Chapter

Mid-Gastrointestinal Bleeding

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Abstract

Mid-gastrointestinal bleeding constitutes a small proportion of all cases of gastrointestinal bleeding. It is more difficult to manage mid-gastrointestinal bleeding than upper or lower gastrointestinal bleeding. The etiology differs in younger and older age groups. The clinical presentation, investigations, and management are also different. Capsule endoscopy has improved the diagnostic accuracy to a great extent. Device-assisted enteroscopies (balloon-assisted enteroscopies and spiral enteroscopy) have both diagnostic and therapeutic potentials. Most of the time, patients present with obscure gastrointestinal bleeding which could be overt or occult. Another common presentation is iron deficiency anemia. A stepwise approach is essential to accurately diagnose and manage mid-gastrointestinal bleeding.

Keywords: small bowel bleed, occult gastrointestinal bleed, obscure gastrointestinal bleed, capsule endoscopy and gastrointestinal bleed, small bowel angioectasia

1. Introduction

Most of the gastrointestinal (GI) bleeding occurs from the upper and lower gastrointestinal tract. Mid-gastrointestinal (GI) bleeding refers to small bowel bleed anywhere from the ampulla of Vater to the ileocecal valve [1]. It occurs in 5–10% of all cases of gastrointestinal bleeding [2]. It is the most common cause of obscure GI bleeding, i.e., when the source of bleeding cannot be identified anywhere in the gastrointestinal tract [3, 4]. Management of mid-GI bleeding can be challenging to a gastroenterologist although various diagnostic and therapeutic tools are now available to evaluate and treat mid-GI bleeding. Despite the availability of various endoscopies and imaging studies, the exact cause of mid-GI bleeding can be still elusive in about one third of cases [5]. The etiology, clinical presentation, evaluation, investigations, and management of mid-GI bleeding will be discussed in this chapter.

2. Etiology

There are various etiologies of mid-GI bleeding, but their frequency depends on patient's age and underlying comorbidities [6]. Below the age of 40, the most common causes include Crohn's disease, Dieulafoy's lesion, small bowel tumors, Meckel's diverticulum, and polyposis syndrome. Small bowel tumors could be benign or malignant [7]. Benign ones include small gastrointestinal stromal tumors (GIST), benign neuroendocrine tumors (particularly small carcinoid), hemangioma, adenoma, leiomyoma, lipoma, and neurofibroma. Malignant ones include large GIST, adenocarcinoma, lymphoma, malignant neuroendocrine tumors, leiomyosarcoma, and metastatic tumor from melanoma, lung, or breast [8–11].

Rarely, polyposis syndromes involving the small bowel may present with mid-GI bleeding. These include familial adenomatous polyposis, Peutz-Jeghers syndrome, and generalized juvenile polyposis. Over the age of 40, the most common causes of mid-GI bleeding include angioectasia, nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, Dieulafoy's lesion, and small bowel tumors. On rare occasions, other small bowel lesions can cause gastrointestinal bleeding. These include small intestinal diverticuli, small intestinal varices, hereditary hemorrhagic telangiectasia, Kaposi sarcoma, intestinal tuberculosis, blue rubber bleb nevus syndrome, hematobilia, hemosuccus entericus, aortoenteric fistula, infectious enteritis, radiation enteritis, ulcerative jejunoileitis due to celiac disease, cryptogenic multifocal ulcerous stenosing enteritis [12], amyloidosis, Behcet's disease, pseudoxanthoma elasticum, and Ehlers-Danlos syndrome [13]. The incidence of small bowel neuroendocrine tumors (SBNET) has been increasing over the last few decades, and they are now considered as the most common primary malignancy of small bowel. Adenocarcinomas are generally seen in the proximal small bowel, whereas SBNET and lymphoma are commonly located in the distal small bowel. Sarcomas (GIST and non-GIST mesenchymal tumors: leiomyosarcoma, liposarcoma, fibrosarcoma, Kaposi's sarcoma, angiosarcoma) are evenly located throughout the small bowel.

3. Clinical presentation

Patients with mid-GI bleeding generally present with melena, occult gastrointestinal bleeding (anemia with heme-positive stool), or iron deficiency anemia. Sometimes, they may present with hematochezia as well when there is brisk mid-gut bleeding. Hematemesis is rare but can happen if bleeding occurs proximal to the ligament of Treitz. Patients can have abdominal pain, constipation, diarrhea, or constitutional symptoms like fever, anorexia, or weight loss depending on the underlying etiology. Symptoms (fatigue, shortness of breath, dysphagia due to esophageal web) and signs (pallor of conjunctiva, atrophic glossitis, and koilonychia) can be present depending on the severity and chronicity of iron deficiency anemia [14]. Patients may give history of receiving multiple blood transfusions acutely, subacutely, or chronically despite having multiple endoscopies, colonoscopies, and imaging studies.

