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CLINICAL ENDOSCOPY

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Roles of Capsule Endoscopy and Balloon-Assisted Enteroscopy in the Optimal Management of Small Bowel Bleeding

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The small bowel had long been considered a dark unapproachable tunnel until the invention of capsule endoscopy and double-balloon enteroscopy in the 21st century, which revolutionized the diagnosis and management of small bowel diseases, including bleeding. Various imaging modalities such as computed tomographic enterography, angiography, capsule endoscopy, and balloon-assisted enteroscopy play vital roles in the diagnosis and management of small bowel bleeding. The choice of modality to use and timing of application differ according to the availability of the modalities, patient's history, and physician's experience. Small bowel bleeding is managed using different strategies as exemplified by medical treatment, interventional radiology, endoscopic therapy, or surgical intervention. Balloon-assisted enteroscopy enables endoscopic interventions to control small bowel bleeding, including electrocautery, argon plasma coagulation, clip application, and tattooing as a prelude to surgery. In this article, we clarify the recent approaches to the optimal diagnosis and management of patients with small bowel bleeding. **Clin Endosc 2020;53:402-409**

Key Words: Balloon-assisted enteroscopy; Capsule endoscopy; Double-balloon enteroscopy; Small bowel bleeding

INTRODUCTION

The entire length of the small intestine could not be fully visualized until the introduction of capsule endoscopy (CE) in the year 2000. The invention of double-balloon enteroscopy (DBE) in 2001 revolutionized the management of small intestinal diseases by adding diagnostic as well as therapeutic options.[1] Small bowel bleeding is defined as a bleeding originating from any part of the small intestine. The terminology "mid-gastrointestinal (GI) bleeding" is more specific and refers to bleeding distal to the ampulla of Vater up to the terminal ileum, which can be diagnosed using CE, balloon-assisted enteroscopy (BAE), cross-sectional studies, or angiography.[2] Before the era of CE and BAE, small bowel bleeding was called obscure GI bleeding, as it was considered GI bleeding without an obvious cause, because of not being detected by conventional upper and lower GI endoscopies. However, this terminology is now reserved for cases without an identifiable cause in spite of full visualization of the small bowel by CE, BAE, or other imaging modalities.[3] Generally, small bowel bleeding accounts for approximately 5% of all GI bleeding.[4] It can be classified into overt bleeding which presents as hematemesis, hematochezia or melena; and occult bleeding in which the presentation is persistent anemia and a positive fecal blood test.[3]

ETIOLOGY

The causes of small bowel bleeding are generally classified into erosions/ulcers, vascular lesions, and tumors/polyps. Inflammatory lesions such as erosions and ulcers are more

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common in Eastern countries, while vascular lesions are predominant in Western countries.[5]

Small bowel bleeding is more likely due to inflammatory bowel disease, Dieulafoy's lesion, or Meckel's diverticulum in young patients, but tends to be due to vascular lesions, malignancies, or ulcers in older patients.[6] Among vascular lesions, angioectasias are dilated blood vessels with or without an endothelial lining. Small arteriovenous communications develop in them owing to incompetent precapillary sphincters. The pathogenesis of these vascular abnormalities is local hypoperfusion, which stimulates sympathetic nerves to initiate smooth muscle relaxation in the vessel wall to increase blood flow and reverse hypoxia, eventually resulting in an arteriovenous communication through the ectasias. Several systemic comorbidities can be associated with local hypoperfusion.[4]

OBTAINING PATIENT HISTORY

The key point while taking a patient's history is to ask about overt bleeding. If present, the form and color of the bleeding may provide a clue about the location of the bleeding source. Hematemesis usually indicates bleeding above the ligament of Treitz. Tarry stool suggests an upper GI, jejunal, or ileal origin, while bright or dark red stool suggests an ileal or colorectal origin. However, acute massive bleeding in the upper GI tract may cause reddish stools, and scant bleeding from ileal or colonic lesions may cause black stools, especially in constipated patients.[4]

Patients with comorbidities are likely to have vascular lesions. Young patients without comorbidities typically have bleeding from Meckel's diverticulum; Crohn's disease or, in rare cases, an arteriovenous malformation; or small bowel tumors/polyps associated with hereditary polyposis syndrome. Older patients are likely to have non-steroidal anti-inflammatory drug (NSAID)-induced enteritis, chronic inflammatory diseases such as intestinal tuberculosis, Behçet's disease, radiation enteritis, or small bowel tumors such as lymphomas, adenocarcinoma, metastatic tumors, and carcinoid tumors.[7] The presence of chronic epistaxis may point to hereditary hemorrhagic telangiectasia.[8]

