

Capsule Endoscopy Versus Push Enteroscopy for Evaluation of Obscure Gastrointestinal Bleeding with 1-Year Outcomes

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Because of the low diagnostic yield of standard radiologic tests for identifying sources of obscure gastrointestinal bleeding in the small intestine, we compared wireless video capsule endoscopy with push enteroscopy and small-bowel follow-through. Patients referred to Mayo Clinic, Scottsdale, Arizona, between August and December 2001 for evaluation of obscure gastrointestinal bleeding were potential candidates. Eligible patients had previously inconclusive endoscopy, colonoscopy, small-bowel follow-through, and other radiologic studies. Participants underwent capsule endoscopy and enteroscopy (within 24 hr). The primary end point was localization of any bleeding source, with 1-year telephone follow-up. Capsule endoscopy yielded positive findings in 10 of 20 patients (11 men; mean age, 69 years), 6 of whom had negative enteroscopy and small-bowel follow-through. No patient with negative findings on capsule endoscopy had positive findings on enteroscopy and small-bowel follow-through. At follow-up, 19 patients reported fewer transfusions, gastrointestinal procedures, and hospitalizations. Capsule endoscopy identified more lesions and improved outcomes.

KEY WORDS: capsule endoscopy; gastrointestinal endoscopy; gastrointestinal hemorrhage; small intestine; push enteroscopy.

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs despite negative findings from an endoscopic evaluation (1). Evaluation is often unsatisfactory because of the low diagnostic yield of existing tests and the limited technology for adequately examining the entire small intestine.

The usual evaluation consists of a combination of endoscopic and radiologic procedures. Endoscopic procedures include upper endoscopy, colonoscopy, or push en-

teroscopy. Enteroscopy is often used after an initial negative upper endoscopy to evaluate the proximal third of the small intestine. Radiologic studies include small-bowel follow-through (SBFT), enteroclysis, nuclear bleeding scans, and angiography. The diagnostic yield of these studies has been quite low, and better tests are needed.

Wireless video capsule endoscopy (CE) is an advanced technique that enables endoscopic evaluation of the entire mucosa of the small intestine (2, 3). The capsule endoscope usually allows complete exploration of the small intestine. It is ingested after an 8-hr fast and is propelled through the small intestine by peristalsis.

The use of CE as a diagnostic tool for assessment of OGIB has not been well studied. The primary aim of this study was to evaluate the diagnostic yield and accuracy of CE compared with enteroscopy and SBFT in identifying lesions of the small bowel in patients with OGIB.

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A secondary aim was to evaluate the three tests for findings in the esophagus and stomach that may have been missed in previous endoscopic examinations of the gastrointestinal tract. Patient preferences were also assessed. A third aim of this study was to determine the impact of CE findings on long-term clinical outcomes of patients with OGIB.

MATERIALS AND METHODS

All patients consecutively referred for evaluation of OGIB at Mayo Clinic, Scottsdale, Arizona, between August and December 2001 were invited to participate in the study. A research assistant screened potential participants for inclusion and exclusion criteria. Inclusion criteria were (i) patient's age (>18 years), (ii) a history of OGIB (hemoglobin ≤ 10.0 g/dl or associated with a decrease of 2 g/dl within a 3-month period), and (iii) no cause for bleeding found on endoscopy, colonoscopy, and radiologic or nuclear medicine studies in the preceding year. Exclusion criteria were (i) pregnancy, (ii) clinical or radiologic evidence of intestinal obstruction, (iii) a swallowing disorder that precluded safe ingestion of the capsule endoscope, and (iv) the presence of a pacemaker or other implanted electro-medical device. Patients were examined and their medical records were reviewed by one of three gastroenterologists (J.A.L., V.K.S., D.E.F.). The investigators screened for final eligibility, and the resulting patients were asked for their informed consent. The study and the informed consent form were approved by the Mayo Foundation Institutional Review Board.

The study coordinator completed a computerized case report for each patient. Baseline variables included demographic features (sex, age, weight, height), relevant medical history, physical examination results, and prior findings on laboratory, endoscopic, and radiologic evaluations. All patients underwent SBFT before CE. Patients then were scheduled for CE, followed within 24 hr by enteroscopy, and given procedural instructions.

