
Ascariasis	Primary adenocarcinoma
Amebiasis	Lymphoma
Hookworm	Leiomyoma
Strongyloidiasis	Large adenoma (>1.5 cm)
Tuberculous enterocolitis	Metastases
Cytomegalovirus	Miscellaneous causes
Inflammatory disorders	Oropharyngeal lesions
Peptic ulcer disease	Medications
Cameron erosions	Long distance running
Celiac sprue	Hemobilia
Whipple disease	Epistaxis
Inflammatory bowel disease	Vascular causes
Erosive gastropathy	Angiodysplasias
Nonspecific colitis	Portal hypertensive gastropathy
Eosinophilic gastroenteritis	Dieulafoy lesion
Cecal ulcer	Gastric antral vascular ectasia
Solitary rectal ulcer	Hemangiomas

Approach to Evaluation of Occult Gastrointestinal Blood Loss

The initial evaluation of fecal occult blood loss should begin with the colon as this is the most common site of occult blood loss. The choice of the initial tests is often driven by the expertise of the physician ordering the exam, complication rates, costs of the test, and the patient's overall medical condition [16]. Although there is controversy over which test should be initially performed, the consensus is that colonoscopy is the preferred method of choice for direct evaluation of the colon, however, other options are available [17]. These options include air contrast barium enema, flexible sigmoidoscopy in conjunction with barium enema, and computed tomographic colonography. Air contrast barium enema is very accurate for detecting large colonic lesions when performed by an experienced radiologist, however, the accuracy in detecting smaller lesions is much less when compared to standard colonoscopy [18]. Likewise, CT colonography has not been shown to match the accuracy of colonoscopy when evaluated head to head in studies [19]. It is important to remember that synchronous upper and lower gastrointestinal tract lesions are rare. Therefore, further evaluation is not needed if the potential source is found on initial examination.

When the colon does not yield an etiology for the source of occult blood loss, attention must then be turned to the upper gastrointestinal tract (proximal to the third portion of the duodenum). Studies have demonstrated that significant potential upper gastrointestinal sites of bleeding have been identified in patients with a normal colonoscopy and a positive fecal occult blood test [20]. As stated earlier, it is

important to remember that significant upper GI tract lesions can bleed sufficiently to produce a positive guaiac result [21]. Initial upper gastrointestinal tract testing should start with an upper endoscopy. If iron-deficiency anemia is present, small bowel biopsies should be performed to exclude celiac disease.

If the colonoscopy and upper endoscopy do not reveal an etiology of the occult bleeding source, consideration needs to be given to evaluation of the small intestine distal to the reach of the standard upper endoscope. However, this depends on the clinical scenario. For the positive fecal occult blood test in the absence of iron-deficiency anemia, careful observation is recommended as the prognosis appears to be favorable. When iron-deficiency anemia is present and no etiology is found after initial investigation, a trial of iron supplementation is warranted. If the anemia fails to correct with iron supplementation, attention must then be focused on the mid-to-distal small intestine. Evaluation should proceed with capsule endoscopy or radiographic imaging to localize the potential source of bleeding followed by standard enteroscopy or balloon enteroscopy if treatment needs to be performed. Endoscopic evaluation of the mid-to-distal small intestine will be discussed in a later chapter.

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Obscure GI Bleeding: Capsule and Double-Balloon Techniques

Stephen Philcox

Introduction

Obscure gastrointestinal bleeding is defined as blood loss from the gastrointestinal tract after negative upper endoscopy and colonoscopy and may be overt if there is evidence of bleeding, or occult in the event of persistent iron-deficiency anemia or positive fecal blood test [1]. In spite of this definition, up to one-quarter of patients with a negative initial EGD have had bleeding sources identified on relook endoscopy, which is recommended before labeling a patient as having obscure GI bleeding [2, 3].

Historically, the investigation of obscure gastrointestinal bleeding in the context of non-diagnostic upper and lower endoscopy has relied on radiological studies such as small bowel series with or without enteroclysis, angiography, radionuclide studies, push enteroscopy, and intraoperative enteroscopy [4–6]. The sensitivity of these techniques for the detection of a bleeding source is low and there are potential risks associated with intraoperative enteroscopy.

Both wireless capsule endoscopy and double-balloon enteroscopy are relatively recent technologies, both becoming commercially available in the West in 2003, that have been developed to answer the need for more effective diagnostic and therapeutic access to the small bowel. This chapter will summarize the data currently available on the two technologies and outline their place in the algorithm of managing obscure gastrointestinal bleeding.

Wireless Capsule Endoscopy

At the time of writing there are two wireless capsules commercially available: PillCam SB (Given Imaging Ltd) and EndoCapsule (Olympus Corporation) (Fig. 1).

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Fig. 1 PillCam – actual size

A third capsule using slightly different signal transmission technology is currently undergoing early trials (MirRo).

Both of the currently available battery-powered capsules are 11 × 26 mm in size and are swallowed with a small amount of water after an overnight fast; there is some evidence supporting the use of concurrent bowel preparation and simethicone to improve visibility [7]. Two pictures are taken each second, which are transmitted to sensors that are connected to a recording unit that is attached via a belt around the abdomen. The battery life is approximately 8 h which permits the taking of more than 57,000 pictures. In patients who are unable to swallow the capsule, it may be placed into the duodenum endoscopically. Water may be consumed after 2 h and food may be ingested after 4 h. The patient is able to engage in normal activities and return 8 h later when the recording unit is removed and the images uploaded into software provided by the capsule vendors. This software is then used by the physician to read the images and assist in targeting areas of interest; for example, the software can detect the color red (surrogate for blood) and highlight significant changes between consecutive images. Reading each case can take an hour or more.

Indications, Contraindications, and Complications

VCE has been most extensively used to investigate obscure GI bleeding although it can provide information about other disease processes in the small bowel including Crohn's disease, mucosal injury secondary to NSAID use, small bowel tumors, polyposis syndromes, such as Peutz–Jaeger syndrome, and celiac disease [8] (Fig. 2).

An absolute contraindication to the use of VCE is small bowel obstruction. The use of capsule endoscopy is relatively contraindicated in the following subgroups of patients and the risks need to be weighed against the benefits, given endoscopic placement of the capsule may be required:

- Dementia
- Documented gastroparesis or esophageal dysmotility
- An esophageal stricture or Zenker's diverticulum

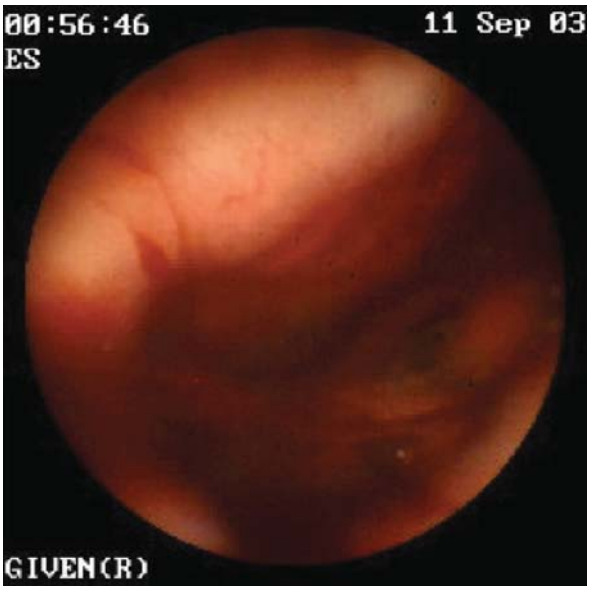

Fig. 2 Bleeding ulcer identified at capsule endoscopy

- Partial or intermittent small bowel obstruction
- Patients who are inoperable or refuse surgery
- Patients who have defibrillators or pacemakers

Capsule retention is the most significant complication associated with this procedure, however, fortunately it is rare, occurring in less than 1% of cases [9]. The patients at greatest risk are those with Crohn's disease (5–13%), radiation enteritis, chronic NSAID use, tumors, post-surgical anastomotic stenosis, clinically apparent adhesions, and those with severe motility disorders [10, 11] (Fig. 3).

