# What is the best diagnostic approach for obscure gastrointestinal bleeding?

Fabián Juliao Baños, MD.<sup>1</sup>

<sup>1</sup> Chief of the Gastroenterology and Digestive Endoscopy Section of the Hospital Pablo Tobon Uribe. Professor at the University of Antioquia and University Pontificia Bolivariana. Medellín, Colombia

Received: 15-04-10 Accepted: 26-05-10

#### Abstract

For the gastroenterologist, the study of patients with obscure gastrointestinal bleeding is a diagnostic challenge. Using recent definitions as starting point for locating and defining the type of obscure bleeding allows better study and classification of these individuals. Since 25% of the causes of obscure gastrointestinal bleeding are within the reach of upper endoscopy and total colonoscopy, we are compelled to make good clinical evaluations and establish quality parameters for performance of these procedures. With the emergence of new techniques such as capsule endoscopy and balloon enteroscopy, the study of the small intestine with higher performance than previously available through imaging studies is now possible in our environment. Rational sequential use of these diagnostic tools, exhaustive reviews of capsule endoscopy images plus and adequate training in performing balloon enteroscopy including the two-way approach when necessary, will help us to establish and treat the cause in most patients with this condition.

#### Keywords

Obscure gastrointestinal bleeding, occult bleeding, capsule endoscopy, balloon enteroscopy.

#### DEFINITIONS

With the advent of new diagnostic methods, the classification of gastrointestinal bleeding by location has changed. Today, upper gastrointestinal bleeding is considered to be that which originates between the mouth and the ampulla of Vater. Mid-gastrointestinal bleeding is located between the ampulla of Vater and the ileocecal valve, while lower gastrointestinal bleeding is located in the colon. This is based on the facts that upper GI bleeding is easily detected by upper endoscopy, while study of middle GI bleeding requires capsule endoscopy or enteroscopy-assisted ball, and lower GI bleeding is in the range of colonoscopy (1).

Obscure gastrointestinal bleeding is defined as recurrent or persistent bleeding of unknown origin after a negative initial diagnostic evaluation. This evaluation normally includes an upper gastrointestinal endoscopy, a colonoscopy to the terminal ileum, and a contrast radiological study of the small intestine (for which enteroclysis is optional). Obscure gastrointestinal bleeding is classified as visible or obvious bleeding when there is the presence of bleeding from mouth or rectum which manifest as hematemesis or hematochezia. It is classified as occult bleeding when there is no visible evidence of gastrointestinal bleeding, but a fecal occult blood test persistently tests positive or the patient has iron deficiency anemia, or both (2).

The recommendation for a fecal blood test for occult bleeding applies only in the context of screening for colorectal cancer. If a colonoscopy is normal and the patient does not have gastrointestinal symptoms or iron deficiency anemia, additional studies are not required and there is no reason to suspect obscure bleeding (3).

## ETIOLOGY

25% of the lesions which produce obscure gastrointestinal bleeding are found in the esophagus, stomach, duodenum

and colon and cannot be seen during initial endoscopic evaluations. The reasons these lesions cannot be seen are diverse. Sometimes they have stopped bleeding, others bleed very slowly or intermittently, and others do not have any visible clotting. The presence of anemia and hypovolemia make lesions less obvious. Fasting in preparation for a colonoscopy can also make lesions hard to see (3). The most common causes of obscure gastrointestinal bleeding by location and age are shown in Table 1.

**Table 1.** Etiology of gastrointestinal bleeding of obscure origins.Modified from Raju GS, Gerson L, et al. American GastroenterologicalAssociation (AGA) Institute Technical Review on ObscureGastrointestinal Bleeding. Gastroenterology 2007; 133:1697–1717.

