DOI: https://doi.org/10.22516/25007440.583

Editorial

Performance of diagnostic tests on bleeding from the small intestine

Raúl Antonio Cañadas-Garrido, MD.[1]

[1] Internist, gastroenterologist. Associate Professor of Medicine, Pontificia Universidad Javeriana. Gastroenterologist, San Ignacio University Hospital. Head of the Digestive Endoscopy Unit, Marly Clinic. Former president of the Colombian Association of Digestive Endoscopy. Bogotá D. C., Colombia.

***Correspondence:**
Raúl Antonio Cañadas-Garrido, MD,
raulcanadas@gmail.com

Received: 27/05/20
Accepted: 08/06/20

Historically, the small intestine has been considered difficult to access organ. For many years it was called the Pandora's box of the gastrointestinal tract, but the story has changed. Lesions that were previously unreachable by endoscopy can now be identified. Possibly, the greatest step in this development was the arrival of the endoscopic video capsule (EVC). Since its introduction in 2001, it has revolutionized endoscopy of the small intestine. Thanks to continuous refinement, incredible rates of lesion detection have since been achieved. Today it is the main diagnostic tool for lesions in the small intestine. With the fundamental objective of achieving a complete study of the intestinal segments, it can achieve 70% complete evaluation figures of the small intestine in up to 90% of patients and has a low rate of diagnostic error. It has become an excellent diagnostic method.

The evolution of EVC is so important in the development of images that it has opened Pandora's box so that we can now speak of endoscopic diagnoses that had never before been seen directly. Its impact has been such that the diagnostic approach to gastrointestinal bleeding of obscure origins, the main indication for EVC, has also changed since many cases that formerly would have been called bleeding of uncertain etiology have stopped being so. This has clearly encouraged a change in terminology. Ultimately, there have been fewer and fewer cases considered to be of obscure origin and further progress has been made to develop interventional treatment modalities for all these new findings that will have to be addressed while being consistent with their development.

Consequently, the definition of gastrointestinal bleeding has changed, and a new term has been created: small bowel (SB) bleeding. It is defined as bleeding originating between the ampulla of Vater and the ileocecal valve. It has partly displaced the previous definition of lower gastrointestinal bleeding which included all disorders originating from the ligament of Treitz to the anus. Even so, there will continue to be cases of obscure bleeding, possibly due to the fact that the small intestine is on average 6 to 7 meters long and 2.5 cm in diameter. This predisposes it to incomplete studies as well as false negatives even with the best technology. These are anticipated together with the mystery of disease in humans.

In accordance with the advances made in the study of the small intestine, the term bleeding of obscure origin is currently reserved only for those patients for whom the cause of bleeding remains unknown despite negative upper endoscopy, colonoscopy, and complementary studies of the small intestine such as EVC, enteroscopy and/or radiological imaging. (1) This evolution will undoubtedly change previous statistics since the new

definitions have only existed for a few years while most performance studies are supported by the previous definitions of obscure, occult and overt gastrointestinal bleeding which very few publications have used in recent years.

The revolution of device-assisted enteroscopy (DAE) has occurred almost simultaneously with the development of EVCs. DAE eroscopy is now another fundamental tool for study and treatment of small bowel pathologies. It complements rather than competes with ECVs which cannot be used for intervention. DAE has arisen to successfully meet all the achievements in the evolution of images. It can be said that DAE is a complementary sister technology which has relevant pros and cons. It has a capacity for intervention, but its main disadvantage is that it is a markedly invasive technique. Nevertheless, in conjunction with EVC, it has allowed the incredulous perception about diseases of the small intestine to be directed towards our approach and understanding of these pathologies. In this sense, we can propose this reflection: EVC would not be so well appreciated without DAE. In fact, enteroscopy would not be as well recognized without EVC because it uses only one exploration route and has as high negative predictive value (NPV). The use of EVCs means that invasive enteroscopy can be avoided in patients with low probabilities of positive findings in the small intestine. In conclusion, the two are symbiotic, they depend on each other. If diagnostic acuity is translated into numbers, the diagnostic performance of EVC and enteroscopy is similar for their main indication: overt bleeding, which reaches 92%. It can be assured that they do not compete, that they are equally good, but that in some special situations there may be a bias in favor of one of them.

To evaluate numbers and objectify results, it is necessary to review the past few years to study the diagnostic yields of each of these tests has had during development and introduction into endoscopy units around the world. Since these tests became available, endoscopists have had many positive experiences using them and have obtained many images that previously would have been impossible to obtain.