4. Clinical evaluation

A thorough history and physical examination are essential in the evaluation of mid-GI bleeding. Besides the symptoms and signs mentioned above, there are certain clinical clues which may direct us to suspect the underlying etiology of mid-GI bleeding:

- Drug history: NSAIDs.
- Personal history: aortic stenosis (suspecting Heyde syndrome), cancer, melanoma, lymphoma, immunosuppressive state including human immunodeficiency virus (HIV) infection, celiac disease, radiation, polyposis syndrome.
- Family history: early colorectal cancer or endometrial cancer (suspecting Lynch syndrome).
- Hyperpigmentation around the mouth and on the lips, fingers, or toes may suggest Peutz-Jeghers syndrome.

- Telangiectasia on the lips and tongue may suggest hereditary hemorrhagic telangiectasia.

- Itchy blistering rash on the extensor aspect of the elbows, knees, buttocks, back, and scalp may suggest dermatitis herpetiformis.

- Cutaneous Kaposi's sarcoma.

- Oral aphthous ulcers, genital ulcers, and uveitis may suggest Behcet's syndrome.

- Cutaneous manifestations of pseudoxanthoma elasticum and Ehlers-Danlos syndrome.

5. Investigations

The various investigations used for management of mid-GI bleeding include wireless video capsule endoscopy (VCE), push enteroscopy, device-assisted enteroscopy (DAE), multiphasic CT enterography (CTE), magnetic resonance enterography (MRE), bleeding scan, Meckel's scan, angiography, and rarely laparoscopy with intraoperative enteroscopy [15–18].

5.1 VCE

VCE has revolutionized the visualization of the entire mucosa of the small bowel. It was approved by the US Food and Drug Administration (FDA) in 2001. The video capsule (size: 13 × 27.9 mm) takes 2 pictures per second with a total of approximately 57,600 color pictures wirelessly over a period of 8 hours [19]. It can detect subtle mucosal changes which cannot be detected by imaging studies. VCE is very useful not only in patients with chronic or intermittent mid-GI bleeding but also in acute overt mid-GI bleeding. VCE should be done as soon as possible after the bleeding episode ideally within 14 days in the case of chronic or recurrent overt mid-GI bleeding and within 24–72 hours of acute overt mid-GI bleeding for maximal diagnostic yield [20]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends that patients should take 2 L of polyethylene glycol (PEG) and simethicone (80–200 mg) prior to VCE. Prokinetic drugs (metoclopramide or domperidone) should be given if the video capsule stays in the stomach for more than 30–60 minutes as shown by real-time VCE viewer [21, 22]. Ideally video capsule should be placed endoscopically into the small bowel by using a capsule endoscope delivery device in patients with dysphagia or abnormal gastrointestinal anatomy or delayed gastric emptying where there will be increased risk of incomplete VCE study [23]. It is safe to perform VCE in patients with cardiac pacemaker, automatic implantable cardioverter-defibrillator (AICD), and left ventricular assist device [24].

5.2 Push enteroscopy

Push enteroscopy is a very useful tool in the evaluation of lesion seen in the proximal part of the small bowel by VCE. Push enteroscopy is generally done by a dedicated push enteroscope (250 cm long) or a pediatric or standard colonoscope. Gastric looping and duodenal angulation prevent advancement of the scope. An overtube back-loaded on to the scope or a stiffening wire through the biopsy channel of the scope helps prevent loop formation of the scope allowing deeper

intubation of the small bowel. The actual depth of insertion of small bowel by push enteroscopy is difficult to measure but varies (120–180 cm beyond the ligament of Treitz) among endoscopists and patients [25]. Push enteroscopy has both diagnostic and therapeutic potential including biopsy, hemostasis, and tattooing [26].

5.3 DAE

DAE includes balloon-assisted enteroscopy (single balloon and double balloon) and spiral enteroscopy.

Single-balloon enteroscopy (SBE) and double-balloon enteroscopy (DBE) were developed in 2006 and 2001, respectively, to examine the entire small bowel mucosa. Both procedures are bidirectional, i.e., the enteroscope is introduced anterogradely through the mouth and retrogradely through the anus, and the midway point is marked by tattooing or endoclipping [27]. Although the rate of complete visualization of the small bowel is three times (66 vs. 22%) higher with DBE than that with SBE [28], the diagnostic and therapeutic yields of these two procedures do not differ significantly [29]. In spiral enteroscopy (SE), the small bowel is pleated on the enteroscope by a screw operated by a machine, and the rotational force is converted into a linear force. In one study, complete enteroscopy was successful in 92% of cases of bidirectional DBE and 8% of cases of SE, although the diagnostic and therapeutic outcomes were not statistically different [30].