Unseen Upper and Lower GI Bleeding:	Mid-GI Bleeding:
Upper GI lesions:	<40 years:
Cameron Erosions	Tumors
Fundic Varices	Meckel's diverticulum
Peptic Ulcers	Dieulafoy's lesion
Angioectasias	Celiac Disease
Dieulafoy's Lesion	Crohn's Disease
Antral Vascular Ectasia (GAVE)	> 40 years:
	Angioectasias
	Enteropathy due to NSAIDs
	Celiac Disease
Lower GI Lesions:	Rare:
Angioectasias	Hemobilia
Neoplasms	Hemosuccus Pancreaticus
-	Aortoenteric Fistulas

Any type of bleeding injury located from the mouth to the anus can cause obscure bleeding. In patients under 40 years of age the most frequent causes include tumors such as lymphoma, carcinoid tumors and adenocarcinomas, familial adenomatous polyposis, and Meckel's diverticulum. In patients over 40 years of age the most common cause of small bowel bleeding is angioectasias which is present in 40% of these cases. Approximately 5% of patients with gastrointestinal bleeding have normal upper endoscopies and colonoscopies. 75% of these patients have bleeding from the small intestine. The remaining 25% are within reach of upper endoscopy or of a total colonoscopy, but their bleeding was not detected in initial studies (27, 28). 30% to 60% of patients with obvious obscure GI bleeding have angioectasias in the small intestine. The cause of bleeding of these vascular lesions has been related to alterations of the von Willebrand factor and multimeric glycoproteins which are essential for platelet aggregation. In situations which cause stress on microcirculation leading to microcirculatory deficiencies, active bleeding can be caused (4). Figures 1, 2, 3, 4 and 5 show findings from capsule endoscopies performed on our patients in the Hospital Pablo Tobon Uribe. All of

these patients were diagnosed with obscure gastrointestinal bleeding.



**Figure 1.** 77 year old patient with iron deficiency anemia in study and who were diagnosed with ileal Crohn's disease.



Figure 2. 80 year old with obscure gastrointestinal bleeding with angiectasia type 1b.

# **EVALUATION**

# Medical history and physical exam

Patients with recurrent hematemesis of unknown origin do not require colonoscopies because it is assumed that the source of bleeding is located in the upper digestive tract. On the other hand, for patients with mild anemia which is stable over time and who have multiple comorbidities, studies should be performed prudently, without exposing patients to unnecessary risks of invasive procedures. The physician should check the patient's history of use of drugs such as NSAIDs that damage the GI mucosa. In the physical examination the physician should check the patient's skin, since entities such as Hereditary Hemorrhagic Telangiectasia, Cavernous angiomas, celiac disease, HIV infection (Kaposi's sarcoma), Henoch–Schönlein purpura, Ehlers-Danlos syndrome, Plummer-Vinson syndrome and others present skin manifestations (3).



**Figure 3.** 40 year old patient with liver cirrhosis and obvious obscure gastrointestinal bleeding with hypertensive enteropathy.

## Diagnosis

When the physician suspects that there is a lesion which cannot be seen in an upper endoscopy or colonoscopy, or when there are blood clots, or when the patient prepared poorly for the procedure, studies should be repeated. This is especially true when hematemesis are found or there is a history of NSAIDs. The overall performance of repeat colonoscopy is only 6% (5). The lesions usually not seen in the initial upper endoscopy include Cameron lesions (hiatal hernia), Dieulafoy's lesions, vascular ectasia, peptic ulcer and antral vascular ectasia. In patients with a history of abdominal aortic aneurysm, the possibility of an aortoenteric fistula should be considered. In this case it is necessary to examine the region from the distal duodenum to the Vater ampulla to rule out the presence of blood clots and ulcers. When there is a suspicion of celiac disease, even when mucosa appears to be normal, a distal duodenal biopsy should be taken. If hemosuccus hemobilia or pancreatic cancer (pancreatic post-traumatic bleeding) is suspected, use a side view duodenoscope to properly display the ampulla of Vater.



**Figure 4.** 48 year old patient with obvious obscure gastrointestinal bleeding and umbilicated lesion in distal jejunum with postoperative diagnosis of stromal tumor (GIST).