In an effort to reduce this risk, a patency capsule has been developed by Given Imaging (Agile Patency System) that contains lactose with 10% barium and a radiofrequency identification tag that may be detected by a matching scanner and is taken in the same way as the normal capsule; its location is assessed within 30 h by either fluoroscopy or the scanner. Abdominal pain may occur in up to 14% of patients with known strictures with the use of these patency capsules; however, no obstruction has been reported as the capsule will dissolve in less than 80 h [12, 13]. Plain abdominal x-rays are usually recommended after 2 weeks to assess for retention if the patient has been unaware of passing the capsule in their stool; removal is either surgical although there are reports of double-balloon enteroscopy being used to retrieve capsules.

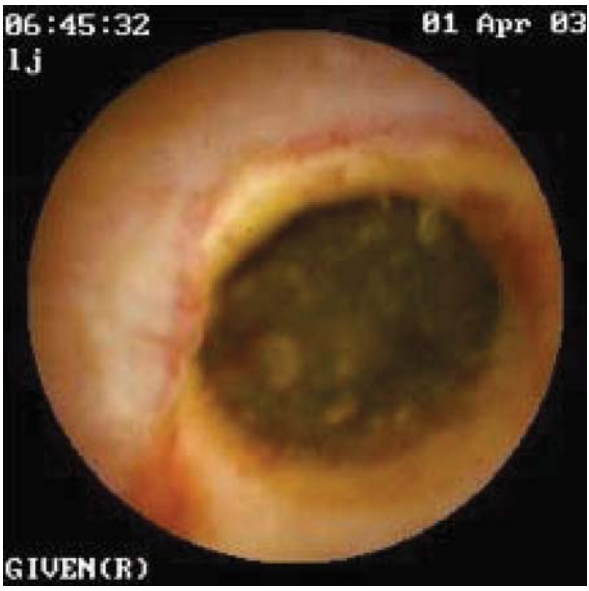

Fig. 3 NSAID-induced ulceration and stricture

Efficacy

A recent meta-analysis assessed the diagnostic yield of VCE in 18 prospective studies, 14 of which directly compared VCE with push enteroscopy, a further 3 that compared VCE to small bowel barium radiography and a single study that compared VCE to CT enteroclysis, mesenteric angiography, small bowel MRI and intraoperative enteroscopy [14]. The superiority of VCE was most clearly demonstrated compared with push enteroscopy (yield 63% vs. 28% $p < 0.0001$) and small bowel radiography (yield 67% vs. 8% $p < 0.00001$), with no clear advantage compared to intraoperative enteroscopy, CT enteroclysis, or mesenteric angiography; small bowel MRI was not shown to be as effective. Double-balloon enteroscopy (DBE) has also been directly compared with VCE and a recent meta-analysis included 11 studies and showed each modality to be comparable with a 57–60% overall yield and a 24% yield with vascular lesions [15]. A second meta-analysis found similar findings but also noted in a sub-analysis that the yield of VCE was significantly better when compared to DBE without the combination of oral and anal approaches, thus both antegrade and retrograde DBE are required to obtain equivalence in yield [16].

Diagnostic accuracy of capsule endoscopy was assessed in one study followed up 100 patients with obscure gastrointestinal bleeding. These patients had all undergone VCE and the investigators calculated sensitivity, specificity, and positive- and negative-predictive values of capsule endoscopy. These were 89, 95, 97, and 83%, respectively, in those 56 patients who had a confirmed diagnosis [17]. Several studies, including this one, have demonstrated the diagnostic yield of capsule to be highest in those with overt obscure bleeding [18].

While the sensitivity of VCE for detecting lesions in the small bowel is clearly superior to other imaging modalities excepting DBE, the impact on outcomes is less well studied. One study surveyed 40 physicians to assess the impact of VCE on clinical decision making and found that two-thirds changed their management strategy post-VCE, with 74% altering their management plan solely on the basis of the VCE result; similar results have been obtained in a number of subsequent studies [19].

The risk of rebleeding after VCE was assessed in a retrospective multicenter study in which VCE identified the source of bleeding in 175 of 285 patients with obscure bleeding with subsequent intervention as appropriate [20]. Rebleeding was seen in 65 of the 240 patients (27%) for whom follow-up data were available. Readmission was required in 42, with risk factors including angioectasias (RR 5), age > 60 (RR 3.8) and anticoagulant medication use (RR 3.0). Interestingly, the rebleed rates were greatest in those who had incomplete treatment of their angioectasias (85.7%). These data suggest that VCE guides therapeutic measures and predicts the risk of recurrent bleeding in small intestinal bleeding.

Double-Balloon Enteroscopy

As discussed earlier, up until recently radiological studies have been the dominant methods used to visualize the small bowel given the tendency of the bowel to stretch during conventional upper endoscopy and push enteroscopy with resultant loop formation and limited advancement of the endoscope. The double-balloon enteroscope (DBE) was designed to overcome this limitation and was first described by Yamamoto et al. in 2001 and utilizes a 140 cm soft overtube and a 200 or 152 cm thin endoscope (Fujinon Inc, Saitama, Japan) with two working channel sizes (2.2 and 2.8 mm). Both the overtube and the enteroscope have an inflatable latex balloon at the distal tip that are connected to an external air pump and may be independently inflated, gripping onto the bowel wall and impeding movement, or deflated permitting movement [21] (Fig. 4).

Technique

The technique is illustrated in Fig. 5 and first involves maximal advancement of the enteroscope through the overtube into the small bowel; the enteroscope position is then fixed by inflating its balloon. The overtube may then be advanced distally over the scope and is then also fixed by inflating its balloon. As both balloons are inflated, the enteroscope and overtube are retracted as a unit to pleat the bowel over the instrument. Then the enteroscope balloon is deflated and the scope is further inserted. Once it is fully advanced, the enteroscope balloon is inflated once again and the overtube balloon may be deflated, allowing advancement of the overtube once again over the scope. This sequence of movements is repeated to achieve deep intubation of the small bowel by exploiting the mobility of the small bowel which

Fig. 4 Fujinon double-balloon enteroscope (EN-450P5). Both the overtube and the enteroscope balloons are inflated in this picture

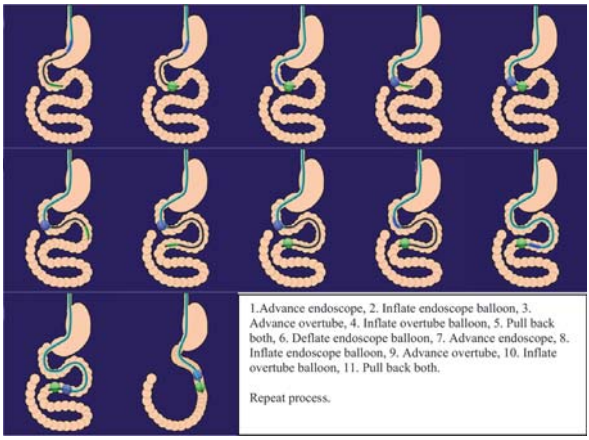

Fig. 5 Double-balloon technique. Figure courtesy of Fujinon Inc. (Wayne NJ)

accordions over the enteroscope; the overtube minimizes looping and stabilizes the scope tip [22].