CE was performed with the M2A (Given Diagnostic Imaging System, Yegneam, Israel) (Figure 1), which comprises three main subsystems: an ingestible capsule endoscope (0.43×1.02 in. [11×26 mm]), a data recorder, and a workstation. During its natural propulsion through the digestive system, the capsule endoscope acquires video images at a rate of two per second. It transmits images by a digital radio frequency communication channel to an external, portable data recorder unit. The data recorder unit consists of a sensor array (antenna) carried close to the body, a receiver, and memory for data accumulation. After the examination, the study nurse or technician transfers the accumulated data by a high-capacity digital link to a computer workstation. The workstation is a modified personal computer intended for off-line storage and analysis of data and for the generation of reports.

Patients scheduled for CE were instructed to eat as usual the day before their examination. They also were told to eat nothing after midnight the evening before the procedure (8-hr fast). After activation of the capsule endoscope, the patient swallowed it with a glass of water.

Enteroscopy was conducted in the standard manner by an endoscopist blinded to the CE findings. The esophagus, stomach, and small intestine were inspected carefully for a source of OGIB. If bleeding lesions were identified, biopsy specimens

were taken or the lesions were treated appropriately with electrocautery or argon plasma coagulation.

A research assistant made a follow-up telephone call 72 hr after CE to gather information about any adverse symptoms (e.g., nausea, vomiting, abdominal pain) and to determine whether the capsule had been excreted. If the patient had not yet witnessed its passage, an abdominal radiograph was obtained. Patients also were asked to complete a procedure preference form comparing CE with enteroscopy.

To evaluate for interobserver variation, two physicians blinded to the enteroscopy findings read each CE video. Findings on both readings were recorded and compared. The likelihood of a lesion causing the OGIB was rated as "definite," "probable," "possible," or "unlikely" (Figure 2). Only those lesions believed to be definite or probable were used for data analysis. Findings of lesions were grouped by their location in the esophagus and stomach or in the small intestine.

Patients who participated in the initial study were contacted 1 year after CE. A telephone script and questionnaire approved by the institutional review board were used to assess long-term outcome in the areas of recurrent bleeding or anemia, the need for hospitalization for anemia or OGIB, and the need for a blood transfusion. Patients also were asked whether they thought CE had a positive effect on their condition.

The primary end point was the occurrence of a finding in the small intestine. The number of findings was compared among methods, and the statistical significance was calculated using the exact McNemar test. Changes after 1 year were assessed using the exact McNemar test or the paired *t* test. All *P* values are two-sided.

RESULTS

Twenty consecutive patients had CE followed by enteroscopy, with 10 each evaluated for occult and overt OGIB. All patients had previously had SBFT. The demographic features and clinical presentations of patients are summarized in Table 1.

Seven other patients were excluded because of the presence of a pacemaker (one patient), a small-bowel stenosis (one), prior abdominal surgery (two), blood hemoglobin > 10.0 within the past month (two), and emergent active bleeding (one). Three patients declined to participate in the study. Two patients had already had CE and were not eligible to participate.

Ten patients had findings that explained their OGIB (Figure 3). Enteroscopy facilitated a diagnosis in 4 of 20 patients (proximal angiectasia, 3; mass, 1). The histologic diagnosis on surgical resection of the tumor was T-cell lymphoma originating from celiac sprue (Figure 4). No lesions were missed on CE, which had positive findings in 10 of 20 patients (angiectasia, 5; masses, 3; ulcers, 3); 1 patient had both a mass and angiectasia. The final diagnoses of the masses, in addition to T-cell lymphoma, were intussusception and lymphangioma. Four patients had positive findings on both CE and enteroscopy (Table 2). In comparison, CE revealed abnormal findings



Fig 1. (A) The capsule endoscope is small enough to be swallowed easily. (B) The sensor array attaches to the data recorder carried on a belt around the patient's waist.

in six patients with negative enteroscopy and SBFT, but no patient with negative findings on CE had positive findings on enteroscopy and SBFT ($P = 0.03$; Table 2). The proportion of patients with findings was 30 percentage points higher with CE, so the number needed to test per additional finding is approximately three.

