Obscure gastrointestinal bleeding: An approach to management

JK Marshall MD MSc FRCP, OA Lesi MD, RH Hunt MD FRCP FACG

Gastrointestinal bleeding is an important clinical problem and accounts for a substantial proportion of cases seen by gastroenterologists worldwide. In most patients, the site of bleeding is accurately localized to the upper or lower gastrointestinal tract, allowing specific therapy to be instituted. However, the remainder may continue to demonstrate macroscopic gastrointestinal hemorrhage, with hematemesis, hematochezia or melena from sites that are not detected by routine endoscopy or radiography. These individuals with 'obscure' gastrointestinal hemorrhage provide a diagnostic and therapeutic challenge, and require a special approach.

The management and investigation of obscure gastrointestinal bleeding can consume a disproportionate amount of health care resources for repeated hospital admissions, investigations, transfusion, and medical or surgical therapy (1). Early and efficient identification of the bleeding site can attenuate the intensity of this resource consumption.

In most cases of obscure hemorrhage, diagnosis is delayed because the source of blood loss is not accessible to routine endoscopic techniques, as in lesions of the small bowel, or because the hemorrhage is too slow or intermittent to reveal frank extravasation during endoscopy, scintigraphy or angiography. In the elderly, multiple potential bleeding sites such as diverticula or angioectasia are often demonstrated, but none can be identified with confidence as the source of bleeding.

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Division of Gastroenterology, Department of Medicine, and Intestinal Disease Research Programme, McMaster University, Hamilton, Ontario

Correspondence and reprints: Dr John K Marshall, Division of Gastroenterology (4W8), McMaster University Medical Centre, 1200 Main Street West, Hamilton, Ontario L8N 3Z5. Telephone 905-521-2100 ext 76782, fax 905-521-4958, e-mail marshllj@fhs.mcmaster.ca

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TABLE 1
Reasons for delayed diagnosis in patients with obscure gastrointestinal hemorrhage

- Inaccessibility of bleeding site to routine radiography and/or endoscopy
- Intermittent or slow rate of bleeding
- Inconclusive evidence of bleeding from potential lesion
- Subtle/atypical or rare lesion

TABLE 2
Diagnoses to consider in the evaluation of obscure gastrointestinal hemorrhage

- Degenerative angioectasia
- Hereditary hemorrhagic telangiectasia
- Watermelon stomach
- Portal hypertensive gastropathy
- Dieulafoy lesions
- Small bowel neoplasms
  - Benign
    - Adenoma
    - Leiomyoma
    - Lipoma
  - Malignant
    - Adenocarcinoma
    - Lymphoma
    - Carcinoid
- Small bowel diverticula
  - Meckel’s
  - Enteric duplication cysts
  - Other
- Hemobilia
- Hemosuccus pancreaticus
- Vasculenteric fistula
- Vasculitides
  - Hiatal hernia (Cameron ulcer)

ETIOLOGY

In most patients who present with acute and overt gastrointestinal hemorrhage, prompt investigation by way of clinical assessment and endoscopy of the upper or lower gastrointestinal tract provides a satisfactory diagnosis. Hematemesis, melena and/or disproportionate elevation of the blood urea nitrate level suggest an upper gastrointestinal lesion. Overt upper gastrointestinal hemorrhage is most commonly attributed to peptic ulcer disease, Mallory-Weiss tears or esophageal varices. Hemorrhage distal to the ligament of Treitz more often presents with gross hematochezia and usually results from hemorrhoids, polyps, colorectal carcinoma, vascular malformations, inflammatory bowel disease or diverticulosis. However, among patients with obscure gastrointestinal blood loss, a different differential diagnosis must be considered and in a different order of probability (Table 2).

Angioectasias: In most series, mucosal vascular abnormalities are the most common source of hemorrhage in patients who present with recurrent but obscure gastrointestinal bleeding (2). Various terms including ‘angiodyplasia’, ‘vascular ectasia’, ‘telangiectasia’ and ‘hemangioma’ have been used synonymously to describe these lesions, leading to some confusion in the literature. It has been suggested that the hereditary lesions of the Osler-Weber-Rendu and ‘blue rubber bleb nevus’ syndromes should be distinguished from the presumably degenerative lesions of advancing age and those associated with chronic renal insufficiency, aortic stenosis and local irradiation (3). Camilleri et al (4) proposed a classification scheme based on the size and type of vessel affected, and the presence or absence of concomitant somatic and dermatological features, but this classification scheme claimed an unproven distinction in morphology among ‘angiodyplasia’, ‘telangiectasia’ and ‘hemangioma’, and has not been widely adopted. As a general descriptor, the term ‘angioectasia’ has been promoted recently by an international working group in endoscopic terminology (5).

