The Role of Provocative Testing and Localization of the Video Capsule Endoscope in the Management of Small Intestinal Bleeding

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KEYWORDS
- Small intestinal bleeding • Provocative angiography • Provocative endoscopy
- Video capsule endoscopy • Device-assisted enteroscopy

KEY POINTS
- Cases of small intestinal bleeding (SIB) are commonly encountered in clinical practice despite advancements in medical technology that allow consistent visualization of the entire gastrointestinal tract.
- The use of antithrombotic agents to provoke bleeding has been found to be revealing in cases of SIB when used in combination with angiography as well as endoscopy.
- The performance of endoscopic procedures, including video capsule endoscopy (VCE) and device-assisted enteroscopy (DAE) on active antiplatelet and/or anticoagulant therapy is considered low risk and may improve diagnostic yield.
- The use of VCE for gastrointestinal bleeding in the inpatient setting has been found to improve diagnostic yield and decrease hospital stay.
- Because DAE is required for therapeutic intervention in patients with small bowel bleeding, access to this technology is essential for effective management in many cases.

Video content accompanies this article at http://www.giendo.theclinics.com/.

OBSCURE GASTROINTESTINAL BLEEDING

Definitions
Small intestinal bleeding (SIB) has been described as bleeding that is undefined in cause despite evaluation by standard upper endoscopy, colonoscopy, and small bowel follow-through (SBFT). The low diagnostic yield of SBFT combined with the advent of higher-yield small bowel studies has resulted in the removal of SBFT from...
algorithms for evaluation of gastrointestinal (GI) bleeding.1,2 Video capsule endoscopy (VCE) is associated with a 38% to 83% diagnostic yield in patients with suspected small bowel bleeding and is therefore recommended as the next step in management after negative esophagogastroduodenoscopy (EGD)/colonoscopy.3 Computed tomography enterography (CTE) may be indicated after negative VCE, or as an alternative if VCE is contraindicated, and has a reported diagnostic yield of 40% in bleeding of suspected small bowel origin.4,5 Device-assisted enteroscopy (DAE) by double balloon, single balloon, or spiral technique is a useful study in patients with suspected small bowel bleeding but is not available in all centers. Rates of total enteroscopy differ by technique but the diagnostic yield for all techniques is similar, around 60% to 80%.6

The widespread adoption of these advanced technologies to evaluate for small bowel bleeding sources resulted in a revision of definitions pertaining to obscure bleeding in 2015. Examples of bleeding with negative evaluation by EGD and colonoscopy are now termed suspected SIB. This group accounts for 5% of bleeding presentations, most of which are small bowel in origin.7 Sources of blood loss in these cases can be grouped into lesions within the reach of standard endoscopy that are missed, accounting for 25% of sources, and lesions in the small intestine, accounting for 75%. The term obscure GI bleeding is now typically reserved for cases in which a bleeding source cannot be identified despite current standard-of-care evaluation, including EGD, colonoscopy, VCE, and/or DAE and radiographic studies.2

Distribution of Bleeding Sources

Missed lesions should be considered as lesions that are difficult to detect (Table 1), which includes lesions that are identifiable on closer inspection as well as vascular abnormalities, such as Dieulafoy lesions, which are difficult or impossible to detect unless actively bleeding (Fig. 1A, B).8 Bleeding sources that are commonly missed on upper endoscopy include Cameron erosions, associated with a large hiatal hernia; gastric antral vascular ectasia, which may appear as benign mucosal erythema; small or concealed angioectasias (Figs. 2 and 3); and peptic ulcers that are positioned in a location difficult to visualize. Missed lesions on colonoscopy include flat neoplasms as well as angioectasias in the right colon. Missed lesions in the small bowel vary according to patient age. In patients older than 50 years, angioectasias are the most common cause of small bowel bleeding in the Western population and are the most common missed small bowel lesion by VCE.2,9 In adults younger than 50 years, tumors of the