The number of applications of capsule endoscopy have grown since its introduction while its initial advantages have been preserved. Some of these are its less invasive nature, the related fact that it does not require anesthesia or sedation, its ability to study the entire small intestine, and its excellent safety profile. For these reasons, EVC of the small intestine is recommended as the first-line investigation in patients with gastrointestinal bleeding of obscure origin (strong recommendation, moderate quality of evidence). (2)

Thanks to the opportunity to write this editorial, I have an opportunity to say that, regardless of the advantages of all the tests for studying small bowel bleeding that I am about to mention in the literature review, none will replace clinical judgment and appropriate selection of patients. They directly impact diagnostic yields and are the keys to perception of this etiology.

In pathologies of the small intestine, it is important to think about the epidemiology and the possibility of the appearance of lesions according to the age of the patient rather than the patient's gender or ethnicity. Age is the key determinant of probable etiologies of small bowel bleeding. When all etiologies are grouped together, vascular causes are the most frequent, followed by inflammatory and neoplastic causes. However, age is taken into account, things change radically. The most important causes in patients younger than 40 years of age are inflammatory conditions such as Crohn's disease, infectious enteritis, intestinal ulcers and Meckel's diverticulum. Tumor and vascular lesions such as angiectasis are less likely. In patients over 40 years of age, the most likely causes are angiectasis, followed by inflammatory causes such as ulcers due to non-steroid anti-inflammatory drugs (NSAIDs) and nonspecific enteritis, as well as neoplasms including adenocarcinoma (most frequently a more proximal location in the duodenum and proximal jejunum), lymphoma, carcinoid tumors and sarcoma. The last three of these are distally located in the jejunum-ileum.

In addition, the clinical approach should explore risk factors for bleeding. These include coagulation disorders such as Von Willebrand disease and aortic valve heart disease which are associated with vascular lesions; histories of chronic kidney failure; hemodialysis; portal hypertension; use of medications including acetylsalicylic acid (ASA), NSAIDs, anticoagulants, and antiplatelet agents; clinical suspicion of vasculitis and amyloidosis; and previous procedures including liver biopsies, liver transplantation, abdominal aneurysm repair, intestinal resection, and radiation therapy. These should be explored without omitting investigation of family history of inflammatory disease, polyposis and familial hereditary telangiectasia. Although this is repetitive, it is the key to improving the diagnostic yield of small intestine tests when selecting patients.

I also invite you to open your minds to think about the rare pathologies that are being recognized in images more and more frequently. These include Osler-Weber-Rendu disease, blue nevus syndrome, Kaposi's sarcoma, portal enteropathy, hereditary polyposis, hemobilia, and Dieulafoy's lesion.

Globally, vascular etiologies are the most common causes of midgut digestive bleeding. Of these, angiectasia deserves special mention: it is the most common vascular malformation of the gastrointestinal tract and the most common cause of small bowel bleeding. High rebleeding rates are a major problem (17% to 40%) although predictors of rebleeding remain to be determined. The apparent exception is the presence of more than three lesions. It is necessary to mention this as part of the problem, and it is

essential that those who interpret EVC make every effort to properly identify these lesions. Ideally, this should be done according to the Saurin classification. The type of vascular lesion observed should be specified and classified. In the case of typical angiodysplasia, it should be marked as a lesion with great potential for bleeding and differentiated semiologically from red spots with uncertain potential for bleeding. Unnecessary invasive procedures and underestimation true angiectasis in need of treatment can be avoided thus impacting the diagnostic yield of EVC.

The gold standard for evidence of small bowel bleeding is intraoperative enteroscopy, but it should be understood that it has high rates of morbidity and mortality. For this reason, parameters for evaluating EVC yield are indirect and do not use that standard as a pattern for comparison. (3)

Several Colombian and international guidelines recommend EVC as the first diagnostic study to be performed in case of bleeding from the small intestine. They emphasize that it should be carried out within the first 14 days of the onset of the condition, or as soon as possible after the episode of bleeding, to maximize performance. (4) The lesion is identified in approximately 67% of cases within this period of time, but yield drops to 33% when the EVC is used 3 to 4 weeks after onset. The difference between 33% and 66% of patients can change management strategy, reduce the number of hospitalizations, and reduce additional tests and the need for transfusions. The fundamental addition of EVC increases enteroscopy's diagnostic yield from 73% and 93% and its therapeutic performance from 57% to 73%. This has been attributed to better determination of the route of the procedure and improved identification of vascular lesions. (5, 6)

I recommend reviewing the position of the European Society for Gastrointestinal Endoscopy (ESGE) regarding the roles of EVC and enteroscopy in diseases of the small intestine. Published in *Endoscopy* in 2015, its recommendations are evidence-based on, and, it remains fully valid to this day due to the strength of the scientific evidence and practicality of its application. This guide is mandatory reading for treating patients with diseases of the middle intestine. I will present its recommendations on the study of bleeding in the small intestine in the following sections according to my perception of which are most relevant to the subject.