Variable success rates of visualization of the entire small bowel have been achieved that reflect factors related to both the patient, such as obesity and presence of adhesions, and the experience of the endoscopist. Intubation may be performed via either an antegrade (per-oral) or a retrograde (per-rectum) approach potentially achieving visualization of the entire small bowel [23], although the retrograde approach is much more difficult [24]. The scope loops in an orderly fashion when performed optimally as shown in Fig. 6.

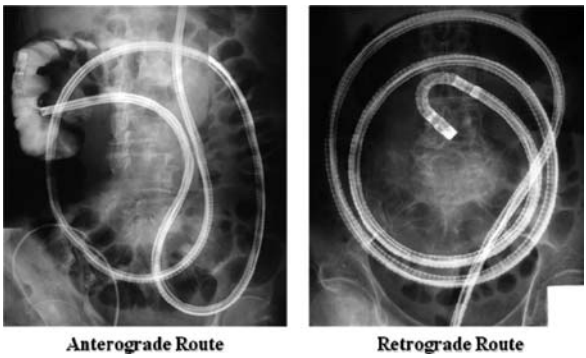

Fig. 6 Fluoroscopic image of the Fujinon enteroscope. Figure courtesy of Fujinon Inc. (Wayne NJ)

The choice of direction of initial DBE may be determined by calculating the position of the lesion on the basis of small bowel transit time; Gay et al. showed that if the lesion was seen in the proximal 75% of the small bowel then an antegrade study could be performed and if seen in the distal 25% a retrograde study could be done with a 95% positive-predictive value for finding the lesion [25]. The review from Yano and Yamamoto suggests using the anal approach first if the location cannot be determined or if the entire intestine must be inspected for multiple lesions followed by the oral route on another day if required, and the oral route if there is ongoing bleeding [22].

A 12 h fast is all that is required to prepare patients for antegrade DBE, and the standard colonoscopy bowel cleansing protocol should be followed for retrograde DBE. Despite improvements in procedure time with increasing experience, these remain relatively prolonged procedures as shown in one European study where the mean procedural time after 10 attempts reduced from 109 ± 44 min to 92 ± 37 min [26]; subsequently it may be more appropriate to use general anesthesia as distinct from conscious sedation although this is not an absolute requirement.

Indications, Contraindications, and Complications

To date, the investigation and management of obscure gastrointestinal bleeding has been the dominant indication for DBE after a negative conventional upper gastrointestinal endoscopy and colonoscopy, accounting for around 50% of cases [22]. Increasingly, DBE is being performed after capsule endoscopy, which has identified either a source of bleeding that may be amenable to endoscopic hemostasis or a finding that requires further intervention such as

1. Tissue biopsy, e.g., masses, strictures, mucosal abnormalities
2. Balloon dilatation of strictures [27]
3. Endoscopic mucosal resection [28]
4. Polypectomy [29]

5. Tissue ablation with argon plasma coagulation
6. Foreign body removal [30]
7. Pre-operative marking of tumors and mass lesions with tattoo to facilitate localization at time of surgery.

In addition, there are small series and case reports of DBE being used for the diagnosis of Crohn's disease of the small intestine, endoscopic and histological diagnosis of obstruction, and enteral stent placement [31]. DBE is also playing an increasing role in performing endoscopic retrograde pancreatography in patients with Roux limb surgery [32, 33] and difficult colonoscopies [34].

There are no specific contraindications to DBE over and above those specified for conventional upper and lower endoscopy; however, there are a few potential specific complications that can occur including mucosal injury secondary to the overtube, prolonged ileus, and perforation, which is most often related to strictures or abdominal adhesions [35]. An infrequent but potentially serious complication is that of pancreatitis, which is seen in 0.3–0.5% of antegrade DBE [35, 36]. The cause of this is unclear but may be due to duodenal contents refluxing into the pancreatic duct secondary to increased duodenal intraluminal pressure or mechanical strain on the pancreas itself. Overall the complication rate is 1–4% with an increased likelihood found in therapeutic procedures versus diagnostic ones (4.3% vs. 0.8%) [35, 37].

Efficacy

Of 12 published studies reporting experience with DBE, in which collectively 723 patients underwent 1,400 examinations, there was an average diagnostic yield of 65% and diagnostic or treatment success in 64% [1]. In patients who underwent DBE for obscure gastrointestinal bleeding, diagnostic or therapeutic success was seen in 55–75% of examinations with angioectasias being the most commonly identified source at 31%. As mentioned previously, the meta-analysis by Pasha et al. [15] showed comparable efficacy in yield between capsule and DBE (60% vs. 57%), however, this equivalence requires combination antegrade and retrograde approaches to be used [16]. This is important when one considers that total enteroscopy rates vary between 29 and 86% depending upon the proceduralist and patient population [23, 38].

There are few data looking at longer-term outcomes after DBE, however, one study by Manabe et al. did demonstrate 91% of patients who received treatment either endoscopically or surgically did not experience recurrent bleeding over a mean of 8.5 $\pm$0.6 months [39].

Since the introduction of the double-balloon enteroscope, several other innovations in small bowel enteroscopy are in the process of being developed that are antegrade systems only. Two of these are the single-balloon enteroscope system developed by Olympus Corporation and the Endo-Ease® Endoluminal

Advancement System developed by Spirus Medical. The former utilizes an overtube with a distal tip balloon and a thin enteroscope without a balloon. The latter system is a revolutionary overtube with spiral tubing as demonstrated in Fig. 7, which has been found to be safe and effective in a recent study when used with a pediatric colonoscope [40]. The diagnostic yield in 25 of 27 patients investigated for obscure gastrointestinal bleeding was 33% and an average depth of insertion of 176 cm (range 80–340 cm) from ligament of Treitz was achieved with an average time of procedure of 36.5 min (range 19–65 min). Precisely where these new technologies will fit into the algorithm for obscure gastrointestinal bleeding is yet to be determined.

Fig. 7 Spirus Medical Endoluminal Advancement System overtube. Picture courtesy of Spirus Medical

Summary

Both capsule endoscopy and double-balloon enteroscopy are exciting new tools in the diagnosis and treatment of obscure gastrointestinal bleeding as well as many other diseases of the small bowel. Comparisons of these two modalities have shown them to have similar diagnostic rates, although neither is perfect. For example, in a study by Hadithi et al., 115 patients underwent both VCE and DBE and the calculated miss rates were 20 and 28%, respectively [41].

Therefore, it appears VCE and DBE are complementary modalities with VCE potentially providing extremely useful information with relatively little risk to the patient and DBE playing both a diagnostic and therapeutic role, venturing into the small bowel in a way that was only possible previously with intraoperative enteroscopy with its higher associated morbidity. At a recent International Conference on Capsule Endoscopy a consensus statement asserted that capsule endoscopy is currently the preferred test for mucosal imaging of the entire small intestine and should be part of the initial investigation in patients with obscure bleeding. Its diagnostic yield is high and potentially it can produce earlier diagnosis. When integrated into a global approach to the patient, capsule endoscopy is helpful in achieving effective decision making concerning subsequent investigations and treatments. This in turn could mean more timely treatment and lower overall utilization and cost. Large prospective studies are however necessary to better assess the impact of capsule endoscopy on clinical outcomes [10].