**Figure 5.** 32 year old patient with occult gastrointestinal bleeding and Ascaris lumbricoides in the proximal ileum.

Contrast radiological studies (enteroclysis is optional) of the small intestines of patients with obscure GI bleeding have low diagnostic yields compared with newer techniques such as capsule endoscopy. For small intestine lesions the comparison is 8% vs. 67%, P < 0.00001, while for clinically significant findings the comparison is 6% vs. 42% with a number needed for diagnosis of 3 (6). The results of

contrast radiological studies using enteroclysis changes the management of only 10% of patients (7). It does not show vascular lesions, so it is indicated only in cases of intestinal obstruction when the cause is suspected to be tumors, Crohn's disease or a history of NSAID use.

Recently studies of small intestine disorders have been performed using enteroclysis in combination with CT enterography or magnetic resonance enterography. Enteroclysis is used to distend the small intestine, and then a helical CT or an MRI is performed. A study has shown that CT enterography with enteroclysis was inferior to capsule endoscopy for detection of vascular lesions (8). Other techniques such as tagged red blood cell scans and angiography require obvious and active obscure GI bleeding for identification of lesions. Angiography is the option for embolization of a bleeding lesion, but its diagnostic performance is very poor.

#### Endoscopic studies

Endoscopic study of the small intestine has evolved in the 21st century beyond invasive intraoperative endoscopy, enteroscopic probes, and push enteroscopy to capsule endoscopy that enables full display with a non-invasive form. Today, the recent development of single and double balloon assisted enteroscopy has made it possible to carry out therapeutic procedures in the small intestine without open surgery.

Intraoperative enteroscopy has been performed since the 1950's. It is intra-operative, involving passage of an endoscope through an enterotomy or bowel incision. In 1980, Bowden described a technique of intra-operative enteroscopy in which a fiberoptic colonoscope was initially passed through the mouth and then through the anus while the surgeon manually slid the tip of the endoscope through the gastrointestinal tract. The terminal ileum was reached in 90% of cases with this technique. With this technique examination of the mucosa must be performed during the insertion and not during removal so that the trauma to the mucosa is not confused with vascular lesions, and so an incision is not needed. The diagnostic yield of this technique ranges from 58% to 88% for obscure gastrointestinal bleeding. This technique is associated with postoperative ileus, perforation. Mortality rates as high as 17% and rates of recurrence of bleeding of 12.5% to 60% have been reported. For these reasons since the advent of balloon-assisted enteroscopy (BAE) this technique has been relegated to the last resort in cases in which enteroscopies are not possible because of factors such as adhesions (3).

The enteroscopic probe is a three meter long instrument with a distal balloon. It is placed in the proximal small intestine and reaches the ileum by peristaltic activity. The test takes seven hours, is uncomfortable for the patient, and therapeutic intervention is not possible. Push and pull enteroscopy uses a 220-250 cm long enteroscope. Sometimes an overtube is used to prevent coiling in the stomach and increase the depth of insertion by 50 cm to 150 cm in the proximal intestine. The diagnostic yield is between 3% and 60% with angioectasias being the most commonly found lesion (found in 7% to 60% of studies). When obscure bleeding is indicated the performance rate is between 15% and 40%. It is higher when the obscure bleeding is evident. This also changes management of 40% to 75% of cases (13).

#### Capsule endoscopy

In 1981, Gavriel Iddan devised capsule endoscopy to visualize the entire GI tract. However, because of technological limitations it was not possible to create a capsule that could be swallowed by humans. In 1996, Paul Swain made another attempt in London. Finally first functional capsule for endoscopy was created almost 20 years later by Given Imaging company, in Yoqneam, Israel. It measures 26 mm x 11 mm, takes pictures, and transmits to a recorder over a radio frequency. Its images are downloaded to a computer to be read. The battery lasts 8 to 9 hours. The capsule is expelled in the stool (9).

