

Diagnosis and management of mid-gastrointestinal bleeding by double-balloon endoscopy

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Abstract: The new methods of capsule endoscopy (CE) and double-balloon endoscopy (DBE) have revolutionized the diagnostic approach to middle (mid) gastrointestinal bleeding (MGIB) in recent years. DBE also has therapeutic options and enables us to treat the MGIB endoscopically. In this review, we discuss endoscopic diagnosis and management of three major categories of sources of MGIB – vascular lesions, ulcers/erosions and tumors/polyps.

Keywords: double-balloon endoscopy, mid-gastrointestinal bleeding, obscure gastrointestinal bleeding

Introduction

Small-bowel bleeding with an origin located between the papilla and the ileocecal valves is defined as mid-gastrointestinal bleeding (MGIB) [Hadithi *et al.* 2007; Raju *et al.* 2007]. Recent advances in diagnostic methods, including capsule endoscopy (CE) (Figure 1) [Iddan *et al.* 2000] and double-balloon endoscopy (DBE) (Figure 2) [Yamamoto *et al.* 2004, 2003, 2001] had enabled us to observe the source of MGIB. The results of recent research using CE and DBE have revealed the clinical features of MGIB [Hindryckx *et al.* 2008; Fujimori *et al.* 2007; Kaffes *et al.* 2007; Ohmiya *et al.* 2007; Hadithi *et al.* 2006; Sun *et al.* 2006]. However, the management strategy for MGIB has not been fully determined. This review discusses up-to-date diagnosis and treatment of MGIB by DBE.

Diagnosis and treatment of MGIB

Conventional small-bowel follow-through (SBFT) has certain sensitivity for mucosal abnormalities with Crohn's disease [Solem *et al.* 2008] or large tumors. On the other hand, SBFT has difficulty in detecting tiny and/or flat lesions, such as vascular lesions and erosions inducing MGIB. Therefore, SBFT has a limited role as an initial examination for MGIB unless a large small-bowel tumor is highly suspected as the bleeding source. CE, which allows noninvasive

visualization of mucosa throughout the entire small bowel, has revolutionized the exploration of small-bowel diseases, particularly the evaluation of MGIB after a negative initial evaluation with esophagogastroduodenoscopy (EGD) and colonoscopy. Several studies showed that CE is highly effective in detecting the source of MGIB [Delvaux *et al.* 2004; Saurin *et al.* 2003; Ell *et al.* 2002]. CE may be the preferred initial diagnostic choice in MGIB because of its noninvasive quality and better tolerance [Pasha *et al.* 2008; Pohl *et al.* 2008]. Four brands of CE (Table 1) are currently available on the market [Cave *et al.* 2008; Bang *et al.*; Li *et al.* 2008]. The Food and Drug Administration (FDA) in the United States has approved two of them. DBE has a high diagnostic yield of MGIB together with therapeutic capability even in the distal small bowel without the aid of surgical laparotomy [Ohmiya *et al.* 2007; Sun *et al.* 2006; Yamamoto *et al.* 2004]. Therefore, recent studies indicate that CE and DBE have complementary roles in the management of MGIB [Kamalaporn *et al.* 2008; Kameda *et al.* 2008; Fujimori *et al.* 2007; Li *et al.* 2007; Sugano and Marcon, 2007; Hadithi *et al.* 2006]. There have been several reports comparing the diagnostic yields of CE and DBE. According to these reports, overall diagnostic yields for MGIB are comparable between CE and DBE [Kameda *et al.* 2008; Li *et al.* 2008; Nakamura *et al.* 2006;

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Figure 1. Pillcam SB (Given Imaging, Yoqneam, Israel). The price of the single-use capsule is US\$450.