Ten patients had negative findings in the small intestine on enteroscopy, SBFT, and CE. However, the diagnostic

yield with respect to the esophagus and stomach was 8 of 10 patients whose lesions explained OGIB (Figure 5), although all patients had entered the study with previously negative upper endoscopies. Enteroscopy clearly had a higher diagnostic yield in the esophagus and stomach. One patient had both esophageal varices and portal hypertensive gastropathy, and one had multiple esophageal ulcers. A third patient had Cameron lesion, gastric angiectasia,

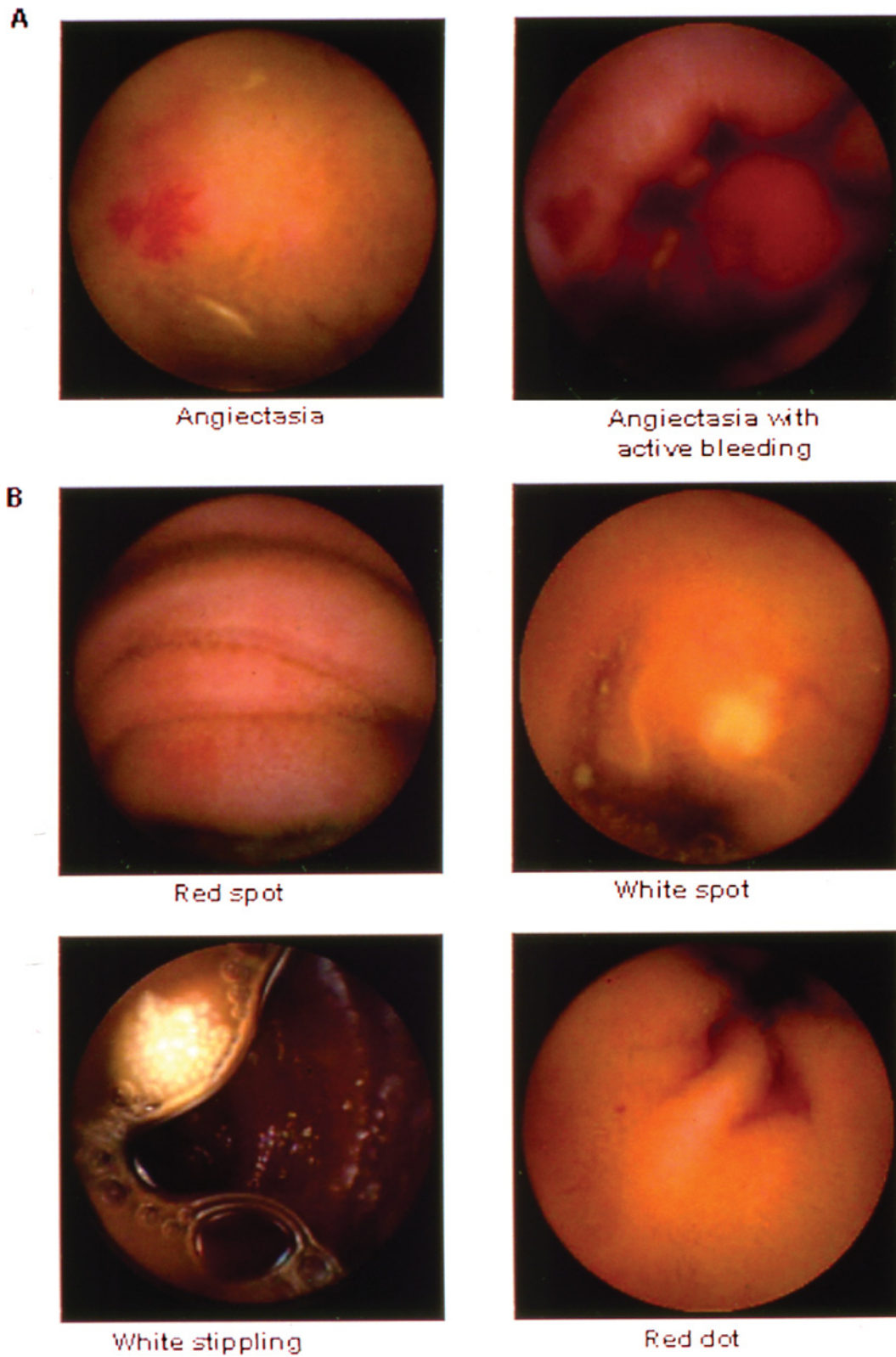


Fig 2. (A) Definite or probable lesions as a source of obscure gastrointestinal bleeding. (B) Possible or unlikely lesions as a source of obscure gastrointestinal bleeding.