An algorithm for the diagnosis and management of obscure gastrointestinal bleeding has been proposed by the American Gastroenterological Association and

a modified version is shown in Fig. 8 [1, 10, 42]. Within this algorithm, the central role of capsule endoscopy is evident in directing management including the use of double-balloon enteroscopy. Research into the diagnostic yield and clinical outcomes of utilizing both these modalities continues to redefine and expand upon their use and how newer advances will be incorporated is an area of active research.

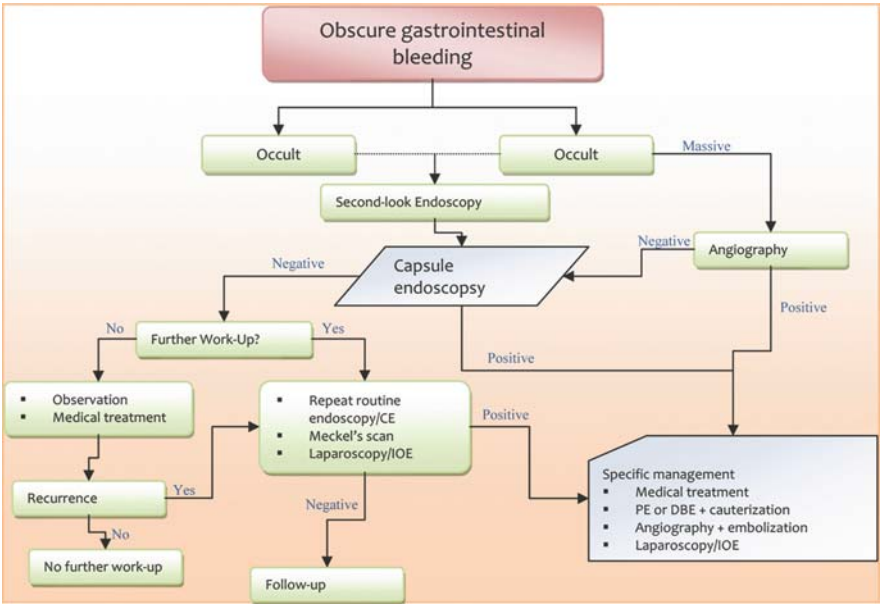

Fig. 8 Proposed algorithm for the diagnosis and management of obscure gastrointestinal bleeding (adapted from [10]). DBE: double-balloon enteroscopy; IOE: intraoperative enteroscopy; PE: push enteroscopy

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Provocative Angiography

Mayur B. Patel, Charles Y. Kim, and Michael J. Miller

Introduction

Determination of the site and etiology of lower gastrointestinal (GI) bleeding may lead to frustration for internists, gastroenterologists, surgeons, diagnostic, and interventional radiologists. The intermittent nature, variable severity, and changes in patient hemodynamic status can result in multiple rounds of diagnostic imaging without an answer. This is especially true in the setting of negative upper endoscopy and limited lower endoscopy due to the amount of blood within the colon. Despite significant blood loss, traditional diagnostic examinations such as tagged red cell scans may be negative or positive without definitive localization of the responsible site. Mesenteric angiography is the definitive imaging tool for localization of the bleeding site. This can, however, lend to confusion when multiple vascular lesions are identified without visible bleeding. With the addition of super-selective microcatheter embolization, angiography has become both diagnostic and therapeutic, and in many institutions, the first-line intervention for the management of lower GI bleeding. The main limitations of angiographic detection are the temporal relation of the arteriogram to the intermittent nature of the bleed, as well as the volume of bleeding. To help improve the sensitivity of angiography, practices have combined catheter-based delivery of pharmacologic agents with intermittent angiography in hopes of increasing the yield of angiography without compromising safety or efficacy. Now, known as provocative angiography, this technique has been applied to assess fore-, mid-, and hindgut bleeding that is refractory to traditional diagnostic and therapeutic modalities.

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Review

In 1982 Rösch [1] first described "pharmacoangiography" to address difficult lower GI bleeding. In his retrospective review of four cases in three patients they described the use of tolazoline, heparin, and streptokinase to improve the detection of the anatomical site of bleeding followed by surgical resection of the offending source. The agents were administered either independently or together resulting in active extravasation of contrast. The theory behind the approach was that vasoconstriction, platelet aggregation, and the creation of a soft intravascular plug resulted in transient hemostasis. Presumably, this patient population teeters on a line between hemostasis and bleeding, such that intentional vasodilation, anticoagulation, and/or fibrinolysis can help reactivate and identify hemorrhage.

In 1987, Koval [2] reported the impact of applying more aggressive angiographic techniques. In 63 consecutive patients referred for angiography, multiple factors were retrospectively reviewed. Incorporation of pharmacologic augmentation of mesenteric angiography in the setting of lower GI bleeding improved the diagnostic yield from 32% (12/37) to 65% (17/26) with the use of heparin, tolazoline, and streptokinase. Streptokinase was used in two patients and a positive result was found in one of the two. Of the ten patients given agents, eight had a lesion identified angiographically. Another factor predictive of positive angiography was the requirement of transfusion of $\geq$3 units of packed red blood cells in the 48 h prior to angiography. This correlated with a positive study in 66% of cases compared with 17%, in those requiring <3 units of packed red blood cell transfusion.

Glickerman [3] reported the first use of urokinase to identify bleeding in the midgut distribution in 1998. They described management of a patient who had been transfused over 150 units of packed red blood cells, undergone seven angiographic procedures, two exploratory laparotomies with one resection, yet continued to bleed. They performed the provocative arteriogram with selective arterial injection into the superior mesenteric artery with 10,000 U heparin, 1,000,000 U urokinase, and 25 mg tolazoline. Among the numerous vascular ectasias, they were able to pinpoint the entity responsible for bleeding. A 3 French catheter was later placed prior to surgery to allow for staining of the distribution with methylene blue which aided in the resection. In the ensuing 9 months, the patient experienced no further bleeding.

Heparin infusion has been used to unmask or amplify bleeding in order to identify a bleeding site angiographically. Following a papaverine augmented angiogram identifying 6 out of 18 GI bleeding patients, 24 h heparin administration in the remaining patients localized six additional bleeds. Thus, 12 out of 18 bleeds (67%) were localized angiographically by Mernagh [4]. This is similar to the yield obtained by Koval.

In 1998, Malden et al. [5] published the results of the first prospective use of provocative radiography, specifically scintigraphy. From September 1991 to May 1996 ten examinations were performed in 9 patients that had two or more hospitalizations for substantial GI bleeding, defined as bleeding requiring hospitalization, transfusion, or a 6% decrease in hematocrit. All recruited patients could tolerate angiography and/or surgical intervention, if needed. All patients had a negative

angiogram within 4 months, and all patients had negative upper endoscopy, lower endoscopy, and a small bowel study (enteroclysis, enteroscopy, or single-contrast barium study). Patients were given systemic heparin and urokinase and scintigraphy was performed. Four of the patients had positive scintigraphy within the first 4 h. However, positive angiography and intervention occurred in only two of the four. Thus only 2 of the ten studies yielded a positive result with the use of systemically heparin and urokinase.