Capsule endoscopy has revolutionized the study of diseases of the small intestine. It allows full viewing in 85% to 90% of cases. It is non-invasive way and is well tolerated by patients. One limitation is that it cannot be maneuvered. Another is that it cannot take biopsies. Consequently, diagnoses are based on endoscopic appearance. Capsule endoscopic is not a therapeutic tool, but it is evolving toward determining the exact location and precise size of lesions. Image quality depends on the preparation of the patient's mucosa while reading of images requires prior training and experience. Finally, there is a 1% to1.5% risk that the capsule will be retained in areas of stenosis.

Taking into account the above limitations it is important to note that at the same time that capsule endoscopy has been being developed, enteroscopy has also been advancing. Balloon assisted enteroscopy (EAB) and spiral enteroscopy allow therapeutic enteroscopy with longer ranges than are possible with push enteroscopy plus they complement the study of small bowel disorders (12).

Particularly for patients with obscure GI bleeding capsule endoscopy is a very important diagnostic tool. It identifies the cause of bleeding in 50% to 60% of cases. Among the factors which can increase its diagnostic performance are active bleeding at the time of the study, a less-than-twoweek interval of time between the last episode of bleeding and the examination, high requirements for transfusions, and levels of hemoglobin <10 g/dl (14). One study compared the "gold standard" of intra-operative enteroscopy with CE. It found that CE had a sensitivity of 95% and a specificity of 75%. Positive predictive values were 95% and 86% negative for small intestine diseases (10). At the same time, Penazzio found a sensitivity of 89%, specificity 95%, and positive predictive values of 97% and 83% negative for detection of the cause of obscure gastrointestinal bleeding in 100 patients who underwent capsule endoscopies (11).

A meta-analysis of 20 prospective studies of 537 patients with obscure GI bleeding showed that capsule endoscopy's performance for clinical findings was better than that of push enteroscopy (56% vs. 26%, P <0.00001), and better than radiological studies of the small intestine (42% vs. 6%, P <0.00001). The number needed to diagnose (NND) for capsule endoscopy was 3. This was most important for the diagnosis of vascular and inflammatory lesions (6). A second meta-analysis covering 17 studies and 526 patients showed that, for the subgroup of patients with obscure GI bleeding, capsule endoscopy had a higher rate of successful diagnostic screening (37%) than did push enteroscopy and radiological studies. The NND was 3 (15).

A recent systematic review of 227 publications with more than 22 840 studies between the years 2000-2008 found that obscure gastrointestinal bleeding is indicated in 66.0% of cases. The detection rate was 60.5%, and angioectasias were the most common lesions associated with obscure bleeding (50%). This was followed by inflammation or ulcers in 29.6% of cases, and malignancies in 8.6%. The rate of complete visualization was 85.3%, and the rate of capsule retention was 1.2% (30).

Capsule endoscopy that does not show obscure bleeding has a favorable prognosis for patients who had previously been diagnosed with this condition because the rate of rebleeding is very low compared to patients whose capsule endoscopies reveal obscure bleeding (42% vs. 11%). Anticoagulants are associated with risk of rebleeding (16). Therefore, a consensus should be observed that no further diagnostic testing is needed for patients with negative capsule endoscopy results (17). When bleeding persists, second look repeat capsule studies have had diagnostic yields of 35% to 75%. They are suitable if bleeding changes from occult to obvious bleeding, or if the hemoglobin value decreases by more than 4 g/dl (18).