5.4 CTE

CTE is a useful tool in the evaluation of mid-GI bleed due to vascular lesion. Characteristic enhancement of the vascular lesion can be seen [31]. They are classified as angioectasia, arterial lesions (Dieulafoy's lesion and arteriovenous malformation), and venous lesions (vascular lesion with unusual morphology). Active bleeding is evidenced by progressive accumulation of contrast material over the three phases on the dependent surface of the intestine or distributed over a wide area by peristalsis. CT enterography is also useful in the detection of inflammatory and neoplastic condition of the small bowel [32].

5.5 MRE

MRE is a noninvasive radiation-free method of evaluating the entire small bowel. It can detect the mural thickening (>4 mm) and mass lesion of the small bowel. These lesions could be secondary to inflammatory and benign conditions (like Crohn's disease, adenoma, lipoma, fibroepithelial polyps) or malignant conditions (like neuroendocrine tumors, GIST, adenocarcinoma, lymphoma, and Peutz-Jeghers syndrome) [33, 34].

5.6 Bleeding scan

Bleeding scan is a nuclear medicine test performed by injecting 99 m technetium-labeled red blood cells (RBC). It can detect extravasation of tagged RBC if the bleeding rate is 0.1 ml/minute or more. It is a highly sensitive test in detecting active bleeding in the gastrointestinal tract and can localize the site of bleeding accurately in 52% of cases [35].

5.7 Meckel's scan

Meckel's scan is also a nuclear medicine test performed by injecting 99 m technetium pertechnetate which has affinity for the gastric mucosa. It is positive in

patients with Meckel's diverticulum with heterotopic/ectopic gastric mucosa. Acid secretion from the gastric mucosa can cause ulceration and bleeding near or adjacent to the diverticulum. In children, Meckel's scan is performed early, whereas in adults, it is generally performed late in the evaluation of mid-GI bleeding.

5.8 CT angiography (CTA)

CTA is increasingly being done in patients with less brisk mid-GI bleeding. CTA can detect the bleeding site if the bleeding rate is 0.3 ml/minute or more [36]. However, CTA exposes the patient to ionizing radiation, and intravenous contrast is required. So patients with contrast allergy, renal failure, and pregnancy should avoid CTA.

5.9 Conventional mesenteric angiography (CMA)

CMA is rarely done in the evaluation of mid-GI bleeding unless there is ongoing significant bleeding and patient had hemodynamic instability, positive CTE, or bleeding scan; and embolization is considered to stop the bleeding. However, there is risk of bowel wall infarction following embolization therapy. CMA can also detect small bowel varices in patients with portal hypertension and Meckel's diverticulum by the finding of an anomalous long branch of superior mesenteric artery traversing the mesentery toward the right lower quadrant and supplying the diverticulum.

5.10 Gallium-68 dotatate PET/CT scan

Gallium-68 dotatate PET/CT scan is now considered as the best scan for detecting SBNET as 70–90% of them have somatostatin receptors. It has much better imaging quality and can detect more lesions than Octreoscan [37]. But it does not replace CTE or MRE for those SBNET which are not somatostatin receptor positive.

5.11 Intraoperative enteroscopy

Intraoperative enteroscopy is done in the operating room when other modalities of investigations fail to detect the source of bleeding. The scope is introduced through the mouth or through an enterotomy, and whole small bowel can be evaluated. It is diagnostic as well as therapeutic in achieving hemostasis in about 70% of cases.

6. Management

A systematic approach is essential to manage mid-GI successfully. Mid-GI bleeding is generally established when no source of potential bleeding is found in the upper or lower gastrointestinal tract after doing bidirectional endoscopy, i.e., upper endoscopy (including examination with a side-viewing duodenoscope) and ileocolonoscopy. Second-look bidirectional endoscopy should be done considering substantial initial endoscopic miss rates [38]. Next step to evaluate is whether the patient is hemodynamically stable or unstable and whether the patient is having occult or overt GI bleeding. The first investigation to evaluate mid-GI bleeding in a hemodynamically stable patient is VCE unless there are contraindications like small bowel obstruction [39]. On the other hand, in a hemodynamically unstable patient, the first investigation will be angiography for both diagnostic and therapeutic purposes [40].