Ohmiya et al. developed a comorbidity index, referred to as the "Ohmiya index" (Table 1), to predict small bowel bleeding attributed to vascular etiologies.[6] By combining the Ohmiya index and the age of onset of small bowel bleeding, the type of lesion can be predicted. In 53% of young patients aged <50 years with an Ohmiya index score of <2, Meckel's diverticulum and Crohn's disease were commonly found. In 72% of elderly patients with an Ohmiya index score of <2, inflammatory diseases, drug-induced injuries, or tumors were found. In 68% of the patients with an Ohmiya index score of ≥2, small bowel vascular lesions were found regardless of age.[6]

Table 1. Ohmiya Comorbidity Index: Weighted Index of Comorbidities[6]

Assigned weight for disease	Condition
1	Angina pectoris
1	Arrhythmia
1	Diabetes mellitus
1	Congestive heart failure
1	Chronic kidney disease without hemodialysis or peritoneal dialysis
2	Chronic kidney disease with hemodialysis or peritoneal dialysis
2	Peripheral vascular disease
2	Valvular heart disease
3	Portal hypertensive disease
3	Hereditary vascular disease such as hereditary hemorrhagic telangiectasia

Assigned weights for each patient's condition. The total equals the score. Example: chronic kidney disease (1) with hemodialysis (2), and portal hypertensive disease (3) = total score (6). Chronic kidney disease: estimated glomerular filtration rate <60 mL/min/1.73 m^2. Arrhythmia includes atrial fibrillation, paroxysmal atrial fibrillation, sick sinus syndrome, and supraventricular tachycardia.

SECOND-LOOK ENDOSCOPY

The result of the initial upper and lower endoscopies may be negative in some patients with upper and lower GI bleeding owing to missed lesions as a result of inappropriate timing of the procedure, difficulty in visualizing the lesion location, massive active bleeding, or poor bowel preparation that results in poor visibility.[9] The diagnostic yield of second-look upper and lower endoscopies were 2%–25% and 6%–23%, respectively.[3]

IMAGING STUDIES

Computed tomographic (CT) enterography/CT enterocly-

sis, CT angiography, and magnetic resonance enterography are cross-sectional imaging modalities that can be used to evaluate patients with small bowel bleeding. Cross-sectional studies provide a diagnostic yield in patients with small bowel bleeding of 17%–48%.[4] These modalities are beneficial in providing an initial diagnostic/therapeutic guidance before endoscopic intervention, or after the failure to identify the bleeding site by CE. For occult bleeding, CT enterography is more suitable. CT enterography is more sensitive for detecting neoplastic or inflammatory lesions than for detecting vascular lesions or Meckel's diverticula.[10] CT angiography is suitable for massive overt bleeding at bleeding rates ranging from 0.5 to 1.0 mL/min, which are equivalent to 2–3 units of blood loss in 24 hours. The absence of oral contrast allows tracking of the extravasated blood, which can point to the bleeding site, and angiography enables the process of embolization of the responsible blood vessels to control the bleeding immediately.[9] Obtaining a chest CT scan is also important, as the etiology of small bowel bleeding could be secondary to a lung disease such as intestinal tuberculosis, metastatic lung cancer, or arteriovenous malformations in hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease).[8]