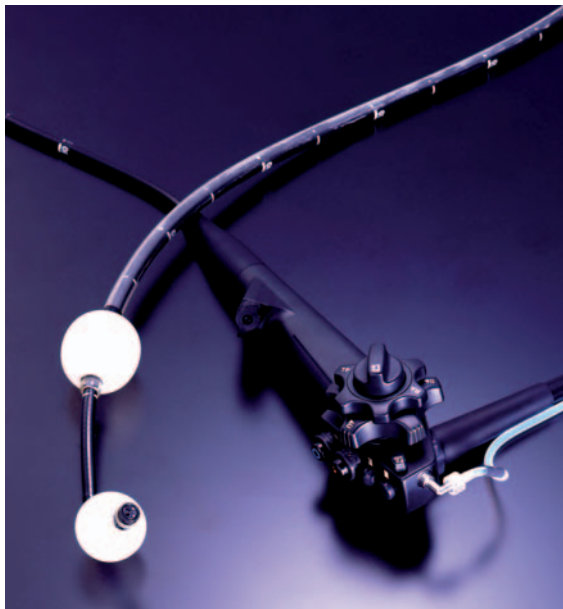


Figure 2. Double-balloon endoscopy (Fujifilm Corp., Saitama, Japan) consists of a video endoscope with a balloon attached at the tip and a flexible overtube with another balloon. A single procedure costs at least US\$246.6 including the costs of the expendable single-use overtube (US\$220) and the tip balloon (US\$26.6).

Matsumoto *et al.* 2005] (Table 2). At the consensus meeting held during the first international workshop on double-balloon endoscopy in 2006, it was proposed that CE and DBE should

be used according to the algorithm (Figure 3) for diagnostic workups and treatment for MGIB [Sugano and Marcon, 2007]. This algorithm primarily recommends DBE using the ‘per oral’ approach for overt ongoing bleeding because bloody contents scarcely flow backward in the small bowel. Therefore, when antegrade DBE encounters a pool of fresh bloody contents in the small bowel, we can easily find the source of the bleeding adjacent to the site. Our data revealed that DBE could detect bleeding sources in approximately 80% of patients with obscure GI bleeding [unpublished results, S. Shinozaki, H. Yamamoto *et al.*]. As for small bowel mass lesions, diagnostic performance of DBE was reported to be superior to CE [Ross *et al.* 2008]. When treatment or definitive diagnosis is necessary, initial DBE may be the least expensive strategy for MGIB. If CE was undergone first, a secondary procedure could be determined according to the CE findings. Considering cost benefit, initial CE may be preferred when visual identification is sufficient [Somsouk *et al.* 2008]. The most frequent side-effect of CE is the non-natural excretion (NNE) of the capsule due to a stricture or tumor in the small bowel. The incidence of NNE was zero in healthy controls and 1.4% in MGIB [Caunedo-Alvarez *et al.* 2008]. The patency capsule (PC) is a new nonendoscopic dissolvable capsule to check the patency of the digestive tract in a noninvasive manner. PC seems to be a useful noninvasive tool to identify which patients with suspected strictures could safely ingest the standard CE [Herrerias *et al.* 2008; Banerjee *et al.* 2007; Spada *et al.* 2007; Signorelli *et al.* 2006; Spada *et al.* 2005].

The major role of DBE is therapeutic, providing endoscopic cautery and/or hemoclips for bleeding sites within the small bowel. Vascular lesions constitute one of the major causes of MGIB, accounting for approximately 20% of cases [Ohmiya *et al.* 2007; Yamamoto *et al.* 2004] in Japan. Endoscopic therapy has been shown to be effective in controlling bleeding from GI vascular lesions, but depth of intubation has previously been limited [Askin and Lewis, 1996]. Before the development of DBE, when faced with a patient with a bleeding site in the mid to distal small bowel, the only option was surgery guided by intraoperative enteroscopy. Currently, DBE has replaced intraoperative enteroscopy in identifying the causes of bleeding seen on CE and in providing therapy. DBE enables us to

Table 1. Characteristics of capsule endoscopy units.

