

Evidence-Based Guide on Capsule Endoscopy for Small Bowel Bleeding

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Abstract: Capsule endoscopy is the diagnostic test of choice for the evaluation of overt and occult small bowel bleeding. Its yield is higher in patients presenting with overt bleeding. The yield is also improved if the capsule is performed soon after the presentation of bleeding. Capsule endoscopy has a complementary role with cross-sectional imaging to triage patients for appropriate management, including deep enteroscopy, surgery, or, if negative, conservative management. Although capsule endoscopy is useful to detect vascular and inflammatory lesions, it appears to have a significant miss rate for solitary small bowel lesions, including tumors. The main adverse event is capsule retention in patients with underlying small bowel obstruction.

The wireless configuration and endoluminal view associated with capsule endoscopy offer advantages over standard endoscopy and radiology for small bowel evaluation. Capsule endoscopy is the only test that allows noninvasive visualization of the entire small bowel mucosa; therefore, it is the most commonly utilized test in suspected small bowel bleeding. Since its introduction, 3 capsule endoscopy systems (PillCam SB, Medtronic; Endocapsule, Olympus; and MiroCam, IntroMedic) have been approved by the US Food and Drug Administration. Most research on small bowel bleeding has been performed with PillCam SB, although preliminary data have demonstrated comparable diagnostic yields and completion rates with the other capsules.¹ The current paper is a concise evidence-based guide on the role of capsule endoscopy in suspected small bowel bleeding.

Indication for Capsule Endoscopy in Small Bowel Bleeding

Small bowel bleeding accounts for approximately 5% of all gastrointestinal bleeding and is the most common indication for capsule endoscopy worldwide.² Iron deficiency anemia (IDA) occurs in 2% to 5% of men and postmenopausal women, with unexplained IDA in 30% of patients.³ Capsule endoscopy has diagnostic utility in

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Capsule endoscopy, small bowel, obscure gastrointestinal bleeding, computed tomography enterography, deep enteroscopy, double-balloon enteroscopy

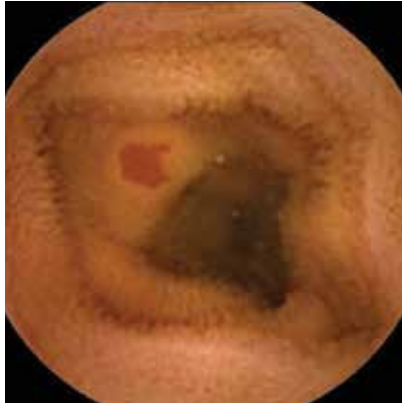
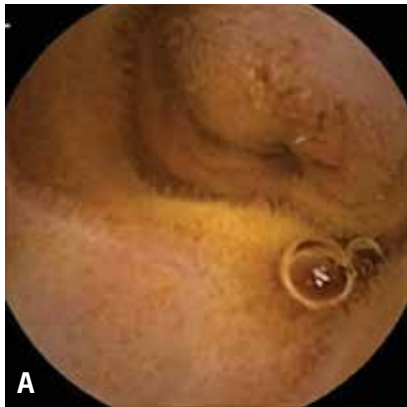


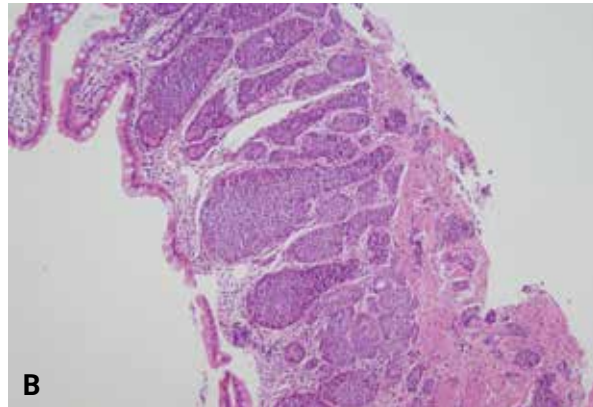
Figure 1. A large angioectasia in the proximal small bowel detected on capsule endoscopy.



Figure 2. A diaphragm secondary to nonsteroidal anti-inflammatory drug enteropathy detected in the distal ileum on capsule endoscopy.



A



B

Figure 3. A submucosal mass lesion with central ulceration detected in the ileum on capsule endoscopy (A). Surgical pathology (hematoxylin and eosin stain, 10× magnification) is consistent with a well-differentiated neuroendocrine tumor (B).

overt small bowel bleeding (melena or hematochezia) and occult small bowel bleeding (unexplained IDA with or without a positive fecal occult blood test result).^{4,5}

In a systematic review of 227 studies, 66% of capsules were used for small bowel bleeding, with a pooled detection rate of 59.4% overall.² Capsule endoscopy had a diagnostic yield of 66.6% in a systematic review of 1960 patients with IDA,⁶ while a single-center cohort study of 971 patients reported a yield of 35%.⁷ In patients with IDA without overt bleeding, the yield may be lower (25.7%).⁸ Angioectasias are the most common findings on capsule endoscopy (50%), followed by inflammation (26.8%) and tumors (8.8%) (Figures 1-3).²