A few series have looked at arterial catheter directed provocation of lower GI hemorrhage. Bloomfeld [6] reported a diagnostic success with two of seven patients (29%) utilizing intra-arterial tolazoline, heparin, and/or urokinase in a provocative angiographic study. Ryan et al. [7] reported 6 out of 16 patients (38%) were positive after provocation with systemic heparin, and selective tolazoline and intra-arterial tPA. Three of these patients were treated with super-selective embolization, but one of these patients required a resection 2 months later for recurrent bleeding. The three remaining positive provocations were treated non-operatively. Interestingly, of the ten patients who were negative during provocation, two had vascular abnormalities, and five rebled. Widlus and Salis [8] described inducing colonic hemorrhage in eight out of nine patients (89%) with occult, recurrent, massive lower GI bleeding using reteplase as the fibrinolytic agent. Microcoil embolization was successful in five, and failed in one, who required a colon resection. Hemorrhage spontaneously stopped in 2 patients. All patients underwent a colonoscopy within 10 days and were without significant findings.

Based upon the available data, an assumption that reteplase may be the optimal agent for the induction of bleeding may be considered. However, equivalent dosing of the medications as well as other factors may have contributed to the variability in sensitivities. Of the fibrinolytic agents available, reteplase has lower fibrin specificity than tPA, however, it has superior clot penetration. Likely, the economic impact of stocking these medications in pharmacy formularies precludes the availability of both at a single institution. Notably, tolazoline is no longer available in our market, and nitroglycerin has replaced it.

Complications and Risk Assessment

Potential complications may occur such as hypotension, puncture site hematoma, and post-procedural hemorrhage requiring transfusion. There is no published literature of the most feared complications associated with provocative angiography: uncontrollable GI, central nervous system, or nontarget bleeding. Patients should be screened prior to provocation for basic exclusionary criteria for fibrinolytic therapy (Table 1). Due to potentially substantial amounts of contrast needed to complete the examination, close attention to renal function is required. Proper hydration and resuscitation of the patient is recommended. Other factors for consideration include life-threatening contrast reaction, as well as the surgical candidacy of the patient. This can be a time-consuming examination requiring the patient being able to lay supine and follow commands, using pain and sedative medications as adjuncts. To

Table 1 Contraindications to provocative angiography

Absolute contraindications	Relative contraindications
Transient ischemic attack within 2 months	Recent major surgery, trauma, cardiopulmonary resuscitation
Cerebrovascular accident within 6 months	Uncontrolled hypertension
Intracranial neoplasm	Endocarditis
Craniotomy within 3 months	Pregnancy and postpartum period
Mobile left heart thrombus	Severe cerebrovascular disease

facilitate the procedure, general anesthesia may need to be considered. Both the interventionalist and the surgeon need to have a well thought out plan prior to the initiation of provocative angiography. At our institution, provocative angiography is only done with the approval of the surgical service.

Methods

Our provocative angiography protocol involves first performing conventional diagnostic mesenteric angiography on fore-, mid-, and hindgut distributions (celiac, superior mesenteric, and inferior mesenteric arteries). Unless the patient is unstable, the majority of patients have undergone scintigraphic imaging to determine the vascular distribution of concern. In the event scintigraphy has identified a bleeding site, the relevant vascular distribution is targeted for provocation. If there is no bleeding on scintigraphy, the superior mesenteric artery is targeted due to the opportunity to cover a greater length of the lower GI tract with vasodilator and fibrinolytic. Others such as Wildus [8] have suggested starting with the inferior mesenteric artery, due to the relative difficulty entering this vessel, as compared to the superior mesenteric and celiac distributions.

Just as there is variation of techniques between institutions, we have had variable approaches to provocative angiography. Over time, we have made an attempt to standardize our approach, in order to improve safety and provide consistency in our own internal reviews. Our current algorithm is depicted in a flow chart (Fig. 1).

This regimen is then repeated for the second most suspicious distribution. Angiography is acquired with the injection rates of 5–7 mL/s into either the celiac or superior mesenteric arterial distribution for a total injection of 20 mL. In the inferior mesenteric arterial distribution, 3 mL/s or hand injection for a total of 10 mL is injected. This allows for adequate opacification of the distal vascular bed where the bleeding originates (Fig. 2a, b, c and d).

Conclusions

Certainly, this is a multi-disciplinary endeavor, not limited to the interventionalist, and involves a consensus of surgical, medical, and radiological colleagues. Rates of diagnostic success are certainly variable due to lack of standardized protocols

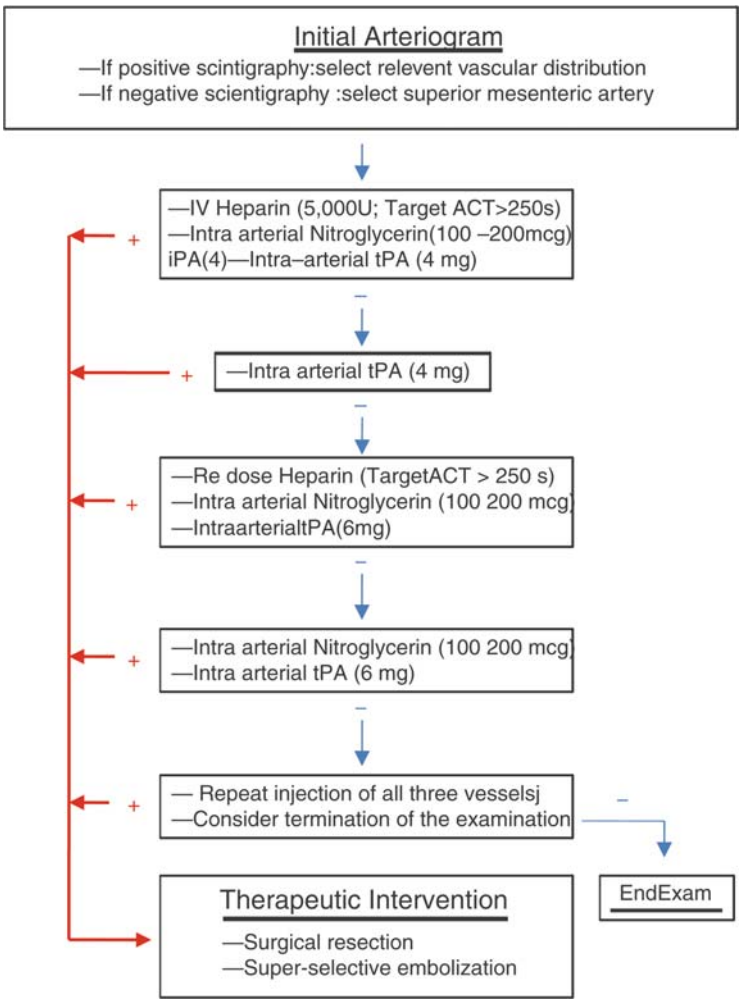

Fig. 1 Provocative Angiography Algorithm

for provocative studies (Table 2). The optimal type, dosing, and combination of vasodilator, anticoagulant, and fibrinolytic agents are unclear. Other factors such as time from active bleeding, institutional, and operator experience all impact the variable success rate reported in the literature. Therapeutic success is also broadly defined and, at least, should be stratified into embolization and surgical. At times, success may be of a hybrid form, where bleeding sites can be marked with methylene blue [9] or fluoroscopically locatable coils [10]. Although provocative angiography appears to be performed safely, the decision to proceed requires thoughtful consideration. Prospective data is scant and a large-scale study would further define the role of provocative angiography.