	Pillcam SB	Endocapsule	Mirocam	OMOM pill
Manufacturer	Given Imaging, Yoqneam, Israel	Olympus America, Allentown, Pa	Intromedic Co, Ltd, Seoul, Korea	Chongqing Jinshan Science & Technology, Chongqing, China
Length (mm)	26	26	24	27.9
Diameter (mm)	11	11	11	13
Weight (g)	3.45	3.8	3.4 ± 0.05	< 6
Frame rate (frames/s)	2	2	3	2
Field of view (degrees)	140	145	150	140
Battery life	8 hours	8 hours	Over 11 hours	6–8 hours
Real-time view	RAPID Real-Time	VE-1	MiroView Real Time Viewer	Real Time Viewer

Pillcam SB and Endocapsule are approved by the FDA. Mirocam with Human Body Communication (HBC) transmission technology achieves longer battery life and more frame works. The cost of OMOM pill is only approximately half of conventional units.

Table 2. Comparative studies between capsule endoscopy (CE) and double-balloon endoscopy (DBE).

Study	Country	Study design	Number of patients	Rate of positive findings [†]			Diagnostic yield [‡]		
				CE	DBE	<i>p</i>	CE	DBE	<i>p</i>
Kameda <i>et al.</i> [2008]	Japan	Prospective, blinded	32	29/32	21/32	0.043 [§]	23/32	21/32	0.789 [§]
Ross <i>et al.</i> [2008]	USA	Retrospective	18	(90.6%) 15/15 (100.0%)	(65.6%) 18/18 (100.0%)	ND*	(71.9%) 5/15 (33.3%)	(65.6%) 18/18 (100.0%)	<0.001 [¶]
Kamalaporn <i>et al.</i> [2008]	Canada	Retrospective	51	45/51 (88.2%)	51/51 (100.0%)	0.041 [§]	ND	ND	ND
Fujimori <i>et al.</i> [2007]	Japan	Prospective, nonblinded	45	ND	ND	ND	18/45 (40.0%)	18/36 (50.0%)	0.368 [¶]
Li <i>et al.</i> [2007]	China	Retrospective	218	118/164 (72.0%)	21/51 (41.2%)	<0.001 [¶]	85/164 (51.8%)	20/51 (39.2%)	0.116 [¶]
Hadithi <i>et al.</i> [2006]	The Netherlands	Prospective, nonblinded	35	28/35 (80.0%)	21/35 (60.0%)	0.045 [§]	23/35 (65.7%)	19/35 (54.3%)	0.221 [§]
Nakamura <i>et al.</i> [2006]	Japan	Prospective, blinded	32	19/32 (59.4%)	12/28 (42.9%)	0.202 [¶]	11/28 (39.3%)	11/28 (39.3%)	ND
Matsumoto <i>et al.</i> [2005]	Japan	Prospective, blinded	22	16/22 (72.7%)	12/22 (54.5%)	0.289 [§]	8 [#] /22 (36.4%)	12/22 (54.5%)	0.134 [§]

[†]Rate of positive findings, number of patients with lesions detected by CE or DBE/number of patients undergoing CE or DBE; [‡]Diagnostic yield, number of patients with definite diagnosis provided by CE or DBE/number of patients undergoing CE or DBE; [§]We assessed the data using McNemar test and considered *p* values <0.05 significant; *ND, no data available; [¶]We assessed the data using Fisher's exact test and considered *p* values <0.05 significant; [¶]We assessed the data using Chi-square test and considered *p* values <0.05 significant; [#]The numerator is number of patients with lesions detected by CE within reach of DBE.

perform endoscopic hemostasis with cautery by using argon plasma coagulation (APC) and/or hemoclip placement. We choose either or both procedures depending on the source of bleeding. Yano *et al.* [2008] investigated vascular lesions of the small bowel and suggested a therapeutic strategy for them. In cases of hemorrhagic polyps, endoscopic polypectomy is preferred to surgical resection with laparotomy. Even for hemorrhagic tumors that require surgical resection, DBE is useful for marking by tattooing at adjacent sites

of the tumors, which facilitates laparoscopic identification and resection.