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<th>Table 1</th>
<th>Culprit sources in suspected small bowel bleeding</th>
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<td>Missed Lesions on Upper Endoscopy</td>
<td>Small Bowel Bleeding Sources</td>
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<td>Cameron erosions</td>
<td>Vascular lesions</td>
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<td>Peptic ulcer disease</td>
<td>• Angioectasias</td>
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<tr>
<td>GAVE</td>
<td>• Dieulafoy lesion</td>
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<td>Angioectasias</td>
<td>• Aortoenteric fistula</td>
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<td>Dieulafoy lesion</td>
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<tr>
<td>Missed lesions on colonoscopy</td>
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<td>• GIST</td>
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<td>Angioectasias</td>
<td>• Adenocarcinoma</td>
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<td>Dieulafoy lesion</td>
<td>• Lymphoma</td>
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Abbreviations: GAVE, gastric antral vascular ectasia; GIST, GI stromal tumor; NSAID, nonsteroidal antiinflammatory drug.
Fig. 1. (A, B) Small bowel Dieulafoy lesion observed by VCE then subsequent DAE.

Fig. 2. Dense gastric angioectasia.

Fig. 3. Actively bleeding angioectasia by video capsule.
small bowel are the most common bleeding source. The miss rate of VCE for small bowel tumors is estimated to be 19%, especially for tumors such as GI stromal tumor (GIST) that can be endophytic (Fig. 4). Therefore CTE is recommended after VCE in patients less than 50 years old or in patients more than 50 years old with recurrent bleeding or progressive anemia, although some tumors may remain undetected after both VCE and CTE (Fig. 5). CTE may be combined with PET to show hypermetabolic lesions such as adenocarcinoma (Fig. 6A, B). A Meckel scan is recommended as an additional test, particularly in younger patients (Fig. 7).

Outcomes in Obscure Gastrointestinal Bleeding

Outcomes in patients with bleeding of unknown origin after negative EGD, colonoscopy, and VCE have been evaluated in several studies. Two early studies of SIB patient cohorts reported rebleeding rates of only 6% to 11% over an average 18-month follow-up period. These studies also showed that negative capsule endoscopy (CE) was predictive of lower rebleeding rates compared with patients with positive CE. However, subsequent studies of this patient population conflict with these results. In 1 study, 26 patients with mostly overt obscure GI bleeding (OGIB) were followed over an extended median follow-up period of 32 months and rebleeding was observed in 35% of patients. In addition, this study found that
rebleeding rates between patients with negative CE and positive CE were almost identical and only specific therapy directed to the bleeding source resulted in a change in the frequency of rebleeding.\textsuperscript{15} Although this study was retrospective and complicated by a high rate of incomplete capsule examinations (67%), similar results were shown in another study of patients with SIB and negative CE.\textsuperscript{16} This study found that 47% of patients with a nondiagnostic first CE study experienced recurrent overt bleeding or progressive anemia during a mean follow-up period of 25 months. Management of individual patients should therefore be tailored to the clinical course. In older patients with persistent resolution of bleeding, expectant management after negative VCE may be considered unless additional symptoms or clinical findings warrant further testing.\textsuperscript{1,2} In younger patients and patients with recurrent overt bleeding or progressive anemia, additional testing should be pursued.

Fig. 6. (A, B) Metastatic adenocarcinoma of the ileum by PET–computed tomography (A) and DAE (B).

Fig. 7. Positive Meckel scan with tracer uptake in the gastric body (red arrow) and Meckel site (yellow arrow).
Repeat Testing in Obscure Gastrointestinal Bleeding

Additional testing in patients who experience progressive anemia attributed to GI blood loss or recurrent, overt bleeding after negative initial evaluation by EGD, colonoscopy, VCE, and/or DAE and CTE should be individualized. Supplemental history should be obtained, including previous history of epistaxis, blood donation, menstrual bleeding, frequent minor rectal bleeding, diarrhea, abdominal pain, history of radiation exposure, history of abdominal aortic aneurysm repair predisposing to aortoenteric fistula (Figs. 8 and 9), nonsteroidal antiinflammatory drug use, olmesartan use, and family history of inflammatory bowel disease or celiac disease. After review of this additional history and previous studies, subsequent testing should be divided into 2 groups based on bleeding pattern as progressive anemia attributed to GI blood loss (occult bleeding) versus discrete episodes of hematochezia or melena (overt bleeding).