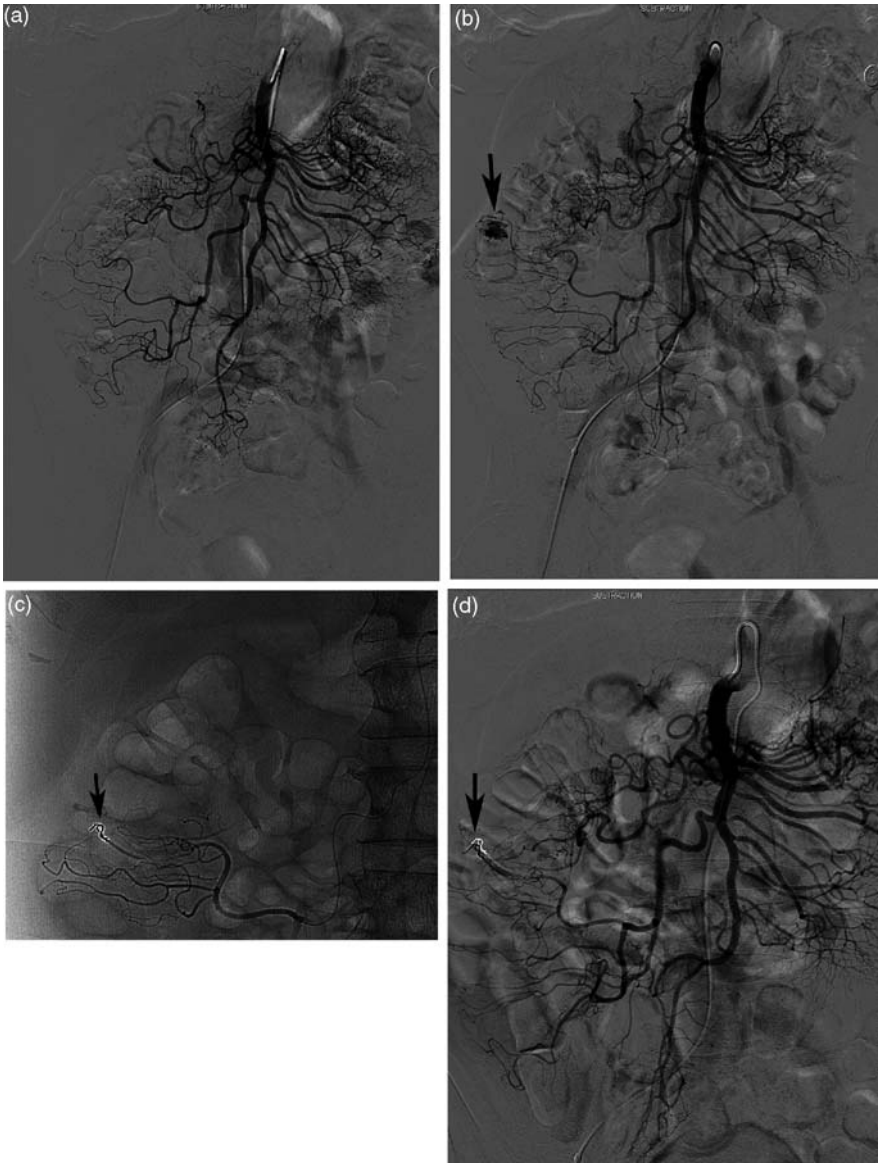

Fig. 2 (**a**) 53-year-old male presents with positive scintigraphy in the hepatic flexure, transient hypotension with prior bleeding episode, and one previous negative arteriogram. Initial injection of the superior mesenteric artery is normal without extravasation. (**b**) Injection of the superior mesenteric artery following the administration of 5,000 U Heparin, 200 mcg Nitroglycerin, and 4 mg tPA demonstrates active bleeding (*arrow*) from a branch from the right colic which was suspected on scintigraphy. (**c**) Injection through the microcatheter following placement of coils (*arrow*) within the arcuate branches supplying the area of extravasation. (**d**) Completion arteriogram demonstrates coils (*arrow*) with no further bleeding and preserved collateral supply to the region of colon

Table 2 Provocative angiography series

References	Class study	Agents	Dose	Delivery[a]	Diagnostic extravasation (%)	Therapeutic modality
Widlus [8]	Retrospective	Reteplase	a. 5 U in 20 mL NS over 1 min	a. Arterial	8/9 (89)	5 Embolized 1 Embolized then required operation 2 Spontaneous cessation
Ryan [7]	Retrospective	a. Heparin b. Tolazoline c. tPA	a. 3,000–10,000 U b. 25–100 mg c. 10–50 mg over 15 min	a. IV b. Arterial c. Arterial	6/16 (38)	2 Embolized 1 Embolized then required operation 2 Estrogen 1 Medical
Mernagh [4]	Retrospective	a. Papaverine b. Heparin	a. 65 mg b. 5,000 U Bolus then 24 h infusion to PTT 60–85 s	a. Arterial b. IV	12/18 (67)	All confirmed with endoscopy or surgery
Bloomfeld [6]	Retrospective	a. Tolazoline b. Heparin c. Urokinase	a. 25 mg b. 1,000–10,000 U c. 250,000 U aliquots to max total dose of 1,000,000 U	a. Arterial b. Arterial c. Arterial	2/7 (29)	2 Operation
Malden [5][b]	Prospective	a. Heparin b. Urokinase	a. 10,000 U bolus then 500 U/h × 3 h b. 250,000 U/h bolus then 250,000 U/h × 3 h	a. IV b. IV	2/9 (22)	1 Embolized 1 Operation
Koval [2]	Retrospective	a. Heparin b. Tolazoline c. Streptokinase	a. 5,000–10,000 U b. NR c. NR	a. IV b. Arterial c. Arterial	8/10 (80)	NR

[a]Arterial delivery implies selective celiac, superior mesenteric, or inferior mesenteric arterial delivery; IV implies systemic intravenous delivery
[b]Provocative scintigraphy study
Abbreviations: IV, intravenous; NR, Not Reported; NS, Normal Saline

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The Unstable Patient with Obscure Gastrointestinal Bleeding: Surgical and Non-surgical Management

Rebecca P. Petersen and Aurora D. Pryor

Obscure Gastrointestinal Bleeding – Definitions, Causes, and Epidemiology

Obscure gastrointestinal bleeding (OGIB) is defined as intermittent or persistent loss of blood that occurs or reoccurs after evaluation by upper gastrointestinal and lower gastrointestinal endoscopy [1]. The clinical presentation can vary dramatically, from occult blood loss that is only detectible by hemoccult testing, manifesting as iron deficiency to overt clinical manifestations of hematemesis, melena, or hematochezia requiring transfusion and hospitalization. The differential diagnosis of OGIB is extensive and the most common causes are listed in Table 1 [2]. Overall, OGIB represents approximately 5% of all episodes of gastrointestinal bleeding [1, 2]. Importantly, the most common causes of OGIB vary with age. Among patients less than 25 years old, the most common etiology is Meckel's diverticulum and other embryonic remnants. Among patients age 30–50 years old, various small bowel tumors tend to predominate, and older patients greater than 50 years old tend to have vascular pathology leading to bleeding [3, 4].

Provided the patient is hemodynamically stable, it is useful to try and narrow the potential etiologies prior to engaging in diagnostic procedures, as the differential diagnosis for OGIB is extensive. Detailed medical history regarding prior episodes, travel history, concomitant medical conditions such as pancreatic disease, coagulopathies, HIV status, and prior surgical procedures including vascular and gastrointestinal bypass surgery are important. A detailed approach to the history can often define the appropriate diagnostic approach to the patient and improve the chances of an accurate diagnosis.