CAPSULE ENDOSCOPY VS PUSH ENTEROSCOPY

TABLE 1. TABLE 1. DEMOGRAPHICS, CLINICAL PRESENTATION, AND FINDINGS ON CAPSULE ENDOSCOPY (CE) AND ENTEROSCOPY (ENT) AND AT 1-YEAR FOLLOW-UP IN PATIENTS WITH OBSCURE GASTROINTESTINAL BLEEDING

Patient No.	Age (yr)	Sex	Indication	Hgb (g/dl)		No. of events before evaluation (1 year after evaluation)			Duration of symptoms (mo)	Small intestine findings	
				Lowest*	Recent†	Procedures	Hospitalizations	Transfusions		CE	ENT
1	80	M	Occult	6.7	NA	4 (NA)	2 (NA)	1 (NA)	60	Tumor	Tumor
2	61	M	Occult	6.3	14	5 (4)	13 (1)	25 (8)	17	Angiectasia	None
3‡	37	M	Overt	9.9	NL	6 (0)	1 (0)	0 (0)	2	Angiectasia	Angiectasia
4‡	68	F	Occult	8.1	12.8	3 (2)	1 (0)	1 (0)	6	Ulcers and strictures	None
5‡	58	F	Overt	10.6	NL	11 (0)	0 (0)	0 (0)	94	Duodenal ulcer	Angiectasia
6‡	67	M	Overt	10.0	15	7 (0)	1 (0)	1 (0)	6	Angiectasia	Angiectasia
7	81	F	Overt	9.0	12	4 (0)	1 (0)	1 (2)	12	None	None
8‡	82	F	Occult	8.1	NL	4 (0)	2 (0)	2 (0)	24	None	None
9‡	66	M	Overt	9.3	15.5	6 (0)	4 (0)	4 (0)	60	None	None
10	67	F	Occult	8.5	NL	8 (0)	0 (0)	1 (0)	3	None	None
11	75	M	Occult	7.4	10	4 (0)	1 (0)	6 (5)	36	None	None
12	65	F	Overt	7.4	11.1	6 (3)	1 (1)	1 (1)	6	Tumor	None
13	66	M	Overt	6.5	16	5 (0)	1 (0)	2 (0)	3	Ulcer	None
14‡	77	M	Overt	6.3	10	4 (0)	1 (0)	3 (0)	28	None	None
15	71	F	Overt	6.0	NL	6 (0)	8 (0)	5 (0)	2	None	None
16‡	68	M	Occult	8.5	14.6	8 (1)	0 (0)	1 (0)	12	None	None
17	78	F	Occult	8.8	NL	4 (0)	1 (0)	3 (0)	15	None	None
18	72	F	Occult	5.6	11.9	5 (1)	1 (0)	2 (0)	3	None	None
19‡	72	F	Occult	7.7	11.2	4 (0)	2 (0)	2 (0)	180	Mass and angiectasia	None
20‡	65	M	Overt	7.0	10.6	5 (5)	20 (2)	15 (18)	60	Angiectasia	None

Note. Hgb, hemoglobin; NA, not available; NL, normal level.

*At time of referral for evaluation of obscure gastrointestinal bleeding.

†At 1-year follow-up.

‡Patient who expressed a preference for capsule endoscopy at 1-year follow-up (n = 10).

and portal hypertensive gastropathy. Among the other five patients, findings in the stomach were angiectasia (two). Only two of the eight patients whose lesions explained OGIB had positive findings on CE (watermelon stomach) that also were observed on enteroscopy. SBFT, including the upper gastrointestinal tract, was negative in all patients.

CE findings were then examined by two unblinded readers. There was perfect concordance (100%) between the readers for the diagnosis of definite or probable lesions.

The patient preference forms also were evaluated. Seventeen patients preferred CE, whereas three patients preferred enteroscopy. Reasons for preferring enteroscopy included concerns about passing the capsule endoscope, the cumbersome and visible CE belt, and inability to have any bleeding sites found by CE treated immediately.