## Balloon Assisted Enteroscopy (BAE)

Double-balloon enteroscopy (DBE), designed by Yamamoto in 2001, allows visualization of the small intestine using a 200 cm long endoscope with a 140-cm overtube. A ball located at the tip can be inflated and deflated with air with a pressure pump (19). Antegrade (oral) or retrograde (anal) studies can both be performed achieving a full view of the small intestine in an average of 29% of cases (0% to 86%). Nevertheless, various publications report that in most cases the antegrade approach is used initially because most bleeding lesions in the small intestine are found in its proximal two thirds. Consequently, retrograde DBE is required in only 30% of cases. If capsule endoscopy has been performed prior to DBE, its results can help define the initial path of approach. This procedure is safe, with a perforation rate of 0.3%. There have been reports of pancreatitis, adynamic ileus and post-polypectomy bleeding after the procedure. Also, since it is an invasive procedure, it causes discomfort to the patient and requires general anesthesia and sometimes fluoroscopy. Finally, the learning curve for physicians using this technique is long (3, 25, 26).

Recently, single balloon enteroscopy was introduced (21) with results similar to DBE but with less complete visualization of the small intestine. Akerman has designed an enteroscope with a spiral overtube which has had very promising results (22).

Diagnostic performance of DBE for cases of obscure bleeding ranges between 50% and 75%, and is 100% in patients with obvious persistent bleeding. It is only 48.4% for cases of prior obvious bleeding, and 42.1% for cases of occult bleeding. This study found a sensitivity of 92.7%, a specificity of 96.4%, a positive predictive value of 98.1% and a negative predictive value of 87.1%. These figures are similar to those reported for capsule endoscopy (20). Push DBE results in a 230 visualization of the small intestine. This is more complete, and thus allows a higher rate of lesion detection (63%), than the 80 cm visualization which can be achieved through antegrade enteroscopy (with a detection rate of 44%) (23).

A recent meta-analysis based on 11 studies (n = 397)compared DBE with capsule endoscopy. It found comparable diagnostic performances, 57% for DBE (n = 360) and 60% for capsule endoscopy (n=397) (24). A recent study in Japan found similar detection rates for capsule endoscopy and anterograde and retrograde double balloon enteroscopy. Total enteroscopy achieved similar rates for both procedures, with good agreement between both results (Kappa index of 0.76) (32). A second meta-analysis of four studies found that capsule endoscopy's diagnostic performance was better than that of double-balloon enteroscopy for obscure bleeding. However, in one study combined anterograde and retrograde double-balloon enteroscopy produced better results than did capsule endoscopy (33). A recent study compared double balloon and single balloon enteroscopy and found that double balloon enteroscopy was able to achieve complete coverage in 66% of cases, while single balloon enteroscopy was only able to achieve

complete coverage in 22% of cases. Diagnostic yields were 72% and 48% respectively (34).

A recent study of cost-effectiveness found that the best strategy for diagnosing obscure gastrointestinal bleeding is initial use of antegrade double-balloon enteroscopy followed by retrograde DBE if the initial result is negative. Nevertheless, by starting with capsule endoscopy and advancing to double-balloon enteroscopy depending on the findings, better results with fewer complications associated with retrograde procedures can be achieved (31). A second cost analysis believes that DBE is more cost effective than capsule endoscopy for the management of obscure occult GI bleeding. However when the cost of DBE exceeded US \$1,870.00, or sensitivity was below 68%, it became more cost effective to use capsule endoscopy (29).

# CONCLUSIONS

Unlike in the twentieth century, in this new century we have balloon assisted enteroscopes and capsule endoscopy for diagnosis and treatment of diseases of the small intestine in our environment. The principal problem is angioectasias, especially when they are diffuse. This is because they have high probability of rebleeding even after therapeutic management even though 40% of them stop bleeding spontaneously each year (14).