First of all, it should be noted that there has been significant progress in EVC technology. In fact, a 2015 metaanalysis found that the overall performance of these capsules for obscure gastrointestinal bleeding was 61.7% (95% confidence interval: 47.3 to 76.1). According to Dr. Pennazio, EVCs currently achieve a diagnostic yield of 92.3% for overt bleeding, 67% when there is a history of prior overt bleeding, and 44.2% for occult bleeding. (2) The literature says that EVC has a greater capacity for finding lesions when the following conditions are present:

- Hemoglobin <10 g
- Duration of bleeding > 6 months
- Overt bleeding
- Performance of EVC within 2 weeks of bleeding onset (with maximum yield between 48 and 72 hours)
- More than 1 bleeding episode
- Male patients
- Patients over 60 years of age
- Hospitalized patients
- Patients with cardiac and renal comorbidities.

Another quality that makes EVC the first study of choice is the fact that the risk of rebleeding is very low, between 5.6% and 11%, after a negative EVC which highlights its accuracy and supports its high NPV. (7)

Because of EVC's tolerability, efficacy, excellent safety profile of, and potential for complete enteroscopy, the ESGE recommends small-bowel EVC as the first-line examination for study of small bowel bleeding before any consideration of device-assisted enteroscopy (strong recommendation, moderate-quality evidence). A comparison of diagnostic yield of EVC with that of double balloon enteroscopy (DBE) for occult bleeding has found the combined diagnostic performance for EVC to be 61.7% (95% CI: 47.3 to 76.1) while it was 55.5% (95% CI: 48.9 to 62.1) for DBE. EVCs have demonstrated a higher rate of complete enteroscopies and a lower rate of complications and is less invasive. It has also proved to be an effective tool for guiding the selection of the enteroscopy route (oral versus anal). (8)

When EVC is not available or contraindicated, the ESGE suggests device-assisted enteroscopy be considered as the first diagnostic option for these patients with the same time lapses, as soon as or close to the bleeding episode (weak recommendation, low-quality evidence). In addition, when lesions located in the proximal small intestine are considered, the diagnostic performance of push enteroscopy is comparable with the double balloon technique, but sedation, examination time and X-ray exposure are lower with push enteroscopy. Therefore, its use could be defined as a diagnostic and treatment tool when it is known that a lesion is in the most proximal segments of the small intestine. This saves resources and costs and reduces morbidity.

EVC is also superior to mesenteric angiography and CT angiography for determining the cause of bleeding. In a controlled trial that compared EVC and angiography, Leung et al. evaluated the diagnostic yield and long-term outcomes in 60 patients with overt bleeding. The diagnostic yield for EVC was significantly higher than that of angiography: 53.3% vs. 20.0% (difference of 33.3%; 95%

CI: 8.9% to 52.8%). The cumulative risk of rebleeding in the angiography and EVC groups were 33.3% and 16.7%, respectively. This indicates that the Angiography did not identify lesions potentially in need of surgery in some patients. (9) At present, angiography is reserved for those patients with hemodynamically unstable manifest small bowel bleeding. Multiphasic CT angiography is reserved for manifestly persistent hemodynamically stable bleeding without prior identification of the origin of the bleeding.

The ESGE suggests that emergency small bowel EVC or device-assisted enteroscopy should be considered for patients hospitalized with obscure gastrointestinal bleeding. They note that enteroscopy allows treatment during the same procedure (weak recommendation, moderate quality of evidence). The possibility of using EVC for ongoing severe overt bleeding is attractive due to the relative safety, ease, and feasibility of the procedure. In addition, it has already been established that the performance of early EVC confers superior diagnostic performance (70%) which translates into a better management approach and positive patient outcomes. In this same sense, data on the role of emergency device-assisted enteroscopy for the diagnosis and treatment of severe overt bleeding are limited. To date only scant evidence has been presented, with small case series and a small number of patients for whom emergency device-assisted enteroscopy was performed within 24 hours of clinical presentation. The diagnostic and therapeutic yields were 90%. (10)

In terms of diagnostic yield, is it ever necessary to repeat ECV? The ESGE recommends that an alternative approach is warranted in cases of persistent overt bleeding or the need for blood transfusions. In such patients, repeat EVC can produce positive results, especially in patients with a drop in hemoglobin of at least 4 g/dL and in those whose clinical presentation has changed from occult to overt bleeding. (11) Alternatively, device-assisted enteroscopy or CT angiography can sometimes produce a positive finding when the initial EVC cannot locate the source of persistent bleeding.