Vascular lesions

Vascular lesions constitute the major cause of MGIB, accounting for approximately 50–80% in the Western world [Kaffes *et al.* 2007; Askin and Lewis, 1996]. By contrast, the lesions are responsible only for approximately 20% of MGIB in Japan [Ohmiya *et al.* 2007;

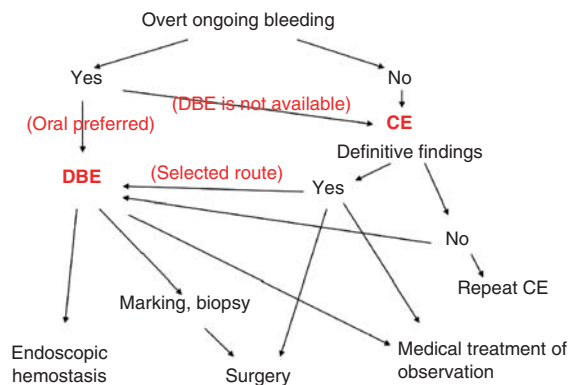


Figure 3. Algorithm for diagnostic workup for obscure GI bleeding: role of capsule endoscopy (CE) and double-balloon endoscopy (DBE) [Sugano *et al.* 2007].

[Yamamoto *et al.* 2004]. Ethnic differences may explain this difference. Small-bowel vascular lesions observed by endoscopy vary in appearance. The terms used for vascular lesions in the GI tract have not been standardized, and the terms ‘angiodyplasia’ and ‘arteriovenous malformation’ (AVM) have been used without precise definitions. Yano *et al.* [2008] developed a simple classification system for intestinal vascular lesions. The classification consists of six categories (Figure 4). Being different in size from one another, types 1a and 1b are considered angioectasias. An angioectasia is a venous/capillary lesion and thus is likely to be treated by endoscopic cauterization. Type 2 lesions, subclassified into type 2a and 2b based on the presence or absence of protrusions, are arterial lesions and are considered Dieulafoy’s lesions. Type 3 represents AVMs. An AVM is a condition in which arteries and veins are directly connected without capillary beds. Dieulafoy’s lesions and AVMs may cause arterial bleeding, which requires endoscopic treatment with hemoclip placement (Figure 5) or laparotomy for large lesions. Type 4 is a vascular lesion with unusual morphology and is unclassifiable. However, based on our experience, patients with vascular lesions had a significantly shorter rebleeding-free interval than those with ulcerative lesions, because multiple synchronous and metachronous vascular lesions are not rare.

Ulcers/erosions

Ulcers/erosions were the most common source of MGIB in Japan [Ohmiya *et al.* 2007]. Endoscopic cauterization is rather effective for

- Type 1a: Punctate erythema (less than 1 mm) with or without oozing
- Type 1b: Patchy erythema (a few mm) with or without oozing
- Type 2a: Punctate lesions (less than 1 mm) with pulsatile bleeding
- Type 2b: Pulsatile red protrusion without surrounding venous dilatation
- Type 3: Pulsatile red protrusion with surrounding venous dilatation
- Type 4: Other lesions not classified into any of the above categories

Figure 4. Endoscopic classification of small-intestinal vascular lesions (Yano–Yamamoto classification) [Yano *et al.* 2008].