Given that 25% of the lesions which cause obscure GI bleeding are within reach of upper endoscopy or total colonoscopy, the initial strategy for these patients is to repeat these studies. Subsequently, if the bleeding is obscure, occult or only intermittently evident, and there are no signs of intestinal obstruction, the study of choice is the capsule endoscopy. This procedure is noninvasive, is well tolerated, and it allows complete visualization of the small intestine in most cases. It can also be used to determine the initial route for BAE if there is a positive finding, and if a biopsy or therapeutic procedure is required. Patients with obvious persistent obscure bleeding can benefit from early BAE as long as it is combined antegrade and retrograde BAE is available. The goal is to achieve therapeutic management using argon plasma coagulation, polypectomy, or some other method. In case of massive bleeding of obscure origins and hemodynamic instability, it is better to perform mesenteric angiography which is ideal for active bleeding (> 0.5-1.0 mL/min.). Figure 6 presents an algorithm for diagnosis and management of patients with obscure gastrointestinal bleeding.



Figure 6. Flowchart for management of obscure GI bleeding. Modified from: Pennazio M. Enteroscopy in the Diagnosis and Management of Obscure Gastrointestinal Bleeding. Gastrointest Endoscopy Clin N Am 2009; 19: 409-426.

## REFERENCES

- 1. Ell C, May A. Mid-gastrointestinal bleeding: capsule endoscopy and push-and-pull enteroscopy give rise to a new medical term. Endoscopy 2006; 38: 73-75.
- Gralnek IM. Obscure-Overt Gastrointestinal Bleeding. Gastroenterology 2005; 128: 1424-1430.
- Raju GS, Gerson L, et al. American Gastroenterological Association (AGA) Institute Technical Review on Obscure Gastrointestinal Bleeding. Gastroenterology 2007; 133: 1697-1717.
- Veyradier A, Balian A, Wolf M, Giraud V, Montembault S, Obert B, Dagher I, Chaput JC, Meyer D, Naveau S. Abnormal von Willebrand factor in bleeding angiodysplasias of the digestive tract. Gastroenterology 2001; 120: 346-353.
- 5. Leaper M, Johnston MJ, Barclay M, Dobbs BR, Frizelle FA. Reasons for failure to diagnose colorectal carcinoma at colonoscopy. Endoscopy 2004; 36: 499-503.
- Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 2005; 100: 2407-2418.
- Malik A, Lukaszewski K, Caroline D, Parkman H, DeSipio J, Banson F, Bazir K, Reddy L, Srinivasan R, Fisher R, Miller L. A retrospective review of enteroclysis in patients with obscure gastrointestinal bleeding and chronic abdominal pain of undetermined etiology. Dig Dis Sci 2005; 50: 649-655.
- Voderholzer WA, Ortner M, Rogalla P, Beinholzl J, Lochs H. Diagnostic yield of wireless capsule enteroscopy in comparison with computed tomography enteroclysis. Endoscopy 2003; 35: 1009-1014.
- Gerber J, Bergwerk A, Fleischer D. A capsule endoscopy guide for the practicing clinician: technology and troubleshooting. Gastrointestinal endoscopy 2007; 66(6): 1188-1195.
- 10. Hartmann D, Schmidt H, Bolz G, Schilling D, Kinzel F, Eickhoff A, Huschner W, Moller K, Jakobs R, Reitzig P, Weickert U, Gellert K, Schultz H, Guenther K, Hollerbuhl H, Schoenleben K, Schulz HJ, Riemann JF. A prospective two-center study comparing wireless capsule endoscopy with intraoperative enteroscopy in patients with obscure GI bleeding. Gastrointest Endosc 2005; 61: 826-832.
- 11. Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology 2004; 126: 643-653.
- 12. Monkemuller K, Fry LC, Bellutti M, et al. Balloon-assisted enteroscopy: unifying double-balloon and single-balloon enteroscopy. Endoscopy 2008; 40(6): 537.
- Bezet A, Cuillerier E, Landi B, et al. Clinical impact of push enteroscopy in patients with gastrointestinal bleeding of unknown origin. Clin Gastroenterol Hepatol 2004; 2(10): 921-7.