Four of the 20 capsules (20%) did not reach the colon before their batteries were depleted. Of the four patients with incomplete examinations, three patients (75%) had major lesions in the small intestine. One CE video had sequence gaps that may have affected the quality of the study. There were no complications with either CE or enteroscopy. All capsule endoscopes were excreted spontaneously, but three patients did not observe the passage of the capsule. At 72 hr, two of these three patients had excreted the capsule without their knowledge. The

third patient, who was asymptomatic despite slow passage of the capsule endoscope, was followed with serial radiographs and spontaneously excreted the capsule in 2 weeks.

At 1-year follow-up, we were able to contact 19 of 20 patients who had been enrolled in the initial study. Of these 19 patients, 10 had overt OGIB and 9 had occult OGIB. CE had identified a cause for the OGIB in 12 patients (60%). Of these 12 patients, 5 had surgery (for T-cell lymphoma, carcinoid tumor, intussusception, Meckel diverticulum, or small-bowel angiectasia) or endoscopic treatment of the lesion and 2 were treated medically. At 1-year follow-up, 12 of 19 patients (63%) had no further bleeding or anemia. Seven patients (37%) had persistent symptoms, and five of them required repeat blood transfusions. Fourteen patients (74%) had not required any blood transfusions. Thirteen patients (68%) had no additional procedures. Sixteen patients (84%) required no further hospitalization. There were significant reductions in the number of patients within the previous year who required transfusions (17 vs 5; *P* < 0.001), gastrointestinal procedures (19 vs 6; *P* < 0.001), or hospitalization (16 vs 3; *P* < 0.001). There was also a significant improvement in mean (±SD) hemoglobin (n = 13; 10.8 ± 2.1 vs 12.7 ± 2.1 g/dl; change, 1.9 ± 2.4 g/dl; *P* = 0.02). Ten

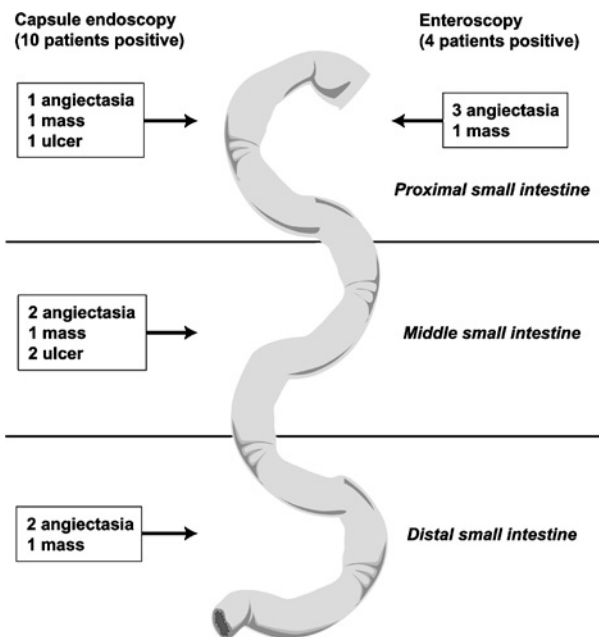


Fig 3. Findings in the small intestine on capsule endoscopy and enteroscopy in 20 patients with obscure gastrointestinal bleeding. Most of the additional findings on capsule endoscopy were beyond the reach of enteroscopy. Eleven lesions are reported in 10 patients who had capsule endoscopy because 1 patient had two lesions (one mass and one angiectasia).

patients (53%; 5 surgical, 5 nonsurgical) reported that CE had affected their condition positively.

DISCUSSION

OGIB can involve either overt or occult bleeding. Overt OGIB is associated with visible bleeding (e.g., hematemesis, melena, hematochezia); occult OGIB is associated with either a positive fecal occult blood test or iron deficiency anemia. Most cases of occult OGIB are thought to be due to bleeding from the small intestine. The differential diagnosis is extensive and can include tumors, inflammatory conditions, vascular disorders, infections, bleeding, and other less common causes (4).

Overt gastrointestinal bleeding is defined by gross bleeding in the gastrointestinal tract (4). It may manifest as hematemesis, hematochezia, or melena. Approximately 5% of patients with overt gastrointestinal bleeding will not have a source identified after upper endoscopy and colonoscopy (5). Additional evaluation is warranted if bleeding recurs or persists.