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Table 1 Common causes of obscure gastrointestinal bleeding

Missed upper or lower gastrointestinal source
Vascular anomalies: lymphangioma, extraluminal AVM, submucosal vessel, angiodysplasia/ectasia
Neoplasm: primary, metastasis, or invasion by local spread, lipoma, GIST
Complications from previous surgery
Aortoenteric fistula: primary or secondary, also iliac-enteric
Extraluminal source: hemobilia, hemosuccus pancreaticus
Inflammation: celiac disease, IBD (Crohn's), sarcoidosis
Meckel's diverticulum, or other ectopic tissue
Other small bowel diverticuli or duplication cysts
Intussusception
Medical: coagulopathy, liver disease with small bowel varices, drug induced
Infectious: CMV, TB, whipworm, salmonella

Initial Management and Approach to the Unstable OGIB Patient

Patients with unstable OGIB present similarly to common unstable acute causes of gastrointestinal bleeding. Thus, the initial medical management and stabilization should be similar to standard management for gastrointestinal bleeding as patients could be presenting with a de novo source. Initial maneuvers should include assessment of hemodynamic volume status, obtaining adequate intravenous access, and gastrointestinal lavage as appropriate. Additionally, appropriate bloodwork should be performed, typical pharmacotherapeutic measures should be instituted, and patients should be placed on NPO status.

All patients with overt OGIB require admission to the hospital, which for the OGIB patient with obscure bleeding affords an excellent opportunity to engage in directed diagnostic testing. As previously noted, diagnostic testing should be directed according to potential risk factors based on a detailed medical history. An algorithmic approach to the diagnostic evaluation is useful to avoid unnecessary testing and to focus the evaluation (Fig. 1). Among all patients, the most likely etiology of OGIB is an upper or lower gastrointestinal tract source that was initially missed on prior endoscopic examination. A review of published studies suggests that between 35 and 75% of presumed OGIB lesions are actually found on repeat upper or lower endoscopy [5–13]. Hence, once hemodynamic stability has been achieved, the first maneuver for all patients should be to repeat the previous esophageal, gastric, and duodenoscopy, and then colonoscopy if negative. Ideally, the repeat endoscopy should be performed within 48 h of the current acute bleeding event to achieve the greatest diagnostic success.

If the repeat endoscopies are negative, we recommend the next diagnostic maneuver be stratified by age and any other pertinent medical history. In the absence of other clear risk factors for other causes, younger patients should undergo nuclear imaging for a Meckel's diverticulum. Middle-age patients (30–50 years old) should be considered for push, double–balloon, or capsule enteroscopy, depending on the available diagnostic equipment. Older patients (greater than 50 years old) should be

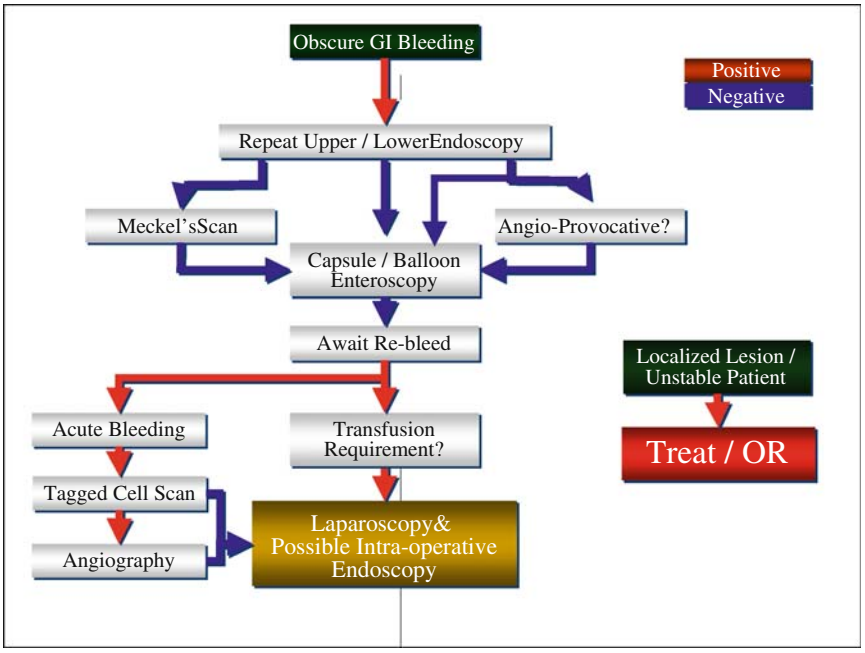

Fig. 1 Diagnostic algorithm

considered for evaluation of a vascular etiology, including vascular ectasias, hemangiomas, and Dieulafoy's malformation. As the initial diagnostic maneuver in the older patient, either an enteroscopic approach or an angiographic approach can be considered.

Among stable older patients without active bleeding, push or pill enteroscopy is preferred as angiograms and tagged red blood cell scanning are only effective when active bleeding is suspected. In some cases in which hemodynamic instability is not a concern or previous enteroscopic imaging has been performed, consideration can be given to a diagnostic challenge with an anticoagulant. It is important to select an anticoagulant that can be easily reversed in the event of severe bleeding. Typically administering up to 5,000 IU of unfractionated heparin is a reasonable approach, as it can be reversed with protamine in a ratio of 1 mg per 100 IU of unfractionated heparin, up to a maximum dose of 50 mg. Importantly, patients receiving NPH insulin may have a severe anaphylactic reaction to protamine, and hence diabetes should be considered a relative contraindication to this approach. A challenge should be performed in a coordinated effort with the appropriate radiology resources in anticipation of further angiographic imaging once bleeding occurs. If the source can be treated endovascularly after diagnostic angiography, we strongly recommend this approach before proceeding to surgery.

If these initial tests are unrevealing or do not localize a source, it is not in the best interest of the patient to proceed with an undirected open surgical approach to

diagnosis. Historical data have suggested that open laparotomy was only diagnostic in 30 of 100 cases, and of these 30, 17 (58%) likely would have been made with non-invasive techniques available today [14]. A more recent series found that while a diagnosis was made in 29 of 53 OGIB cases by open laparotomy, 15 additional cases were diagnosed by enteroscopy, and importantly 29% of patients had a re-bleeding episode with overall mortality 7.5% [15]. Thus, we prefer to consider less invasive approaches to diagnosis when available. In the absence of a clear diagnosis after initial stratified testing in an otherwise stabilized patient, we prefer either to wait for another episode of bleeding or to consider provocative testing with an anticoagulant.

Laparoscopic Approach to Diagnosis and Management of OGIB

If a source is localized by non-invasive or angiographic imaging or the patient continues to be hemodynamically unstable or require transfusion, we recommend an initial diagnostic laparoscopic approach coupled with use of intraoperative endoscopy if necessary (Fig. 2). Specifically, for a patient with a non-localized lesion, a diagnostic laparoscopy should be performed. Of course, if the patient has an absolute contraindication to laparoscopy a laparotomy is then recommended. Access is achieved either with an open technique with insertion of the Hasson cannula at the umbilicus or by an insertion of a Veress needle. Additional 5 mm ports are initially placed in the lower quadrants to facilitate running of the small bowel from the ligament of Treitz to the cecum. Additional ports can be placed or the 5 mm ports may be exchanged over for 12 mm ports if necessary depending on the intraoperative findings (Fig. 3). All four quadrants of the abdomen are initially explored and attention is then turned to a thorough investigation of the small bowel from the stomach to the cecum. If an obvious etiology is identified a suture may be placed to mark the region. It is important to realize that intralumenal blood clots may resemble a mass upon extra-lumenal exploration. Prior to resection, the surgeon must be confident that indeed the identified pathology is the cause of the ongoing hemorrhage.