CAPSULE ENDOSCOPY

CE was the first breakthrough in the diagnosis of small bowel diseases. CE takes two digital images per second (PillCam SB2; Medtronic, Minneapolis, MN, USA, EndoCapsule; Olympus Co., Tokyo, Japan, and OMOM; Jinshan Science & Technology, Chongqing, China), three per second (MiroCam; IntroMedic, Seoul, Korea), or 20 per second (CapsoCam; CapsoVision, Saratoga, CA, USA). PillCam SB3 (Medtronic) has a faster adaptable frame rate system (two or six images per second), depending on the transit speed. PillCam (Medtronic) has new v9.0 software with a "Top 100" feature, which automatically identifies the 100 most clinically relevant images using artificial intelligence algorithms. This facilitates detection of 83.5% of lesions with a high bleeding potential and >95.5% of angioectasias.[11] CE is safe and noninvasive, with a diagnostic yield of 41%–80%. It can also aid in the identification of the nearest route for BAE.[4] The major drawback of CE is retention, with a retention rate of 1.4% when used to identify causes of small bowel bleeding.[12] Retention is defined as failure of capsule excretion after ≥2 weeks. The known risk factors of retention are small intestinal Crohn's disease, previous abdominal surgery, and abdominal radiotherapy. In patients with these factors, intestinal patency should be assessed by using a dissolving patency capsule from PillCam, which was introduced in 2012, before CE became available. The other disadvantages of CE include the inability to obtain biopsies, inaccurate identification of the lesion site, and false-positive and false-negative results especially in proximal intestinal lesions, diverticula, and submucosal tumors.[8]

BALLOON-ASSISTED ENTEROSCOPY

DBE was the first type of BAE and was introduced in 2001 by Yamamoto et al.[1] BAE allows passage of the endoscope to the distal small bowel using an overtube with a balloon. DBE has an additional endoscope balloon, while single-balloon enteroscopy (SBE) uses only an overtube balloon. In patients with small bowel bleeding, the diagnostic yield of BAE is 55%–78%.[8] BAE has relatively good maneuverability in the distal small bowel, allowing hemostatic procedures to be performed, such as clipping and argon plasma coagulation. Hong et al. analyzed the data of 1,108 BAE procedures and reported a complication rate of 1.1% (12/1,108).[13] The most common complications were bleeding ($n=4$), perforation ($n=4$), pancreatitis ($n=2$), and post-polypectomy syndrome ($n=2$).[13] Aspiration pneumonia with oral BAE has also been mentioned in some reports. A meta-analysis by Wadhwa et al. revealed that the diagnostic yield, therapeutic yield, and incidence of adverse events were comparable between DBE and SBE.[14] However, the rate of complete enteroscopy was significantly higher in DBE than in SBE, although the clinical impact of complete enteroscopy is controversial.[14]

COMPARISON OF DIAGNOSTIC YIELD AMONG MODALITIES

A comparison between CT enterography and CE in patients with small bowel bleeding revealed a significantly higher diagnostic yield with CE, mainly due to the better detection of angioectasias by CE, while the sensitivity for tumor detection was comparable, with superiority of CT enterography.[15] In another pooled analysis, CE had a significantly higher diagnostic yield in small bowel bleeding than DBE performed in a single route, but the diagnostic yield of CE was lower than that of complete DBE when both antegrade and retrograde routes were used.[16] To perform BAE, the selection of the route (antegrade or retrograde) is determined on the basis of previous information such as medical history, and CT and CE findings. Prior to BAE, contrast-enhanced CT is recommended to avoid overlooking small bowel tumors such as GI stromal tumors.

FACTORS THAT ENHANCE DIAGNOSTIC AND THERAPEUTIC YIELDS

The diagnostic yield of CE was significantly higher in the patients with ongoing overt obscure GI bleeding than in those with previous overt and occult obscure GI bleeding.[17] Patients aged ≥60 years have a non-significantly higher diagnosis rate (74.2% vs. 60.6%) than those aged <60 years.[18] A greater number of packed red blood cell (RBC) transfusions was associated with a higher diagnostic yield of CE. One study showed that >50% of patients with a positive CE study had received >3 units of packed RBCs before the procedure, which is more than that given to patients with a negative CE (21.2%).[17] Other factors associated with increased diagnostic yield include moderate/severe renal disease and treatment with antiplatelet drugs.[17] The low yield associated with late intervention may be due to the healing of small mucosal defects; resolution of bleeding from a Dieulafoy's lesion, which may then appear as a normal mucosa; and small nonbleeding angioectasias between intestinal folds that are easily missed.[4]

We previously reported the importance of the timing and diagnostic yield of DBE in patients with overt obscure GI bleeding.[19] Patients who underwent DBE within 1 month of the most recent episode of overt bleeding had a significantly higher diagnostic yield than other patients (84% vs. 57%, $p=0.002$). We also reported a significant negative correlation between positive DBE findings and the length of interval since bleeding ($p<0.001$). Therefore, endoscopic investigations should be performed as soon as possible after overt bleeding.