Congenital or hereditary angioectasias typically are found in patients under 50 years of age (2,6). While these lesions can occur anywhere in the gastrointestinal tract, those that present with obscure hemorrhage are usually found in the jejunum and proximal ileum. Patients with hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu syndrome, may suffer from frequent epistaxis and may be aware of a family history of similar bleeding episodes. HHT also may occur in association with von Willebrand’s disease (7). In female patients with HHT, the rate of bleeding may be altered by the menstrual cycle, pregnancy, menopause or hormone supplementation (4,8,9). Further clues to the diagnosis of HHT can be found by close inspection of the skin and oropharynx for additional vascular lesions.

Degenerative angioectasias are commonly referred to as angiodyplasia and are a significant source of hemorrhage in patients over 60 years of age. While they are localized most frequently to the cecum and ascending colon, the lesions can also occur throughout the gastrointestinal tract (10). Boley et al (11) suggested that degenerative angioectasias result from partial obstruction of submucosal veins where they traverse the longitudinal and circular layers of the muscularis propria. The resulting pressure gradient may lead to incompetence of the precapillary sphincter and development of direct arteriovenous communication.

An unusual form of angioectasia, occurring in the upper gastrointestinal tract, is the gastric antral vascular ectasia (GAVE), or watermelon stomach. Although this lesion has characteristic endoscopic and histological features, its appearance can be easily confused with gastritis by an inexperienced endoscopist (12). In some patients, GAVE may be indistinguishable from portal hypertensive gastropathy, both endoscopically and histologically, particularly in the absence of associated features of portal hypertension. However,
Management of obscure gastrointestinal hemorrhage

Vasculoenteric fistulae: An aortoenteric fistula is a rare lesion that may occur spontaneously or more commonly as a late complication of reconstructive aortic surgery. Such fistulas may form between the graft prosthesis and any portion of the gastrointestinal tract, but most commonly involve the third part of the duodenum. Their classic presentation is a brisk bleed that stops spontaneously, the herald hemorrhage, only to be followed by massive exsanguination 24 to 48 h later. Occasionally, however, aortoenteric fistulae may present with intermittent overt bleeding over a period of several months (28). In such patients, the diagnosis can be made only if the physician maintains a high index of suspicion and carries out appropriate diagnostic studies including full duodenoscopy, computed tomography and angiography.

Hemobilia: Acute hemobilia classically presents with the triad of jaundice, right upper quadrant abdominal pain and hematemesis. Hemobilia may complicate tumors of the hepatic parenchyma and biliary tree, cholelithiasis, ascariasis and invasive hepatobiliary procedures such as percutaneous liver biopsy, percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography and surgical cholecystoenterostomy (29). While urgent duodenoscopy in a patient with acute hemobilia may reveal bleeding from the papilla, many patients bleed intermittently and the diagnosis can be overlooked unless considered. Treatment of refractory hemobilia usually requires resection of the responsible lesion, arterial ligation or angiographic embolization.

Hemosuccus pancreaticus: Recurrent gastrointestinal hemorrhage through the pancreatic duct has been reported in association with chronic pancreatitis (30). A peripancreatic artery typically is eroded by a pancreatic pseudocyst, or develops an aneurysm that erodes into the pancreatic duct or gastric lumen. Splenic artery aneurysms may calcify and be apparent on standard abdominal flat plates. Treatment carries out appropriate diagnostic studies including full duodenoscopy, computed tomography and angiography. Acute hemobilia classically presents with the triad of jaundice, right upper quadrant abdominal pain and hematemesis. Hemobilia may complicate tumors of the hepatic parenchyma and biliary tree, cholelithiasis, ascariasis and invasive hepatobiliary procedures such as percutaneous liver biopsy, percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography and surgical cholecystoenterostomy (29). While urgent duodenoscopy in a patient with acute hemobilia may reveal bleeding from the papilla, many patients bleed intermittently and the diagnosis can be overlooked unless considered. Treatment of refractory hemobilia usually requires resection of the responsible lesion, arterial ligation or angiographic embolization.