Depending on the location of bleeding lesion in VCE, push enteroscopy or DAE should be done, i.e., push enteroscopy for lesion in the proximal part of the small bowel and DAE for lesion in the mid or distal part of the small bowel. If the VCE is negative, the next step will depend on whether the patient has ongoing blood loss, the rate of blood loss, and the presence of comorbidities:

a. If the patient has ongoing blood loss without significant comorbidities, DAE, CTE/MRE, or even laparoscopy with intraoperative enteroscopy should be considered to stop the bleeding.

b. If the patient does not have ongoing blood loss, further evaluation can be stopped.

c. If the patient has significant comorbidities and slow rate of blood loss, further investigation could be reasonably stopped. Patient should be observed with periodic monitoring of complete blood count (CBC), and iron supplementation and/or blood transfusion should be given as necessary basis.

Definitive therapy should be given according to the findings seen in the above investigations. Treatment modalities of some of the common conditions are listed below:

- Small bowel angioectasia: it is by far the commonest cause of mid-GI bleeding. Endoscopic ablation is the treatment of choice. Sometimes patients may present with recurrent anemia due to bleeding from widespread or inaccessible angioectasia, and endoscopic treatment is risky because of patients' comorbidities or old age. Pharmacologic treatment is generally offered in those cases. Thalidomide prevents angiogenesis by inhibiting vascular endothelial growth factor (VEGF). One study showed that thalidomide was effective in reducing the rate of recurrent small bowel bleeding due to vascular malformations [41]. Octreotide decreases mesenteric blood flow, inhibits angiogenesis, and improves platelet aggregation. One meta-analysis showed that octreotide therapy reduced the transfusion requirement in patients with recurrent bleeding from gastrointestinal vascular malformations [42]. Other treatment modalities for different conditions include:

- Isolated jejunal and ileal bleeding ulcers due to NSAIDs: hold NSAIDs, endoscopic treatment, and/or embolization. In rat model, proton pump inhibitors were found to worsen NSAID-induced small bowel injury by inducing dysbiosis [43].

- Dieulafoy's lesion: endoscopic (argon plasma coagulation, hemoclip, injection therapy) or angiographic intervention (embolization) or surgery if those interventions fail [44].

- Small bowel varices: endoscopic treatment if within reach of endoscope. Angiography, transjugular intrahepatic portosystemic shunt (TIPS) placement, or surgery if endoscopic hemostasis fails or is beyond the reach of endoscope [45].

- SBNET: surgical resection is the treatment of choice for locoregional disease. Long-acting somatostatin analogs are given for functional and nonfunctional metastatic SBNET because of their antiproliferative effects and ability to control carcinoid symptoms [46].

- Adenocarcinoma of small bowel: surgery, chemotherapy, and checkpoint inhibitors.
- GIST: surgery and tyrosine kinase inhibitors.
- Non-GIST mesenchymal tumors: surgery.
- Benign tumors:

  Adenoma: endoscopic resection.

  Lipoma, leiomyoma, and hamartomas: segmental resection.

  Peutz-Jeghers syndrome: segmental resection or endoscopic resection. Because some patients are young with widespread polyps, endoscopic treatment should be preferred [47].
- Metastatic tumor to the small bowel: palliative treatment.
- Meckel's diverticulum: surgery.
- Crohn's disease: endoscopic treatment, embolization, corticosteroid, 5-aminosalicylic acid, 6-mercaptopurine/azathioprine, infliximab, and surgery [48].
- Ulcerative jejunoileitis due to celiac disease: surgical resection of the ulcerated segment, corticosteroid, elimination diet, and total parenteral nutrition.

7. Prognosis

Prognosis depends on the etiology of the lesion causing mid-GI bleeding. Vascular lesions carry a good prognosis if they can be successfully treated endoscopically, radiologically, or surgically. Most of the time, vascular lesions can be managed endoscopically. Surgical intervention is required if the bleeding cannot be managed endoscopically or by interventional radiology. Surgery is also required for benign and malignant small bowel tumors, ulcerative jejunoileitis due to celiac disease, and refractory bleeding Crohn's ulcers. Sometimes, patients' comorbidities or old age do not allow invasive procedures or surgery. Symptomatic and palliative treatments are offered in those cases. Sometimes, mid-GI bleeding remains obscure. Patients end up getting multiple hospitalizations, multiple diagnostic tests, and multiple blood transfusions.

8. Conclusion

Mid-GI bleeding is common in our day-to-day clinical practice. Capsule endoscopy and imaging studies have made the diagnostic evaluations much easier than before. Balloon-assisted enteroscopy and spiral enteroscopy are generally done for therapeutic interventions. Interventional radiology and surgery are required if there is massive bleeding or endoscopic therapeutic interventions fail. After hemostasis is obtained, treatment of the underlying condition should be done. Patient's age, comorbidities, pros and cons of the procedures, and radiological and surgical interventions should be considered.

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