STRATEGIES FOR EVALUATION AFTER OBTAINING A NEGATIVE CAPSULE ENDOSCOPY OR BALLOON-ASSISTED ENTEROSCOPY FINDING

Otani et al. found that repeat CE (73.2%) had a significantly higher diagnostic yield than DBE (39.6%) in patients with obscure GI bleeding with a previously negative CE finding.[20] Japanese guidelines recommend assessing the need for further workup after a negative CE result is obtained. For patients with a history of frequent hemorrhage/massive bleeding/severe anemia, they recommend BAE. For young patients, they recommend a Meckel's scan because Meckel's diverticulum is often missed on CE. For patients with a low likelihood of a false-negative study result, the guidelines recommend follow-up only. If bleeding occurs earlier in the follow-up period, BAE should be performed. If bleeding recurs well into the follow-up period, repeated upper and lower GI endoscopies are advisable. Whenever both imaging studies yield negative results, CE should be repeated.[8] In case of a negative BAE with persistent bleeding, angiography, intraoperative enteroscopy, or a Meckel's scan should be considered. If the bleeding has spontaneously resolved, follow-up alone is recommended.[4]

We previously reported the long-term outcomes of patients with negative DBE findings for overt obscure GI bleeding.[21] Of 42 patients, 16 (38%) developed overt rebleeding during the follow-up period (5.4 years on average) and 14 underwent further investigations. In 10 (71%) of the 14 patients, the bleeding source was identified. Hence, repeated enteroscopy should be performed in patients with overt rebleeding even after a negative enteroscopy finding was obtained.

ANGIOGRAPHY

Angiography can be both diagnostic and therapeutic. It has a variable diagnostic yield depending on the bleeding rate. Yields are high (77%) in overt bleeding and low (<20%) in occult bleeding.[9] Angiography has a significantly lower diagnostic yield than CE in patients with overt small bowel bleeding (20% vs. 53.3%).[22] Angiography can be used as the first-line diagnostic modality in patients with hemodynamic instability or as the last-line modality in patients with negative BAE despite ongoing bleeding. The complication rate is 10%, with renal impairment, infection, and infarction being the most common. Provocative angiography can be used if the bleeding has stopped and the source could not be identified. This is performed with the use of anticoagulants, thrombolytic agents, and vasodilators. However, it is associated with an increased incidence of bleeding complications.[9]

NUCLEAR MEDICINE SCANS

The most frequently used nuclear medicine scan to assess patients with acute obscure GI bleeding is performed with ^{99}m-Tc-labeled autologous RBCs. The minimal bleeding rate needed for positive results is 0.1–0.4 mL/min.[23] The drawbacks are the poor localization of the bleeding source and the lack of immediate availability. The overall diagnostic yield of tagged RBCs is approximately 50%.[9] Meckel's scan using ^{99}m-Tc-pertechnetate can be used in small bowel bleeding if all previous modalities were non-diagnostic. Positive Meckel's scans only indicate an ectopic gastric mucosa in the small intestine, but it is a reasonable study if a Meckel's diverticulum is suspected after failure of other modalities.[7] This is not recommended as a first-choice imaging study.

INTRAOPERATIVE ENTEROSCOPY

Intraoperative enteroscopy can be performed by transoral or transrectal insertion, or through an enterotomy. It is performed with upper or lower endoscopy or BAE. The indication for using this approach in patients with obscure GI bleeding is limited to patients with failed BAE and angiography-related therapies, or failed localization of small bowel lesions during surgical exploration. Its diagnostic and therapeutic yields range from 58% to 100%. The incidence rate of adverse events varies with patients' conditions (1%–50%). The most commonly encountered adverse events include prolonged postoperative ileus, small bowel obstruction, and wound infection.[24] Undoubtedly, it is more invasive than BAE and is not a first-choice modality.

WHICH STUDY SHOULD BE PERFORMED FIRST?