Several tests can be used to evaluate OGIB. They can be categorized broadly into endoscopic and radiologic studies. Endoscopic procedures include upper endoscopy, colonoscopy, enteroscopy, and intraoperative enteroscopy.

Repeat upper endoscopy may detect previously missed lesions of the upper gastrointestinal tract (6). Biopsy specimens of the small bowel also may be obtained for patients with iron deficiency anemia in whom celiac sprue is a consideration. Enteroscopy is recommended after negative upper endoscopy and colonoscopy. Its overall diagnostic yield is reported to be 30% to 50%. Most studies have used either a pediatric colonoscope or a specially designed push enteroscope. Enteroscopy has the advantage of allowing direct examination of the mucosal surface and immediate treatment of mucosal lesions (e.g., angiectasia). The biggest limitation is inability to intubate and examine beyond the proximal third of the small intestine. In patients with suspected OGIB, repeat upper endoscopy may be best accomplished with enteroscopy so that the small intestine can be examined at the same time. Another endoscopic method used to evaluate the small intestine is Sonde enteroscopy, which consists of a long endoscope (8.86–13.12 ft [270–400 cm]) advanced through the small intestine by normal peristalsis (7). It has a reported diagnostic yield of 26% to 77% in patients with OGIB. However, Sonde enteroscopy is seldom used, because it is time-consuming and difficult to master, and because identified lesions cannot be treated. Intraoperative enteroscopy may be used for persistent bleeding from unidentified causes, but this is the most invasive test for OGIB. It is performed during exploratory laparotomy to identify lesions and provide endoscopic or surgical treatment. No controlled trials have compared intraoperative enteroscopy with other procedures, but it appears to be safe and effective and to have a high diagnostic yield (8).

The radiologic tests available for evaluation of OGIB include SBFT, enteroclysis, nuclear bleeding scans, and angiography. SBFT, which has a diagnostic yield of 0% to 5.6% (9, 10), and enteroclysis have been used to visualize the small bowel beyond the reach of standard endoscopes. The diagnostic yield of enteroclysis is better but still less than 21% (11–13). In a retrospective study of 128 patients with OGIB who had enteroclysis, Moch and colleagues (11) found an overall yield of 21% for confirmed or highly probable lesions. Although most studies suggest that enteroclysis is superior to SBFT for evaluation of the small intestine, many centers continue to rely on SBFT. As with any contrast study, enteroclysis is most useful for identifying mass lesions of the gastrointestinal tract and is relatively insensitive for detecting flat mucosal lesions such as angiectasia (12). Nuclear bleeding scans and angiography usually are indicated in the actively bleeding patient with overt OGIB. However, in clinical practice, the utility of these tests is limited, primarily because of their inability to allow direct examination of the entire