In patients with occult bleeding, repeat upper endoscopy with push enteroscopy is worthwhile to reevaluate for missed lesions in the upper GI tract as well as for angioectasias in the proximal small bowel and to obtain duodenal biopsies, if not previously performed.\(^{17}\) Examination of the duodenum with a side-viewing duodenoscope may also be helpful in identifying bleeding sources in the duodenal wall or associated with the ampulla of Vater. Repeat colonoscopy with more extensive intubation of the terminal ileum can be considered to reevaluate for a flat neoplasm or angioectasias in the right colon as well as to further investigate for evidence of Crohn disease involving the distal ileum. In cases in which the initial CE study was incomplete or in which anemia is progressive, repeat CE should be considered. One study of second-look CE in 20 patients with occult bleeding reported a 35% diagnostic yield of a second CE.\(^{18}\) Another study, which included 48 patients with occult, obscure bleeding, showed that repeat CE was successful in identifying a likely bleeding source in 65% of patients with progressive anemia, as defined by a 4-g/dL decrease in hemoglobin level. In patients who converted from occult to overt bleeding, the diagnostic yield of repeat CE was 100%.\(^{16}\) If 1 or more of these studies is unrevealing, evaluation of the remaining small bowel through DAE should be pursued depending on availability. Intraoperative enteroscopy is the test of last resort in patients with severe anemia who have been evaluated by all other means.

Recurrent, overt SIB is often frustrating for both patients and clinicians but can usually be managed successfully with persistence. Repeated standard endoscopy, CE, angiography, and/or DAE should be performed as soon as possible after a...
presentation with overt bleeding until bleeding stops or the bleeding site is localized. Multiple attempts may be required to successfully identify the bleeding source. Tagged red blood cell (RBC) scan is a useful adjunct to endoscopy because of its availability and lack of risk, although it is often unrevealing or nonspecific. Computed tomography angiography (CTA) may provide images that are easier to obtain and more localizing compared with tagged RBC scan. Patients with recurrent overt bleeding are considered to be the primary candidates for provocative testing.

PROVOCATIVE TESTING IN THE EVALUATION OF OBSCURE GASTROINTESTINAL BLEEDING

Provocation is defined as the introduction of a stimulus in attempt to elicit a specific response. Provocative testing is well established in the management of certain medical conditions, such as the stimulation of arrhythmias in electrophysiology. Provocative angiography for the management of difficult cases of GI bleeding is included in the American Society for Gastrointestinal Endoscopy (ASGE) algorithm for evaluation of obscure GI bleeding but is practiced in a limited number of centers. The use of provocation combined with endoscopy may be practiced in the community in low volumes but the current body of literature pertaining to this practice is limited to 4 case reports and 1 large retrospective study. Although these techniques seem extreme, reported complication rates associated with these interventions are low, with reasonable diagnostic yields.

Provocative Angiography

The body of literature pertaining to provocative angiography includes 9 series and 7 case reports totaling 126 cases (Table 2). The first series published by Rosch and colleagues in 1982 described 3 cases of recurrent, overt bleeding in which the administration of systemic heparin, intra-arterial heparin, and/or an intra-arterial vasodilator was used as an adjunct to conventional angiography with successful treatment of the bleeding source in all 3 cases. A subsequent study of provocation by Malden and colleagues involved the administration of systemic heparin and systemic

Fig. 9. Vascular tuft with early draining vein (arrow) consistent with AVM.
urokinase after initial negative mesenteric angiography followed by tagged RBC scan. Positive tagged RBC scans were documented in 4 of 10 cases, but angiography was diagnostic in only 2 of these, resulting in an overall success rate of 20%. Systemic heparin alone was used in another study by Mernagh and colleagues after initial negative angiography, which was associated with positive repeat angiography in 6 of 12 initial negative cases (yield of 50%). All of the remaining protocols have involved the use of systemic heparin accompanied by intra-arterial infusion of a vasodilator and/or thrombolytic, resulting in a wide range of diagnostic yields (18%–80%). The 2 most recent case series of provocation using a combination of heparin, intra-arterial nitroglycerin, and intra-arterial tissue plasminogen activator (tPA) reported success rates of 26% to 31%.