The American College of Gastroenterology (ACG) guidelines recommend performing CE before BAE in patients with small bowel bleeding.[3] However, the Japanese guidelines recommend performing contrast-enhanced (preferably dynamic) CT as the first step in BAE management, especially in patients with overt bleeding. If the bleeding stopped after a negative CT finding was obtained, CE may be considered.[8]

ACG guidelines recommend BAE with a negative CE finding under a high clinical suspicion of a small bowel lesion or active bleeding.[3] Antegrade BAE is recommended as the first approach for overt ongoing bleeding because bloody enteric contents usually progress distally via peristalsis. When bloody enteric content is first observed, a clip should be placed to mark the approximate location of the bleeding lesion in the small intestine. If the bleeding site is suspected to be in the distal ileum on CT, retrograde BAE should be considered first.[25]

TREATMENT AND MANAGEMENT

Conservative treatment

Intravenous or oral iron together with blood transfusions may be given, if needed, to treat anemia.[3] Although anticoagulant use is a risk factor of rebleeding, no data support the concept that anticoagulant cessation decreases rebleeding.[3] Small intestinal ulcers associated with the use of NSAIDs may result from disturbed microbiota.[26] Cessation of NSAIDs should be considered if possible.

Somatostatin analogues

Octreotide is a somatostatin analogue that can be used to treat patients with small bowel bleeding, with a low-level evidence supporting the benefits of its use.[3] The possible mechanisms of action include angiogenesis inhibition, reduction of splanchnic flow, and improvement of platelet aggregation.[9]

Thalidomide and bevacizumab

The pathogenesis of vascular lesions responsible for small bowel bleeding might be related to overexpression of the vascular endothelial growth factor (VEGF).[27] Trials were conducted using anti-VEGF agents such as thalidomide, which showed a significant reduction in the incidence of bleeding episodes and the need for blood transfusions.[28] However, this response was only observed in one third of the patients. Other concerns regarding thalidomide include an unknown optimal dose and duration and neurotoxicity with long-term administration.[28]

Intravenous bevacizumab was used effectively to control refractory GI bleeding in patients with hereditary hemorrhagic telangiectasia.[29] It was also used in patients with gastric antral vascular ectasias and small bowel angioectasias that were unresponsive to other therapeutic modalities. Bevacizumab administration resulted in a significant reduction in transfusion requirements and the need for endoscopic therapy in half of the patients. However, the trial included only 21 patients and provided no data regarding the optimal dose or duration of the therapy.[29]

Hormonal therapy

Many studies have used hormonal therapies, mainly estrogen plus progesterone, to treat small bowel bleeding on the basis of their efficacy in the treatment of angioectasias. However, no conclusions support this concept, and the study results were disappointing.[27]

Alternative treatments

Heyde's syndrome is associated with aortic stenosis and GI bleeding. The supposed hypothesis for the pathogenesis of the syndrome is that the increased blood flow velocity through a stenosed valve, which increases shear stress, results in the disintegration of the von Willebrand factor along with the development of angioectasia.[28] Surgical repair of the aortic valve has also been reported to result in the resolution of GI bleeding and improvement of anemia. Tsuchiya et al. published a case report of resolution of angioectasia after transcatheter aortic valve implantation proven by endoscopic images.[30]

Endoscopic management

With its capability of achieving distal small intestinal intu-

bation with good maneuverability, BAE enables endoscopic hemostatic measures such as electrocautery and clipping. Vascular lesions can be treated according to the Yano-Yamamoto classification, which classifies vascular lesions into six categories (Fig. 1).[31] Types 1a and 1b are angioectasias, which are capillary or venous in origin, and can be treated with electrocautery. Types 2a and 2b are considered Dieulafoy's lesions of arterial origin and can be treated with hemoclip placement. If the lesion is considered too large, then surgical management or transcatheter arterial embolization should be considered. Type 3 lesions are arteriovenous malformations in which veins and arteries are connected without intervening capillaries, which can cause arterial bleeding, and can be managed in the same manner as Dieulafoy's lesions. Tattooing with India ink can be performed by BAE to guide the surgical management of lesions not suitable for endoscopic therapy such as neoplastic lesions, Meckel's diverticula, and large vascular lesions.[8] Hemoclips are also useful as markers for transcatheter arterial embolization and radiological therapeutic modalities. For bleeding ulcers, oozing can be managed with argon plasma coagulation, while visible vessels are managed with hemoclips. Hemorrhagic polyps such as those of Peutz-Jeghers syndrome and small hemangiomata are better treated with polypectomy.