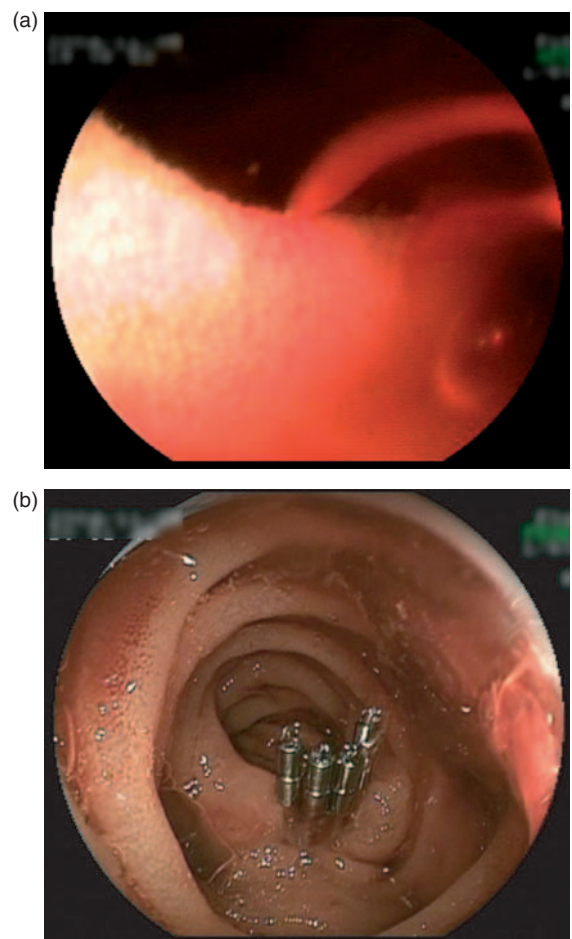


Figure 5. (a) Vascular lesion classified into type 2a according to Yano–Yamamoto classification (this is a punctate lesion, with pulsatile bleeding); and (b) after hemoclip placement.

diffuse oozing from ulcers/erosions (Figure 6). On the other hand, hemoclip placement is useful for active bleeding from exposed vessels in the lesions.

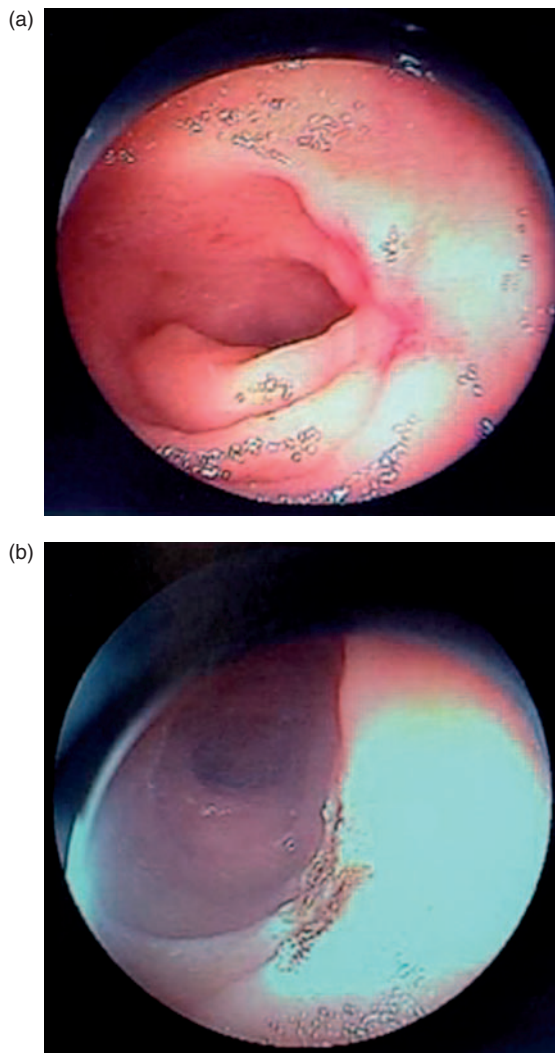


Figure 6. Endoscopic view of the NSAID-induced ulcer with oozing hemorrhage in the ileum: (a) before cauterization; (b) after cauterization.

Based on our experience, NSAID use is the major cause of small-bowel ulcers/erosions. Matsumoto *et al.* [2008] reported NSAID enteropathy occurred in one-half of patients administered nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, it is very important to obtain a careful history of NSAID use from a patient with MGIB. The most important point in the diagnosis and treatment was that the symptoms of MGIB improved after cessation of NSAIDs. Moreover, if the endoscopic findings of the lesions improve after stopping NSAIDs, it is more definite. The mainstay of treatment for NSAID-induced ulcers is discontinuation of NSAIDs. However, long-term cessation of NSAIDs is frequently inappropriate for patients with chronic pain or antiplatelet therapy even if