Despite concerns regarding the risk of bleeding associated with angiography in the setting of anticoagulation, the rate of complications in these reported series was low. Major complications were noted in only 3 of 126 cases. Rosch and colleagues reported 1 episode of hematemesis during angiography after infusion of heparin, tolazoline, and streptokinase that stabilized with protamine infusion and transfusion of 2 units of blood. Koval and colleagues reported 1 case of arterial wall puncture site hematoma after infusion of streptokinase. Kim and colleagues reported 1 case of intestinal ischemia resulting in perforation requiring surgery after embolization of a lesion in the ileum, which was subsequently diagnosed as a carcinoid tumor during surgery.

The availability of mesenteric angiography varies by center according to the expertise and interest of the interventional radiology and interventional cardiology staff. The use of provocation combined with angiography is likely to be limited to interventionists with a specific interest in and comfort level with mesenteric angiography. Mesenteric angiography is associated with risks of vascular injury, including hematoma and other bleeding complications, and these risks may be increased when combined with anticoagulant, antiplatelet, or thrombolytic agents. If an intervention such as embolization is planned, there is a risk of subsequent intestinal ischemia requiring surgery, which must be also be considered.

### Table 2

<table>
<thead>
<tr>
<th>Series</th>
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<th>Systemic Agents</th>
<th>Intra-arterial Agents</th>
<th>Success Rate (%)</th>
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<td>Rosch et al, 2017</td>
<td>3</td>
<td>Heparin</td>
<td>Tolazoline</td>
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<td>Bloomfeld et al, 1987</td>
<td>7</td>
<td>—</td>
<td>Heparin Tolazoline Urokinase</td>
<td>28</td>
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<tr>
<td>Ryan et al, 2020</td>
<td>16</td>
<td>Heparin</td>
<td>Tolazoline tPA</td>
<td>37</td>
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<td>Mernagh et al, 1982</td>
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<td>Heparin</td>
<td>—</td>
<td>50</td>
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<td>Wildus et al, 1987</td>
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<td>—</td>
<td>Reteplase</td>
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<td>Kim et al, 1987</td>
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<td>Heparin</td>
<td>Nitroglycerin tPA</td>
<td>31</td>
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<td>Zurkiya et al, 1984</td>
<td>19</td>
<td>—</td>
<td>Heparin Nitroglycerin tPA</td>
<td>26</td>
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**Abbreviation:** tPA, tissue plasminogen activator.
Provocative Endoscopy

The body of literature pertaining to provocative testing combined with endoscopy consisted of only 4 case reports before 2017. The first, by Berkelhammer and colleagues\(^2\) in 2000, involved a 62-year-old man with an ileostomy who experienced recurrent overt bleeding. Upper endoscopy, ileoscopy, and provocative angiography were negative. Provocation with a 10,000-unit intravenous (IV) heparin bolus followed by a heparin 1000 unit/h infusion resulted in active bleeding 90 minutes later. Emergent ileoscopy subsequently revealed a Dieulafoy lesion 5 cm proximal to the stoma, which was treated definitively by distal ileal resection. In 2004, Wright and colleagues\(^2\) described a 77-year-old man who presented with melena and hypotension resulting in intestinal ischemia and myocardial infarction. Repeat endoscopic testing and imaging by tagged RBC scan were negative for a bleeding source despite bleeding requiring transfusion of a total of 80 units of packed RBCs. Provocation with 5000 units of IV heparin resulted in active bleeding 2 hours later, indicated by bloody nasogastric tube output. Subsequent EGD revealed a Dieulafoy lesion in the stomach that was treated endoscopically. Reider and colleagues\(^2\) published a case report in 2006 describing a 59-year-old man with a history of overt OGIB. EGD, colonoscopy, enteroclysis, push enteroscopy, and VCE did not identify a bleeding source. Provocative CE was performed with heparin IV infusion initiated 12 hours before the procedure and targeted to a partial thromboplastin time between 72 and 108 seconds (normal range, 26–36 seconds). Blood was observed in the proximal jejunum by VCE, and a subsequent laparotomy resulted in removal of a GIST. In addition, in 2007, Kumar and colleagues\(^2\) published a case report of an unsuccessful provocative endoscopy attempt in a 65-year-old man presenting with hematochezia. Upper endoscopy and colonoscopy did not reveal a bleeding source. Tagged RBC scintigraphy localized the bleeding to the distal small bowel, whereas angiography localized the bleeding to the hepatic flexure; however, bleeding ceased and a lesion was not identified on subsequent colonoscopy despite provocation with 10,000 units of IV heparin and endoscopic observation for 75 minutes. The patient was taken to surgery, where a distal ileal carcinoid was found as the source of bleeding.