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Vasculitis: The gastrointestinal tract is affected in a substantial proportion of patients with systemic vasculitis (32). Overt gastrointestinal hemorrhage has been reported in association with isolated leukocytoclastic vasculitis, systemic lupus erythematosus, Henoch-Schövlein purpura, cytomegalovirus (CMV)-associated vasculitis, Behçet’s disease and Wegener’s granulomatosis (33-38). Endoscopy may reveal local hyperemia, mucosal purpura or the typical features of idiopathic inflammatory bowel disease (32,39-41). Abdominal radiographs may be normal or demonstrate thumb printing or pneumatosis intestinalis. Definitive diagnosis requires biopsy tissue for immunofluorescent staining and may only be achieved after laparotomy for an acute episode of refractory hemorrhage or perforation (32,33,36).

Hiatal hernia: In patients with large hiatal hernias, linear erosions of gastric folds at the level of the diaphragm have been reported and may be associated with chronic, obscure blood loss (42). These so-called ‘Cameron ulcers’ can be overlooked at initial endoscopic evaluation but should be specifically sought in patients with obscure bleeding and a...
The diagnostic evaluation of patients with obscure gastrointestinal bleeding includes esophagogastroduodenoscopy and colonoscopy by an experienced endoscopist using a conventional endoscope, whose tip can be advanced by the endoscopist much like a regular endoscope, although it often requires the assistance of fluoroscopy and/or external abdominal compression. While push enteroscopes generally cannot be advanced as far as sonde enteroscopes into the distal small bowel, they usually are equipped with a deflectable tip for better mucosal inspection, and a biopsy channel for endoscopic intervention. An overtube can be used to prevent looping of the endoscope shaft in the stomach and duodenum. Most authors report routine placement of push enteroscopes, which measure 2 to 3 m in length, 30 cm to 150 cm beyond the ligament of Treitz (46-48).

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INVESTIGATION

The diagnostic evaluation of patients with obscure gastrointestinal bleeding includes endoscopy of the upper and lower gastrointestinal tract, radionuclide scintigraphy, selective visceral arteriography and even exploratory surgery. Enteroscopy is increasingly available and fast becoming a standard diagnostic tool. As a general rule, the clinician should proceed from the simplest and least invasive tests to the more complex and invasive procedures (Figure 1).

Repeat endoscopy and colonoscopy: A repeat esophagogastroduodenoscopy and colonoscopy by an experienced endoscopist are mandatory in all patients with unidentified bleeding from the gastrointestinal tract. An upper endoscopy should also be performed using a colonoscope, whose tip can be advanced beyond the ligament of Treitz to examine the proximal jejunum. In this setting, the smaller diameter of a pediatric colonoscope may be better tolerated by patients. The colonoscopy should follow meticulous cleansing of the colon to allow detailed inspection of the mucosa for angioectasias. Excessive insufflation of the cecum and ascending colon can blanche angioectasias and should be carefully avoided because they are slow to refill. Angioectasias can also be difficult to detect in the presence of severe anemia, and transfusion before endoscopy may augment the diagnostic yield. When thorough repeat esophagogastroduodenoscopy and colonoscopy are confidently reported as normal, the site of hemorrhage is usually localized to the small bowel.

Enteroscopy: Endoscopic imaging of the small intestine is most commonly attempted by oral passage of an adult or pediatric colonoscope to the proximal jejunum. However, specialized centres may also have access to sonde or dedicated push enteroscopes. The sonde enteroscope is passed orally or transnasally, advanced to the ligament of Treitz piggybacked to a regular endoscope and then released. Guidewire approaches to initial placement of the instrument are also available. Once in the distal duodenum, a balloon on the instrument’s tip is inflated and a prokinetic agent is administered parenterally to facilitate passive advance by peristalsis. The endoscopic assessment is then performed during withdrawal of the instrument. In experienced hands, sonde enteroscopes, which measure up to 400 cm in length, allow visualization of the distal jejunum in up to 90% and the terminal ileum in 60% of cases (44,45). However, most of these devices do not permit tip deflection, have no biopsy channel, cannot accurately localize lesions for subsequent intervention, and require 4 to 8 h to complete examination of the small intestine.