If there is no obvious source identified after running the small bowel and closely investigating the colon, intraoperative endoscopy should be performed. Enteroscopy may be performed orally, anally, or through an enterotomy. If investigation is initially taken via a natural orifice then a colonoscope or enteroscope may be preferentially used. The investigated bowel is telescoped over the scope as it is advances. If no obvious pathology is identified then bowel clamps can be placed distally or proximally to mark the limits of the natural orifice endoscopy. Next, the small bowel is eviscerated from an umbilical incision which may need to be extended and an enterotomy is made following placement of a purse string suture in an effort to avoid gross contamination. The gastroscope is then inserted and the small bowel is thoroughly examined using a telescoping technique between the previously placed laparoscopic proximal and distal clamps which designate the limits of the natural orifice endoscopy. Usually two surgeons are required. If the source is identified then resection may be performed laparoscopically (Fig. 4).

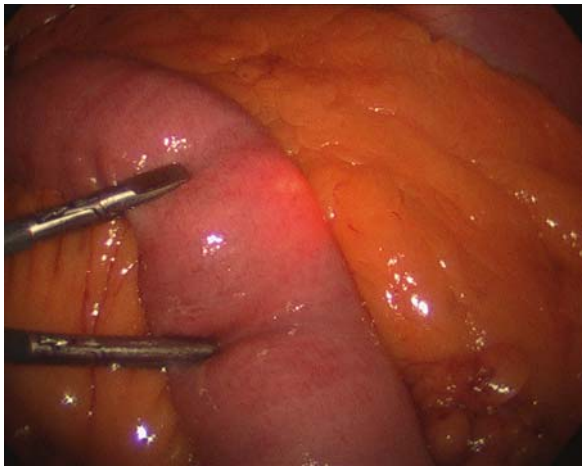

Fig. 2 Intraoperative enteroscopy. An endoscope, preferably an enteroscope, is passed transorally and the bowel is run over the scope with the assistance of laparoscopic graspers. Lesions identified with this approach can be diagnosed and treated in the same setting

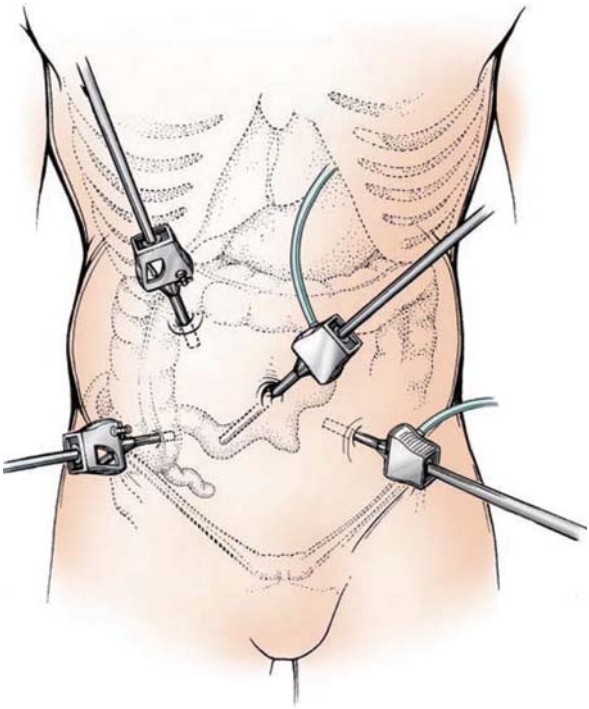

Fig. 3 Diagnostic laparoscopy. Initial set-up includes three or four 5-mm trocars to facilitate full exploration of the abdomen. If pathology is identified, one or more trocars may be upsized to allow for passage of a surgical stapler and specimen extraction

Several case reports and small case series have been described using this technique [16–18]. However, given the rarity of OGIB, there have been no large cohort series described thus far.

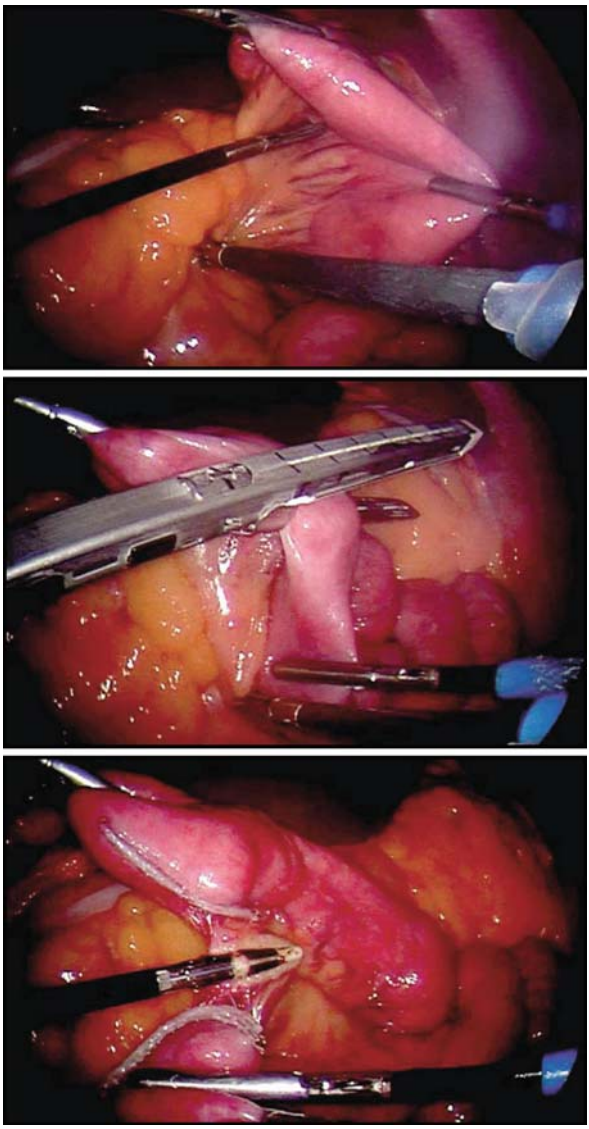

Fig. 4 Laparoscopic small bowel resection. A mesenteric window is created bluntly at the resection point (**a**). The bowel is transected with a surgical stapler (**b**). The mesentery is divided with an electrosurgical device (**c**). The anastomosis is then competed with surgical staplers ± sutures

Summary

OGIB is one of the most challenging diagnostic scenarios for gastroenterologists and surgeons alike. As the differential diagnosis is large and the causes are rare, a focused approach toward diagnostic testing should be taken, guided by key aspects of the medical history. Importantly, a second round of standard upper and lower endoscopy should be considered for all patients as the most common cause of OGIB is a previously missed lesion on endoscopy.

Further evaluation should be guided by medical history and the patient's clinical condition. Stable patients should be evaluated with capsule, push, or double-balloon enteroscopy, depending on available resources. Patients with active bleeding that are not hemodynamically unstable should be evaluated with non-invasive and angiographic imaging as open diagnostic laparotomy carries a significant risk of morbidity and mortality, and frequently the diagnosis can be made using less invasive techniques. For some patients, a challenge with a reversible anticoagulant can be considered in coordination with the appropriate imaging resources. Finally, if surgery for OGIB is required to evaluate the small bowel, we recommend a combined laparoscopic and endoscopic approach as the first-line approach.

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Note: Letters 'f' and 't' following locators denote figures and tables respectively

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