The authors published a retrospective review in 2017 of a databases of 824 DAE procedures. We identified 38 instances in which provocation with antiplatelet and/or anticoagulant agents was used as part of an OGIB evaluation in 27 patients.\(^2\) Procedures were divided into 3 groups based on the method of provocation: cases in which an antiplatelet or anticoagulant agent was reintroduced because of a prior history of bleeding exacerbation related to this agent (provocation experienced); cases in which an antiplatelet or anticoagulant agent was administered without any such history (provocation naive); and extreme cases of recurrent, overt OGIB in which a combination of clopidogrel and IV heparin was administered for provocation (LSU protocol). The diagnostic yield of provocative testing per procedure was 53% in the provocation-experienced group, 27% in the provocation-naive group, and 71% in the full-protocol group. Provocative testing was revealing in 15 out of 27 patients with angioectasias, and Dieulafoy lesions were found to be the most common lesions (Video 1). Provocative testing was not beneficial in 4 patients, who were eventually diagnosed with bleeding caused by intestinal angioectasias (3) and 1 patient with an aortoenteric fistula. The bleeding source was never found in 8 patients out of 27. There were no complications associated with any of the 38 procedures performed.

The ideal agent for provocative testing would have no adverse effects and would provoke bleeding consistently but not increase the risk of endoscopy. Antiplatelet agents such as clopidogrel are attractive because of evidence of platelet dysfunction
being the culprit for precipitation of bleeding from angioectasias in several settings, such as bleeding from acquired von Willebrand factor deficiency in Heyde syndrome and in patients with left ventricular assist devices.\(^{36,37}\) There is emerging evidence that endoscopy such as colonoscopy with polypectomy and DAE with argon plasma coagulation (APC) for treatment of angioectasias may be performed safely in the setting of active clopidogrel therapy.\(^{38,39}\) If clopidogrel is selected as the stimulus, patients may be given a loading dose of 150 mg or 300 mg 8 hours before endoscopy in order to achieve 35% to 45% or 40% to 50% platelet inhibition, respectively.\(^{40}\) In extreme cases of overt bleeding, a combination of clopidogrel and IV heparin may be considered to allow for both antiplatelet and anticoagulant effects with the ability to withdraw heparin (or reverse with protamine sulfate) resulting in endoscopy in the setting of clopidogrel alone. The use of systemic thrombolytic agents should be avoided because of the risk of major complication, such as stroke, associated with systemic administration of these agents and low yield observed in previous study of systemic thrombolics.\(^{28}\)

Many antiplatelet, anticoagulant, and antithrombotic agents have been introduced over the past 20 years. Each agent could be considered for inclusion in a provocation protocol depending on its effect, pharmacokinetics, and risk. One anticoagulant that might be considered for future protocols is dabigatran (Pradaxa), because a standard dose of 150 mg peaks in 2 hours and can be immediately reversed with IV infusion of idarucizumab (Praxbind).\(^{41}\) Regarding antiplatelet agents, the glycoprotein IIb/IIIa inhibitor abciximab (ReoPro) can also be considered reversible because its short plasma half-life allows its hemostatic inhibition to be reversed with platelet administration.\(^{42}\)

The ability of the endoscopist to reach the bleeding source is also a critical factor when considering provocative endoscopy, particularly when the bleeding segment has not been localized. The authors recommend that centers that might consider provocative endoscopy have the capability to perform total enteroscopy by DAE, preferably with double balloon enteroscopy. The ancillary resources of the center should also be assessed, including access to intensive care, angiography, and surgery services.