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In patients investigated for obscure gastrointestinal blood loss, enteroscopy has revealed a bleeding source in 20% to 75% of patients undergoing examination at experienced centres (44,46,47,49-51). In most of these series, approximately half of the lesions were identified proximal to the ligament of Treitz and within reach of a conventional endoscope but had been overlooked. Thus, the true incremental diagnostic yield of enteroscopy after careful repeat examination by an expert endoscopist using a conventional endoscope or pediatric colonoscopy remains unclear. Angioectasias and small bowel tumours appear to be the two most common lesions identified in the small bowel at enteroscopy, although the former can be confused with traumatic submucosal hemorrhage. Angioectasias may be amenable to definitive endoscopic therapy through injection or electrocautery, while tumours can be removed by snare (if small) or biopsied to direct further management.

Small bowel radiography: Single contrast barium radiography of the small bowel has a low diagnostic yield in patients investigated for obscure bleeding (52). In contrast, small bowel enteroclysis may detect a potential source in 10% to...
20% of these patients (17,53) and is considered the gold standard for detection of small bowel tumours and diverticula (54). However, even double-contrast barium radiography may fail to detect superficial lesions such as mucosal angioectasias, and hence a negative study cannot exclude the small bowel as a bleeding source. Barium imaging has no role in the evaluation of patients with active bleeding because residual contrast can interfere with subsequent endoscopic or mesenteric arteriographic procedures.

**Nuclear-labelled red cell scans:** Scintigraphy following intravenous injection of red blood cells labelled with 99mTc-technetium is a technique commonly used to localize low grade but clinically overt gastrointestinal bleeding. The long intravascular half-life of the labelled cells allows sequential imaging for up to 24 h after injection, and extravasation may be detected with a bleeding rate as low as 0.1 to 0.2 mL/min (55). In positive studies, the localization of colonic bleeding often can be straightforward because the large bowel is relatively fixed anatomically and because extravasated blood shows little transit. However, bleeding at the splenic and hepatic flexures may be obscured by pooling of technetium in the liver and spleen and give a false negative result.

The use of scintigraphy in the diagnosis of obscure bleeding is limited by its relative inability to localize bleeding in the small intestine, where most bleeding sources are often identified. Thus, red blood cell scanning in this population may do little to direct further therapy or surgical resection. Nevertheless, scintigraphy is relatively safe, and detects low grade or intermittent bleeding, with a sensitivity of approximately 75% (56). A negative scan implies a good prognosis and may indicate that arteriography will not reveal a bleeding site (57-58).

**Meckel’s scan:** Radionuclide scintigraphy may allow detection of a Meckel’s diverticulum by intravenous injection of 99mTc-technetium-pertechnetate, which is taken up preferentially by ectopic gastric mucosa. Using this technique, Sfakianakis and Conway (21) reported a sensitivity of 85% and a specificity of 95% in a referral population. The sensitivity of the standard Meckel’s scan may be increased by priming the patient with pentagastrin to stimulate mucosal uptake, or with an H2 receptor antagonist to prolong the residence time of the isotope (59-60). False positive results have been reported in inflammatory bowel disease and enteric duplication or gastric cysts (21,61), while false negative results have been reported in adult patients (62).

**Arteriography:** The role of selective visceral arteriography as a diagnostic and therapeutic intervention in active gastrointestinal hemorrhage is clearly established in the literature. Although active bleeding in excess of 0.5 mL/min is necessary to detect frank extravasation, arteriography may be useful in patients with obscure hemorrhage who are not actively bleeding. For example, a vascular tuft or early filling vein may suggest an angioectasia, or a tumour blush may localize a small bowel neoplasm. Despite the intermittent nature of many obscure gastrointestinal bleeds, a diagnostic yield of 44% has been reported using angiography after an extensive noninvasive workup (63). However, selective mesenteric arteriography is a sophisticated technique that requires expensive digital equipment, and highly specialized radiographic and radiological training.

Repeat arteriography in ‘obscure bleeds’ with an initial negative study is a controversial but occasionally rewarding procedure. The ‘second look’ may coincide fortuitously with an episode of bleeding or, more commonly, may fill different branch vessels to increase the diagnostic yield (64).