temporary cessation of the NSAIDs is possible. Until recently, some trials showed the efficacy of metronidazole and sulphasalazine for treatment of NSAID-induced injury [Leite *et al.* 2001; Bjarnason *et al.* 1992, 1990, 1988]. However, their effectiveness has not been fully confirmed. The diaphragm-like stricture is thought to be pathognomonic of NSAID enteropathy, which is likely a scarring reaction secondary to ulcerative injury during long-term NSAID use [Kelly *et al.* 2005; Matsushashi *et al.* 1992]. Clinical presentation of the diaphragm disease is nonspecific and may include obstructive symptoms, GI blood loss, or abdominal pain [Bjarnason *et al.* 1988; Lang *et al.* 1988; Kelly *et al.* 2005; Onwudike *et al.* 2002; Matsushashi *et al.* 1992]. We should suspect diaphragm disease when we see a patient with both obstructive symptoms and chronic NSAID use. Obstructive symptoms due to diaphragm-like strictures are unlikely to resolve without dilation because the stricture is a complication of scarring of a circular ulcer. Intestinal resection was formerly the only option for patients with diaphragm diseases in the small bowel. Recently, DBE enabled us to treat the diaphragm disease in the small bowel including afferent limb using through-the-scope balloon dilator [Kamata *et al.* 2006; Mehdizadeh and Lo, 2006].

Crohn's disease causes small-bowel ulcers/erosions with MGIB. Endoscopic features of small-bowel lesions in Crohn's disease are discrete ulcers without surrounding mucosal inflammation tending to align longitudinally, which extend into longitudinal ulcers (Figure 7). Moreover, in addition to the extension of the longitudinal ulcers, a cobblestone appearance develops with additional inflammatory changes or edema in the remaining mucosa. The longitudinal ulcers in Crohn's disease are located mainly on the mesenteric side in the small bowel. It was pointed out that the location of the lesion on the mesenteric or antimesenteric side would give an important diagnostic clue [Sunada *et al.* 2007]. The efficacy of endoscopic hemostasis for Crohn's ulcer has been obscure yet. We put emphasis on the systemic treatments rather than endoscopic treatments for bleeding in Crohn's disease.

Meckel's diverticulum occasionally induces MGIB (Figure 8). Meckel's diverticulum is located within approximately 0.6–1 m of the ileocecal valve in adults, whereas it is located within

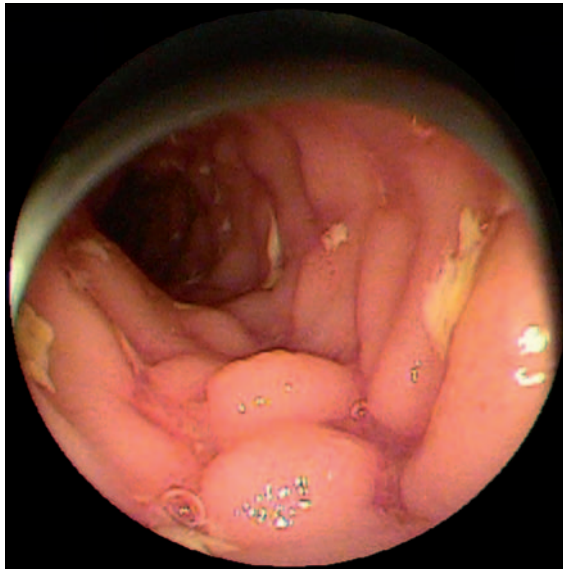


Figure 7. Longitudinal ulcer of the ileum associated with Crohn's disease.

0.4 m of the lower ileum in newborn infants. Meckel's diverticulum is a digitiform true diverticulum approximately 1–11 cm in length, located on the antimesenteric margin [Sunada *et al.* 2007]. ^{99m}Tc-sodium pertechnetate may be helpful in determining the existence of Meckel's diverticula because of its reactivity with the gastric mucosa [Martin *et al.* 2000]. However, positive results of it do not always indicate that Meckel's diverticulum is responsible for the bleeding. Shinozaki *et al.* [2007] investigated five cases of Meckel's diverticula and concluded endoscopic observation of the ulcers in Meckel's diverticula was important evidence of bleeding in patients with MGIB. Other sources of bleeding should be considered when ulcers are not found in Meckel's diverticula [Shinozaki *et al.* 2007]. Laparoscopy can be useful in the management of Meckel's diverticulum [Sanders, 1995; Huang and Lin, 1993]. Tattooing beside Meckel's diverticulum during DBE makes laparoscopic identification and resection easier.