**BLEEDING LOCALIZATION WITH VIDEO CAPSULE ENDOSCOPY**

Accurate localization of the bleeding source is essential in CE interpretation. Experienced capsule readers can identify pitfalls in which the landmarks can be mislabeled, and small bowel transit times may be misleading. A fair estimate of the location of the bleeding segment can typically be made if the capsule transits through the entire small bowel. However, retention of the capsule endoscope in the duodenum for an extended period before transit through the deep small bowel is a source of confounding. The video capsule may reflux back and forth into the stomach after the first duodenal image. Residue or blood may interfere with proper delineation of landmarks as well as capsule transit. Early CE technology included a sensory array designed to show the capsule location in the abdomen in addition to obtaining images. However, this technology was abandoned with adoption of the sensor belt. CE technology has recently advanced to estimate progress more effectively through the small bowel by computer analysis of redundant images.\(^{43}\) This software may still be fooled by inaccurate landmarks from the reader or by retention in the duodenum but shows promise for accurate assessment of location in most studies.

An experienced capsule reader may rely on the original study to determine an impression of where the lesion lies in the small bowel before intervening by DAE. A general rule for planning DAE after VCE is selection of an oral route for lesions
observed in the first 60% of small bowel transit versus anal route for lesions observed in the last 40% of small bowel transit. In some cases, DAE may be deferred if the abnormality observed on VCE appears to be within reach of standard upper endoscopy, push enteroscopy, or colonoscopy.

SUMMARY

Advances in techniques to evaluate bleeding sources have advanced to the point where obscure GI bleeding is now restricted to an estimated ~1% to 2% of all bleeding cases. However, in this small subset of patients, the bleeding source may remain undefined despite exhaustive testing. Where do clinicians go from here?

Attempts to intentionally stimulate bleeding for the purpose of identifying the bleeding source by angiography or endoscopy should be considered for select patients with recurrent, severe anemia or recurrent overt bleeding in whom exhaustive repeat testing is negative. A detailed discussion of the risks and benefits of provocative testing with the patients and their families is needed before attempting stimulation of bleeding. This discussion should include a review of the risks of angiography and/or endoscopy, which may be increased in the setting of active antiplatelet and/or anticoagulant therapy; the risk of stimulating bleeding that might not be successfully contained; and the increased risk of surgery in the event of uncontrollable bleeding or a procedure-related complication. However, provocative testing may be a justifiable intervention in highly selected cases in which the morbidity associated with recurrent bleeding justifies the additional risk.

VCE studies should be performed while maintaining routine antiplatelet and/or anticoagulant therapy. The performance of DAE as well as other endoscopic procedures should also be pursued on antithrombotics because these are considered low risk if diagnostic or include only APC and/or hemostatic clip placement. Our study of DAE on active thienopyridine supports the safety and efficacy of this practice. The performance of inpatient VCE may be limited in certain hospitals because of concerns about loss of capital. However, studies have shown that timely inpatient VCE significantly decreases hospital stay to offset the cost of the video capsule and improves diagnostic yield.

In the future, advancements in artificial intelligence may allow computer localization of intestinal angioectasias, which may be present on only 1 of thousands of images. These technologies may increase capture rate for this disorder and reduce read time. Progressive development of a motorized spiral enteroscope is an additional technology on the horizon that has been anxiously awaited by small bowel endoscopists because of its potential for rapid small bowel examination.

DISCLOSURES

D.L. Raines: speaker and consultant for Medtronic. D.G. Adler: consultant/Advisory Board for BSC, Merit, Olympus; Speaker’s Bureau for AbbVie.

SUPPLEMENTARY DATA

Supplementary video related to this article can be found at https://doi.org/10.1016/j.giec.2021.01.001.

REFERENCES


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bleeding when clearly indicated; performance of endoscopic procedures on active antithrombotic therapy; and progressive adoption of VCE and device-assisted enteroscopy in the inpatient setting.

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