In selected patients, ‘pharmacocoangiography’ may enhance the yield of ‘second look’ arteriography. In these techniques, a vasodilator (eg, tolazoline), anticoagulant (eg, heparin) or thrombolytic agent (eg, urokinase) is administered before arteriography to prolong, augment or reactivate hemorrhage. Various reports have described positive provocative angiograms in challenging patients with extensive prior negative workup (65-68). However, because life-threatening hemorrhage is an obvious potential complication of pharmacocoangiography, patients must provide informed consent and full resuscitation facilities must be available.

**Laparotomy:** When all prior diagnostic modalities have failed to disclose a source of clinically significant bleeding, exploratory laparotomy should be considered. This may be particularly rewarding in patients under the age of 50 years, in whom small bowel tumours and Meckel’s diverticula are more commonly found (2). In patients who are actively bleeding, intraoperative red blood cell scintigraphy or mesenteric arteriography has been suggested (69). When a source is identified at angiography, direct injection of methylene blue dye into the culprit vessel may assist surgical resection (70).

Intraoperative endoscopy is perhaps the most useful adjunct to diagnostic laparotomy. In most cases, once the abdominal cavity is opened, a colonoscope is passed orally and advanced by the endoscopist to the proximal jejunum. The surgeon then pleats the bowel over the endoscope until the cecum is intubated. Alternatively, a surgical enterotomy can be created to allow caudad and cephalad passage of a sterilized gastroscope. Novel techniques for the laparoscopic assistance of enteroscopy have also been described (71).

Careful inspection of the mucosa while the endoscope is advanced is advocated to avoid false positive findings due to endoscopic trauma when the bowel is repositioned during withdrawal of the instrument (72). With the lights of the operating room dimmed and the bowel transilluminated by the endoscope, the vascular pattern of the gut can be carefully examined both externally by the surgeon and intraluminally by the endoscopist. Cross-clamping the terminal ileum is reported to help maintain small bowel insufflation and improve visualization (73). However, the endoscopist must remember to deflate the bowel carefully as the endoscope is withdrawn to facilitate surgical closure of the abdomen. When a bleeding source is identified, treatment can be performed endoscopically (eg, electrocautery, injection) or by surgical resection, depending on the nature of the lesion. Because of the extensive manipulation of the small bowel, a prolonged postoperative ileus can be anticipated.
Intraoperative endoscopy provides a diagnosis in the majority of patients investigated for obscure bleeding (18,74). Lewis et al (18) investigated 137 such patients and performed intraoperative endoscopy in 53 cases. The source of bleeding was identified in 83% of patients, but the postoperative mortality rate was still substantial (7.5%) and largely attributed to uncontrolled hemorrhage. Furthermore, bleeding recurred in 26% of these challenging patients despite ostensibly appropriate surgery. Thus, while laparotomy is a useful tool, it should be considered an intervention of last resort in patients with obscure gastrointestinal hemorrhage.

**MANAGEMENT APPROACH**

The approach to any patient with gastrointestinal hemorrhage is determined by the considered site, extent and rate of bleeding and, importantly, the age of the patient. As with any form of bleeding, the primary consideration should be to provide supportive care, including hemodynamic stabilization, reversal of coagulopathy and blood product transfusion. The strategy proposed below is for patients who are hemodynamically stable with recurrent or persistent hemorrhage requiring transfusion.

In such patients, the history and physical examination should be repeated carefully because important elements may have been overlooked or not volunteered initially. Any overt gastrointestinal blood loss in the form of hematemesis, melena or hematochezia should be carefully confirmed and may help to localize bleeding to the upper or lower digestive tract. Variation in the rate of blood loss with menstruation, menopause or pregnancy, or a family history of recurrent epistaxis may suggest the diagnosis of hereditary hemorrhagic telangiectasia. Any patient with a past history of aortic surgery must be assumed to have an aortoenteric fistula until proven otherwise. Other comorbid illnesses such as chronic renal failure or aortic stenosis are associated with degenerative angioectasias, although this relationship is confounded by age.