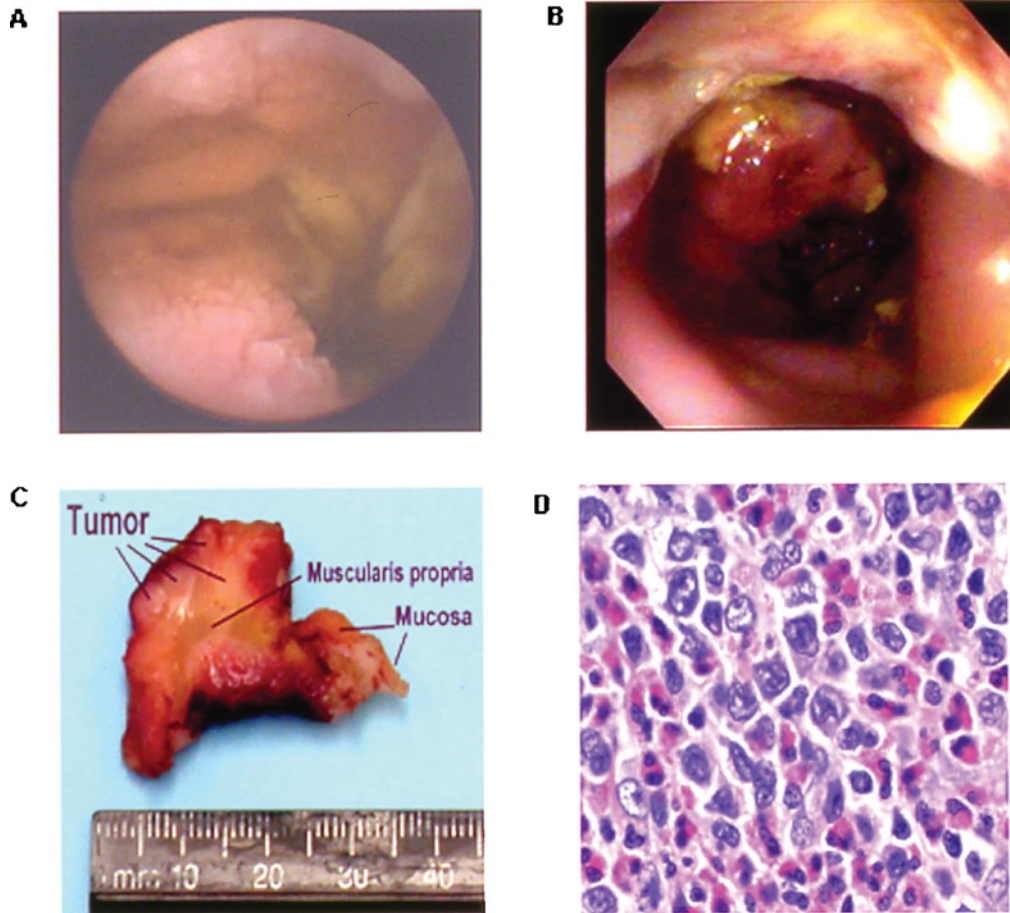


Fig 4. T-cell lymphoma originating in a patient who had celiac sprue diagnosed with capsule endoscopy. (A) Capsule image. (B) Enteroscopy image. (C) Gross surgical specimen. (D) Histologic specimen. (Hematoxylin and eosin; original magnification, 280×.)

mucosal surface of the small intestine. OGIB continues to be a diagnostic and therapeutic dilemma.

CE usually allows inspection of the entire mucosa of the small intestine with minimal invasiveness. Our study suggests that it is more sensitive than enteroscopy or SBFT in detecting lesions of the small intestine that cause OGIB. The diagnostic yield of CE for findings in the small intestine was 50%, compared with a 20% yield from enteroscopy ($P = 0.03$). CE missed no source of bleeding

in the small intestine found by enteroscopy. The most obvious reason for this increased sensitivity is simply the fact that CE can view the entire small intestine, whereas enteroscopy is limited to the proximal third. Although contrast studies allow radiologic visualization of the more distal small intestine, their overall sensitivity and specificity are quite low.

Most patients with negative findings in the small intestine had lesions that could explain their OGIB that were observed in the upper gastrointestinal tract within reach of the endoscope. Numerous studies show that in a significant percentage of patients whose initial examination was negative, a repeat upper endoscopy often yields a source (6, 14–17). Thus, a “relook endoscopy” may be recommended in patients with OGIB as a cost-effective first step before a more extensive evaluation (15). Our diagnosis of OGIB in 16 of 20 patients who had a combination of CE and enteroscopy emphasizes the complementary nature of these two studies.

TABLE 2. COMPARISON OF FINDINGS IN THE SMALL INTESTINE ON CAPSULE ENDOSCOPY AND ENTEROSCOPY IN PATIENTS WITH OBSCURE GASTROINTESTINAL BLEEDING ($P = 0.03$)