With the improved detection of small bowel lesions using new modalities, recent guidelines from the

American College of Gastroenterology have proposed that the term obscure gastrointestinal bleeding (OGIB) be reserved for patients after negative results on small bowel evaluation.⁴

Predictors of Capsule Endoscopy With Positive Results

The performance of capsule endoscopy relies on clinical presentation, and overt bleeding is the strongest predictor of an examination with positive results (odds ratio [OR], 3.8).⁹ In a study of 260 patients, clinically significant findings were detected in 53%, with a higher yield in overt OGIB compared with occult OGIB (60% vs 46%; $P=.03$).¹⁰ An earlier study reported a yield of 92.3% with

overt bleeding, 44.2% with occult bleeding, and only 12.9% with prior overt bleeding.¹¹

Other factors associated with a positive capsule endoscopy result are male sex (OR, 1), age more than 60 years (OR, 1.2), and hospitalization (OR, 1.4).⁹ In a multivariate analysis of 698 capsule endoscopies, a higher number of prior esophagogastroduodenoscopies (EGDs) (OR, 1.17) and transfusions (OR, 1.70 with 3-9 units of packed red blood cells [PRBCs]; OR, 2.72 with ≥ 10 units of PRBCs) and the presence of connective tissue disease (OR, 2.24) were associated with a positive capsule endoscopy result ($P < .045$).¹² Anticoagulation ($P = .02$) and liver comorbidity ($P = .001$) also predict a higher yield with capsule endoscopy.¹³

Early use of capsule endoscopy has a positive impact on its yield. A retrospective study of 154 inpatients reported higher detection of bleeding and vascular lesions (44.4% vs 27.8%; $P = .046$), likelihood of therapeutics (18.9% vs 7.4%; $P = .046$), and reduction in hospitalization (6.1 vs 10.3 days; $P < .001$) with early deployment of capsule endoscopy within 3 days of admission.¹⁴ Two other studies reported a decrease in yield over time—from 87.5% to 11.1% when capsule endoscopy was performed within and after 10 days, respectively, and from 92% to 34% within and after 15 days, respectively.^{15,16}

Comparison of Capsule Endoscopy With Other Modalities

Capsule endoscopy is superior to push enteroscopy in the evaluation of small bowel bleeding. In a randomized trial, capsule endoscopy had a significantly higher yield (72.5% vs 48.7%; $P < .05$), and more patients who underwent push enteroscopy required subsequent capsule endoscopy for persistent bleeding (48.7% vs 22.5%; $P < .05$).¹⁷ An older meta-analysis reported an incremental yield of 35% with capsule endoscopy ($P < .001$) over push enteroscopy, mainly for vascular and inflammatory lesions. There was no difference in the detection of tumors.¹⁸

Capsule endoscopy and multiphase computed tomography scan are complementary tests for noninvasive small bowel evaluation. According to a systematic review, computed tomography enterography (CTE) and capsule endoscopy had a yield of 34% and 53%, respectively (incremental yield, -19%).¹⁹ In a longitudinal study, CTE was superior to capsule endoscopy for the detection of small bowel tumors (94.1% vs 35.3%; $P = .004$),²⁰ which suggests that capsule endoscopy may miss solitary mass lesions.

Capsule endoscopy is superior to mesenteric angiography in active small bowel bleeding. In a single-center study, capsule endoscopy detected the source in a greater proportion of patients (72% vs 56%; $P = \text{NS}$). Capsule

endoscopy had positive results in 86% of patients with positive angiography findings and in 55% of those with negative angiography findings.²¹ In another randomized trial, the yield of capsule endoscopy was significantly higher than that of angiography (53.3% vs 20.0%; $P = .016$), with a lower cumulative rebleeding rate (16.7% vs 33.3%; $P = .10$) over a mean follow-up of 48.5 months. There was no difference in the long-term outcomes of transfusions, hospitalizations, or mortality.²²

Four meta-analyses have confirmed that capsule endoscopy and double-balloon enteroscopy have comparable diagnostic yields (60%-62% vs 56%-57%).²³⁻²⁶ The yield of capsule endoscopy is higher than that of double-balloon enteroscopy performed using a single approach; however, there is no difference between the yield of capsule endoscopy and that of double-balloon enteroscopy performed using a combined approach.²⁴ Capsule endoscopy is the preferred noninvasive test in the evaluation of small bowel bleeding, whereas deep enteroscopy is mainly reserved for therapy.