Finally, Teshima et al. found that the combined diagnostic yield of device-assisted enteroscopy performed after a previously positive EVC was 75.0% (95% CI: 60.1% to 90%). (11) Their subgroup analysis revealed that the joint diagnostic performance of DBE performed after previously negative EVC was 27.5% (95% CI: 16.7% to 37.8%) which reinforces the literature's previously shown in relation of EVCs NPV, but with sufficient reasons to consider that taking alternative studies can achieve positive results in a group of selected patients.

The American College of Gastroenterology (ACG) clinical guidelines make five recommendations on small bowel bleeding (12):

1. EVC should be considered the first-line study for the small intestine, especially for small bowel bleeding.
2. If there is no contraindication, the capsule should always be used before enteroscopy to increase diagnostic yield.
3. Device-assisted enteroscopy may initially be considered in cases of massive manifest obscure bleeding or when EVC is contraindicated or unavailable.
4. If a source of bleeding associated with significant anemia or active bleeding is found by EVC or deep enteroscopy, the patient should be managed endoscopically.
5. When there is manifest acute bleeding in an unstable patient, urgent arteriography is required.

CONCLUSION

Current diagnostic methods for small bowel have excellent yields. Although EVC is considered the first-line study due to its benefits, device-assisted enteroscopy has similar yields plus the advantage that it can simultaneously treat bleeding lesions in the small intestine or mark them in cases of neoplasms or inflammatory lesions. Other techniques, especially radiological ones, are available when specific indications, are present. They are especially important when the hemodynamic status of the patient does not allow waiting for other interventions such as selective arteriography. Development continues to be part of the research into diagnostic techniques in which high hopes continue.

REFERENCES

1. Sandoval Riveros C, Lúquez Mindiola A, Marulanda Fernandez H, Otero Regino W. Sangrado del intestino delgado: enfoque y tratamiento. Rev Colomb Gastroenterol. 2017;32(3):245-57. https://doi.org/10.22516/25007440.156
2. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy.

2015;47(4):352-76.
https://doi.org/10.1055/s-0034-1391855
3. Bonnet S, Douard R, Malamut G, Cellier C, Wind P. Intraoperative enteroscopy in the management of obscure gastrointestinal bleeding. Dig Liver Dis. 2013;45(4):277-84. https://doi.org/10.1016/j.dld.2012.07.003
4. Li Z, Liao Z, McAlindon M. Handbook of Capsule Endoscopy. Dordrecht: Springer; 2014. https://doi.org/10.1007/978-94-017-9229-5
5. Upchurch BR, Vargo JJ. Small bowel enteroscopy. Rev Gastroenterol Disord. 2008;8(3):169-77.
6. Brito HP, Ribeiro IB, Moura DTHD, Bernardo WM, Chaves DM, Kuga R, Maahs ED, Ishida RK, Moura ETHD, Moura EGHD. Video capsule endoscopy vs double-balloon enteroscopy in the diagnosis of small bowel bleeding: A systematic review and meta-analysis. World Journal of Gastrointestinal Endoscopy. 2018;10(12):400-21.
7. Lepileur L, Dray X, Antonietti M, Iwanicki-Caron I, Grigioni S, Chaput U, Di-Fiore A, Alhameedi R, Marteau P, Ducrotté P, Lecleire S. Factors associated with diagnosis of obscure gastrointestinal bleeding by video capsule enteroscopy. Clin Gastroenterol Hepatol. 2012;10(12):1376-80. https://doi.org/10.1016/j.cgh.2012.05.024
8. Li X, Chen H, Dai J, Gao Y, Ge Z. Predictive role of capsule endoscopy on the insertion route of double-balloon enteroscopy. Endoscopy. 2009;41(9):762-6. https://doi.org/10.1055/s-0029-1215009
9. Leung WK, Ho SS, Suen BY, Lai LH, Yu S, Ng EK, Ng SS, Chiu PW, Sung JJ, Chan FK, Lau JY. Capsule endoscopy or angiography in patients with acute overt obscure gastrointestinal bleeding: a prospective randomized study with long-term follow-up. Am J Gastroenterol. 2012;107(9):1370-6. https://doi.org/10.1038/ajg.2012.212
10. Mönkemüller K, Neumann H, Meyer F, Kuhn R, Malfertheiner P, Fry LC. A retrospective analysis of emergency double-balloon enteroscopy for small-bowel bleeding. Endoscopy. 2009;41(8):715-7. https://doi.org/10.1055/s-0029-1214974
11. Teshima CW, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. J Gastroenterol Hepatol. 2011;26(5):796-801. https://doi.org/10.1111/j.1440-1746.2010.06530.x
12. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding. Am J Gastroenterol. 2015;110(9):1265-87; quiz 1288. https://doi.org/10.1038/ajg.2015.246