- 14. Pennazio M. Enteroscopy in the Diagnosis and Management of Obscure Gastrointestinal Bleeding. Gastrointest Endoscopy Clin N Am 2009; 19: 409-426.
- Marmo R, Rotondano G, Piscopo R, et al. Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases. Aliment Pharmacol Ther 2005; 22(7): 595-604.
- Macdonald J, Porter V, McNamara D. Negative capsule endoscopy in patients with obscure GI bleeding predicts low rebleeding rates. Gastrointest Endosc 2008; 68(6): 1122-7.
- Mergener K, Ponchon T, Gralnek I, et al. Literature review and recommendations for clinical application of smallbowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. Endoscopy 2007; 39(10): 895-909.
- Viazis N, Papaxoinis K, Vlachogiannakos J, et al. Is there a role for second-look capsule endoscopy in patients with obscure GI bleeding after a nondiagnostic first test? Gastrointest Endosc 2009; 69(4): 850-6.
- Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001; 53: 216-220.
- Tanaka S, Mitsui K, Yamada Y, et al. Diagnostic yield of double-balloon endoscopy in patients with obscure GI bleeding. Gastrointest Endosc 2008; 68(4): 683-91.
- 21. Kawamura T, Yasuda K, Tanaka K, et al. Clinical evaluation of a newly developed single-balloon enteroscope. Gastrointest Endosc 2008; 68(6): 1112-6.
- Akerman PA, Agrawal D, Cantero D, et al. Spiral enteroscopy with the new DSB overtube: a novel technique for deep peroral small-bowel intubation. Endoscopy 2008; 40(12): 974-8.
- May A, Nachbar L, Schneider M, et al. Prospective comparison of push enteroscopy and push-and-pull enteroscopy in patients with suspected small-bowel bleeding. Am J Gastroenterol 2006; 101(9): 2016-24.
- 24. Pasha SF, Leighton JA, Das A, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2008; 6(6): 671-6.
- Gross SA, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. center. Gastrointest Endosc 2008; 67(6): 890-7.
- Gerson LB, Flodin JT, Miyabayashi K. Balloon-assisted enteroscopy: technology and troubleshooting. Gastrointest Endosc 2008; 68(6): 1158-67.
- 27. Kitiyakara T, Selby W. Non-small-bowel lesions detected by capsule endoscopy in patients with obscure GI bleeding. Gastrointest Endosc 2005; 62(2): 234-8.
- Fry LC, Bellutti M, Neumann H, et al. Incidence of bleeding lesions within reach of conventional upper and lower endoscopes in patients undergoing double-balloon enteroscopy

for obscure gastrointestinal bleeding. Aliment Pharmacol Ther 2009; 29(3): 342-9.

- 29. Somsouk MA, Gralnek IM, Inadomi JM. Management of Obscure Occult Gastrointestinal Bleeding: A Cost-Minimization Analysis. Clin Gastroenterol Hepatol 2008; 6: 661-670.
- Zhuan Liao, Rui Gao, Can Xu, Zhao-Shen Li. Indications and detection, completion, and retention rates of smallbowel capsule endoscopy: a systematic review. Gastrointest Endosc 2010; 71: 280-6.
- Lauren Gerson, Ahmad Kamal. Cost-effectiveness analysis of management strategies for obscure GI bleeding. Gastrointest Endosc 2008; 68: 920-36.
- 32. Akira Fukumoto, Shinji Tanaka, Takayoshi Shishido, Yoshito Takemura, Shiro Oka, Kazuaki Chayama. Comparison of detectability of small-bowel lesions between capsule endoscopy and double-balloon endoscopy for patients with suspected small-bowel disease. Gastrointest Endosc 2009; 69: 857-65.
- 33. Xiang Chen, Zhi-Hua Ran, Jin-Lu Tong. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. World J Gastroenterol 2007; 13(32): 4372-4378.
- 34. May A, Farber M, Ell C, et al. Prospective Multicenter Trial comparing Push-and-Pull Enteroscopy with the Single- and Double-Balloon Techniques in Patients with Small-Bowel Disorders. Am J Gastroenterol 2010; 105: 575-581.