	Enteroscopy	
	Positive	Negative
Capsule endoscopy		
Positive	4	6
Negative	0	10

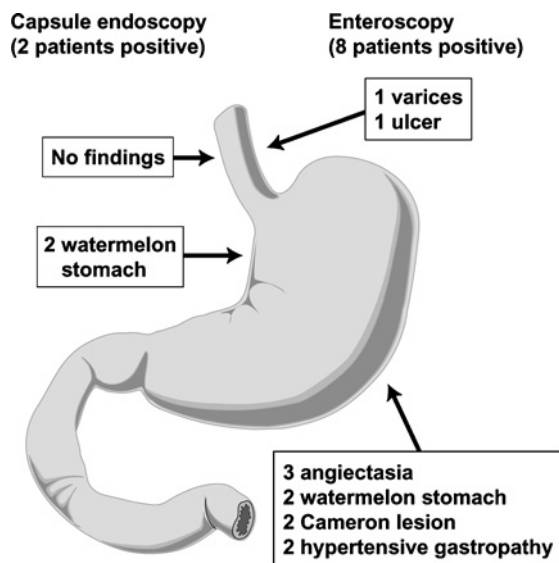


Fig 5. Esophageal and gastric findings on capsule endoscopy and enteroscopy in 20 patients with obscure gastrointestinal bleeding. Enteroscopy had a higher diagnostic yield than capsule endoscopy in the upper gastrointestinal tract. Eleven lesions are reported in eight patients who had enteroscopy because two patients had findings of multiple lesions (one patient had two conditions—varices and hypertensive gastropathy—and one patient had three conditions—Cameron lesion, gastric angiectasia, and portal hypertensive gastropathy).

We also found that most patients preferred CE to enteroscopy. CE allows patients to remain ambulatory, and it requires no sedation, involves little preparation, and is minimally invasive. There are few potential complications and no major side effects. In contrast, enteroscopy has additional possible complications, because it requires an intravenous catheter for sedation and insertion of a long endoscope. Although enteroscopy is quite safe overall, it is still an invasive procedure.

There are no major complications associated with CE. By 2002, there were already 937 ingestions of capsule endoscopes (18) and the number continues to grow at a fast pace. Less than 1% of patients in the 2002 study could not excrete the capsule normally and required surgical removal of the device. Six patients presented with an obstruction or stricture, and one had a bleeding ulcer (18). Another report noted that a patient had an impaction of the capsule at the cricopharynx that required endoscopic removal (19). To our knowledge, there have been no other incidents of obstruction or device-related adverse events.

One drawback of CE is that localization of the lesions it identifies can be difficult. Those that are very proximal or very distal can be localized with some precision, in contrast to lesions in the middle part of the small bowel. Future software technology may improve the localization

process. Another drawback is that therapeutic interventions are not possible at the time of diagnosis. We also do not know how much of the surface area of the small intestine is actually shown by the capsule endoscope. Nevertheless, CE allows identification of lesions previously missed by traditional methods and facilitates the planning of further interventions.

A potential limitation of our study is that we did not calculate the sensitivity and specificity of CE more precisely by comparing it in a double-blind controlled study with other interventions that evaluate the entire small intestine. Enteroscopy is not capable of evaluating the entire small intestine, and methods such as Sonde enteroscopy or intraoperative enteroscopy with surgery that would have allowed such evaluation were not practical. Nevertheless, our results support this new approach to patients with OGIB. For patients with occult OGIB, it is reasonable to proceed with a further evaluation of the small intestine. We recommend CE followed by enteroscopy to check for previously missed sources of bleeding in the upper gastrointestinal tract. CE should be performed first as a means of endoscopically visualizing most of the small intestine. If a proximal lesion is identified, enteroscopy should follow. If a more distal lesion is observed, colonoscopy with ileoscopy or intraoperative enteroscopy can be done. With negative findings of CE and enteroscopy, the benefits of further evaluation must be weighed against potential risks.

For patients with known OGIB, CE should be followed by enteroscopy if the patient is not actively bleeding. If the patient is bleeding, it is reasonable to proceed first with enteroscopy or colonoscopy, because the presence of blood limits visualization by CE. If the enteroscopic or colonoscopic findings are negative, consider nuclear scintigraphy, angiography, or CE.

Although CE introduces a fascinating technological advance for evaluation of OGIB, assessing whether it alters clinical outcome is critical. Such benefit can be measured by a reduced number of bleeding episodes, transfusions, hospitalizations, or further tests or by cost-benefit analyses. An increased diagnostic yield is a key first step, with altered outcomes the most important parameter. Our 1-year follow-up data suggest that CE significantly improves long-term outcomes in patients with OGIB. At follow-up, OGIB had resolved in most of these patients. They also had significant reductions in the number of transfusions, gastrointestinal procedures, and hospitalizations, and they had improvement in hemoglobin levels. More than half the patients reported that CE had positively affected their condition. Larger prospective studies are needed to confirm the benefit and clinical outcomes of CE in patients with OGIB.

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