Tumors/polyps

Tumor and polyps are a frequent cause of occult MGIB. Ohmiya *et al.* [2007] reported tumors and polyps with MGIB consisting of GI stromal tumors (GIST), metastasis or invasion, malignant lymphoma, carcinoma, carcinoid, hemangioma [Iwamoto *et al.* 2007], inflammatory fibroid polyps [Miyata *et al.* 2004], adenoma, lipoma, hamartoma, lymphangioma, and others.

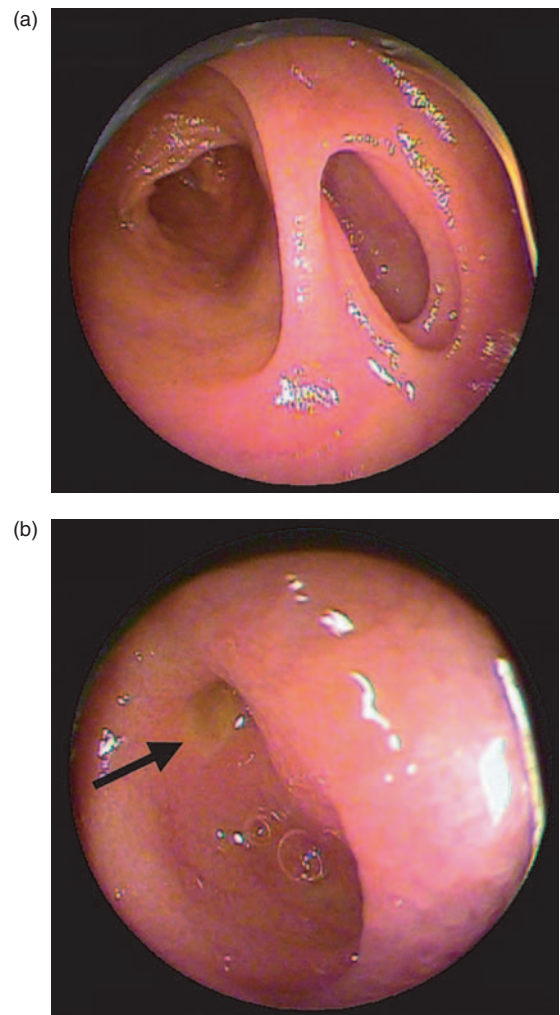


Figure 8. (a) Endoscopic view of Meckel's diverticulum (right) and the ileal lumen (left); (b) an ulcer was detected in the bottom of the diverticulum (arrow).

The biopsy results obtained during DBE were useful in determining medical and surgical treatment. In addition, endoscopic tattooing or clipping near the tumor guides surgical resection. In the cases of hemorrhagic polyps, including Peutz-Jeghers polyps [Ohmiya *et al.* 2005] and a polypoid angiodysplasia [Kita *et al.* 2005], endoscopic resection is preferred to surgical resection because it is less invasive and repeatable.

Conclusions

Recent endoscopic advances including CE and DBE changed the strategy for diagnosis and management of MGIB in a major way. Formerly, the only option for MGIB was laparotomy. However, the new devices enabled us to make a precise

diagnosis and treat it reasonably. In particular, DBE can be used to provide endoscopic therapy and has come to play a major role in the management of MGIB. DBE may be considered the first intervention for active mid-GI bleeding and for definitive treatment after CE has localized vascular lesions, ulcers, or polyps. Vascular lesions can be effectively treated with APC or clips, and bleeding polyps are treated by polypectomy, while NSAID or Crohn's ulcers are best treated medically after confirmation of the lesions with DBE. We expect DBE to become widely used and to contribute to better patient care with MGIB.

Conflict of interest statement

Hironori Yamamoto holds the patent in Japan on double-balloon endoscopy described in this manuscript.

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