On physical examination, the clinician should assess the abdomen for surgical scars and carefully inspect the skin for the cutaneous manifestations of the blue rubber-bleb nevus syndrome, Peutz-Jeghers syndrome or hereditary hemorrhagic telangiectasia. The presence of peripheral adenopathy or hepatosplenomegaly may raise suspicion of a lymphoproliferative disorder. Stigmata of chronic liver disease including splenomegaly may suggest underlying portal hypoplasia or hepatosplenomegaly, although this relationship is confounded by age.

The urgency and extent of further diagnostic workup are determined by the patient’s overall clinical picture. In all patients, a repeat upper and lower endoscopic examination by the most experienced endoscopist is mandatory because previously undetected lesions may become apparent. Where possible, a push or Sonde enteroscope should be used to visualize the proximal small bowel. However, because such instruments are unfamiliar or unavailable to most endoscopists, upper endoscopy using a pediatric colonoscope is a reasonable and useful alternative. If these examinations fail to provide a diagnosis, more invasive investigation is needed only if bleeding is significant enough to require hospitalization and/or repeated blood transfusion, or if the clinical scenario mandates that an underlying malignancy should be excluded.

At the next level of investigation, small bowel enteroclysis should be performed by an experienced gastrointestinal radiologist to exclude reliably a small bowel tumour not seen at enteroscopy. Young adults should also undergo a technetium-pertechnetate scan to rule out a rare but easily treated Meckel’s diverticulum. If these tests are performed adequately and are negative, and if there is no further clinically significant bleeding, most patients can be managed conservatively.

More often, however, patients with a history of obscure gastrointestinal hemorrhage continue to provide signs of intermittent low grade bleeding. For patients who present with recurrent transfusion-dependent anemia, it may be prudent at this point to confirm that blood loss is occurring from the gastrointestinal tract. This can be accomplished by using either a quantitative heme-porphyrin assay (HemoQuant Mayo Medical Laboratories, Rochester, Minnesota) or a chromium-tagged red blood cell scan, although the latter appears to be more accurate (75).

If documented bleeding persists and is considered clinically significant, a technetium-labelled red blood cell scan can be performed, with serial imaging over 24 to 48 h. If the scan is positive, repeat endoscopy, colonoscopy or enteroscopy should be undertaken by an experienced endoscopist with close attention to the area of apparent extravasation. Although controversial, medically fit patients with recurrent bleeding localized to the right colon despite negative colonoscopy may be considered for an empirical right hemi- or subtotal colectomy for presumed angioectasia (76).

If radionuclide scintigraphy is uninformative, or not indicated because the bleeding is too intermittent or slow, elective visceral arteriography should be performed to look for features of angioectasia (vascular tufts or early filling veins) or tumour (vascular blush). Positive findings can be managed endoscopically or surgically, depending on the location and number of lesions. If arteriography is negative, but intermittent bleeding persists, selected patients should be admitted for provocative arteriography following infusion of heparin or a thrombolytic agent to induce or augment hemorrhage.

For patients in whom the above investigations fail to yield a diagnosis but who continue to bleed, elective exploratory laparotomy may be considered, especially if the patient is young. Intraoperative endoscopy should be performed as...
an adjunct, although the specific technique applied depends on local expertise and familiarity. If a suitable patient refuses surgery, or poses a significant operative risk, empirical medical intervention is an alternative that can be both diagnostic and therapeutic. The majority of patients with obscure gastrointestinal hemorrhage ultimately can be proven, by exhaustive investigation, to have angioectasias of the small bowel. Combination hormone therapy with estrogen and progestosterone may reduce blood loss from these lesions, with a favourable adverse effect profile in selected patients (3). Subcutaneous octreotide may offer a similar benefit but at substantially higher cost (62).

SUMMARY

The diagnosis and management of patients with obscure gastrointestinal bleeding pose a significant challenge to the clinician and may consume a disproportionate amount of medical attention and health care resources. Such patients often require multiple hospitalizations and blood transfusions, and an extensive diagnostic evaluation including repeated endoscopy, barium contrast radiography, radionuclide scans, arteriography and even laparotomy. However, a logical stepwise approach should allow a diagnosis to be achieved in the majority. Common sources of obscure hemorrhage in patients who undergo definitive investigation include angioectasias and small bowel tumours. Discrete lesions may be amenable to endoscopic ablation or surgical resection. When no cause is found despite extensive investigation, a trial of empirical hormonal therapy for presumptive angioectasias may be warranted.

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