Interventional radiology

Treatment with angiographic catheter embolization is indicated in patients with hemodynamic instability, failure of BAE therapy, or negative BAE despite active bleeding.[8] If the source of bleeding is visible on angiography, the treatment success rate is 60%–90%.[9]

Surgical management

Surgical treatment is indicated if lesions could not be identified or if the treatment of severely active bleeding of small intestinal lesions by endoscopic and interventional radiological methods is unsuccessful.[24] Surgical management is appropriate as initial therapy for certain causes of small bowel bleeding such as malignant tumors or Meckel's diverticula. The bleeding source can be localized using intraoperative enteroscopy. Localization also can be performed with methylene blue injection through a mesenteric angiography catheter during laparotomy.[3]

Long-term outcomes of endoscopic and repeated endoscopic therapy

Shinozaki et al. followed up 100 patients with small bowel bleeding after DBE management for 29.7 months.[19] The control rate was 61% for all types of lesions. The control rate was higher for small bowel tumors/polyps and lower for vascular lesions (84% vs. 40%).[19] Kushnir et al. followed up 110 patients with small bowel bleeding for 23.9 months after SBE management.[32] The control rate was 55% for all kinds of lesions and 44% for vascular lesions.[32] Type 1a vascular lesions (Yano-Yamamoto classification) are most commonly associated with rebleeding after initial endoscopic therapy because type 1a vascular lesions initially treated with DBE were rarely responsible, and other types of vascular lesions missed on the initial DBE were often found on the subsequent DBE in these patients. Repeated endoscopic therapy for recurrent small bowel bleeding due to vascular lesions improves the long-term outcomes and reduces the number of bleeding episodes.[19]

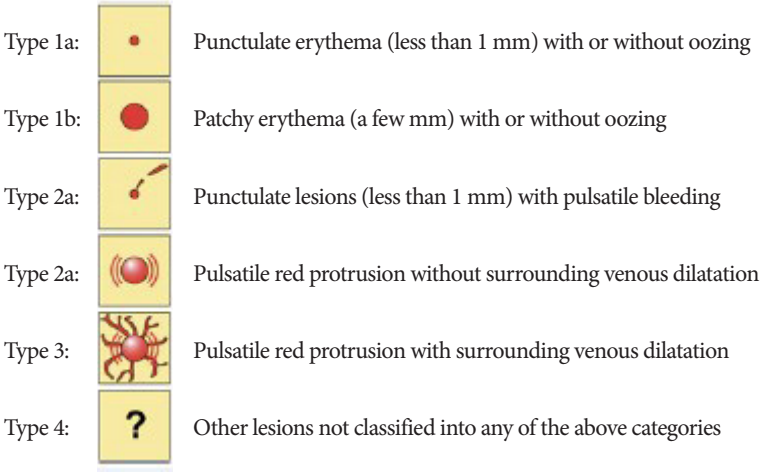

Fig. 1. Yano-Yamamoto classification of small intestinal vascular lesions.[31]

Tips based on our experience in the management of small bowel bleeding using balloon-assisted enteroscopy

The following are some tips for endoscopic management of small bowel bleeding, based on our experience:

- Attachment of a long transparent hood (4 mm) at the tip of the endoscope facilitates the use of various hemostatic measures.
- Use of the water immersion method in patients with occult bleeding enhances mucosal visualization and small lesion detection. However, this cannot be used in patients with overt bleeding, as water mixes with the blood, obscuring the visual field.
- Use of the gel immersion technique in massive overt bleeding can be useful when a clear visual field cannot be established. Gel immersion slows the flow and mixing of blood, enhancing the visual field and facilitating endoscopic management.[33]
- Examination is better during insertion than during withdrawal if mucosal injuries are present.
- A marking clip should be applied as soon as the bleeding source is identified for precise treatment, and to avoid missing the bleeding source in case of undesirable movement or sudden massive bleeding.

CONCLUSIONS

CE and BAE have revolutionized the diagnosis and treatment of patients with small bowel bleeding. Cross-sectional imaging modalities are beneficial to provide an anatomical road map before enteroscopy. On the basis of the patient's history and background, the type of lesion can be predicted. The appropriate therapeutic modalities should be used, with understanding of their advantages and disadvantages.

Conflicts of Interest

Hironori Yamamoto has patents for the double-balloon endoscope described in this article. Hironori Yamamoto also has a consultant relationship with Fujifilm and has received honoraria, grants, and royalties from the company. Tomonori Yano have received honoraria from Fujifilm Co. The other authors have no financial conflicts of interest.

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