When compared to intraoperative enteroscopy, capsule endoscopy has a sensitivity and specificity of 95% and 75%, respectively.²⁷ In a prospective study, capsule endoscopy enabled the detection and treatment of the bleeding source in 68% of patients who were undergoing intraoperative enteroscopy, although rebleeding occurred in 25% over a mean follow-up of 346.3 days.²⁸

Utility of Capsule Endoscopy to Guide Endoscopic Therapy

Capsule endoscopy is useful for the selection of patients to undergo deep enteroscopy. In a meta-analysis of 10 OGIB studies, double-balloon enteroscopy had a higher yield after a positive capsule endoscopy result (75%), compared with all patients (OR, 1.79; $P = .02$) and those with a negative capsule endoscopy result (27.5%).²⁵

In a study of 89 patients with overt OGIB, capsule endoscopy had a sensitivity and negative predictive value of 100% for small bowel lesions that required therapy. Double-balloon enteroscopy was avoided in 60% of patients with a negative capsule endoscopy result.²⁹ A study of 116 patients showed good overall agreement between capsule endoscopy and subsequent double-balloon enteroscopy (kappa value, 0.396; $P < .001$), with maximal agreement for the detection of angioectasias.³⁰

Using capsule transit to determine the insertion route for deep enteroscopy can optimize its diagnostic and therapeutic yields. A time index of more than 0.75 from capsule ingestion to the cecum has a high positive predictive value (94.7%) and a high negative predictive value (96.7%) for the retrograde double-balloon enteroscopy route.³¹ Another study reported 100% accuracy to

predict the antegrade double-balloon enteroscopy route with a time index of less than 0.6 from the duodenum to the cecum.³² However, transit time may not be reliable due to the varying speed of the capsule and when the capsule fails to reach the colon.

Outcomes After Capsule Endoscopy

Patients with a positive capsule endoscopy result have higher rebleeding rates. A retrospective study of 372 patients reported a diagnostic yield of 65.5% and a rebleeding rate of 28.6% over a median period of 48 months. The risk factors for rebleeding were age more than 60 years; positive capsule endoscopy result; hemoglobin level more than 7 g/dL; nonspecific treatment; and anti-coagulant, antiplatelet, or nonsteroidal anti-inflammatory drug (NSAID) use. In patients with a negative capsule endoscopy result, chronic hepatitis was associated with rebleeding ($P=.021$).³³

Vascular lesions are associated with high rebleeding rates despite therapy. In a study of 183 patients with small bowel vascular lesions, rebleeding occurred despite endoscopic treatment in 35% of patients at 1-year follow-up. Risk factors for rebleeding included cardiac disease (hazard ratio [HR], 2.04; $P<.01$) and overt bleeding (HR, 1.78; $P=.03$). There were higher rebleeding rates after treatment of low-risk than high-risk lesions (HR, 1.87; $P=.07$).³⁴

Older studies have reported lower rebleeding rates after a negative capsule endoscopy result: 5.6% vs 48.4% over a median of 19 months ($P=.03$) in a study by Lai and colleagues,³⁵ 11% vs 45% over a mean of 17.3 months ($P<.01$) in a study by Macdonald and colleagues,³⁶ and 16.4% vs 45.1% over a median of 24 months (χ^2 test; $P=.00001$) in a study by Riccioni and colleagues.³⁷ However, 2 studies reported no significant difference between patients with a negative or positive capsule endoscopy result: 22.8% vs 36.8% over a median of 23 months ($P=.205$) in a study by Koh and colleagues³⁸ and 26.7% vs 21.2% ($P=.496$) in a study by Kim and colleagues.³⁹ Additional evaluation can usually be avoided after a negative capsule endoscopy result unless the small bowel examination was incomplete or suboptimal or patients have alarm symptoms or recurrent bleeding.

Role for Repeat Capsule Endoscopy

A repeat capsule endoscopy may be useful for the evaluation of rebleeding after a negative or nondiagnostic capsule endoscopy result. Studies have reported a diagnostic yield of 35% to 75% with repeat capsule endoscopy and alteration in management in 39% to 62.5% of patients.⁴⁰⁻⁴³ Factors that predict a positive

result include a change in clinical presentation from overt to occult bleeding and a decrease in hemoglobin level by at least 4 g/dL.⁴²

When there is a high clinical suspicion for a small bowel tumor, CTE and/or deep enteroscopy may be preferred over a repeat capsule endoscopy.^{20,44}

Role for Emergent Capsule Endoscopy

The role of emergent capsule endoscopy in acute gastrointestinal bleeding has been described. In a small single-center study, 20 patients underwent capsule endoscopy after a negative EGD result. Capsule endoscopy had a diagnostic yield of 75% and guided further intervention. Colonoscopy could be avoided in 55% of patients.⁴⁵

A study of 49 patients showed that capsule endoscopy is useful to triage patients for early EGD. Capsule endoscopy was superior to nasogastric tube aspiration for the detection of blood in the upper gastrointestinal tract (83.3% vs 33.3%; $P=.035$). There was no significant difference in peptic/inflammatory lesions detected with capsule endoscopy and EGD (67.5% vs 87.5%; $P=.10$; OR, 0.39).⁴⁶

A feasibility study showed that capsule endoscopy enables effective triage of emergency department patients who do not require admission. There was no difference in rebleeding rates and 30-day mortality in patients randomized to capsule endoscopy or standard endoscopy. Hospital admission was reduced if capsule endoscopy was used instead of the Glasgow-Blatchford Bleeding score to triage patients.⁴⁷

Larger prospective studies are needed to evaluate the role of emergent capsule endoscopy in acute gastrointestinal bleeding before the procedure can be considered in clinical practice.

Limitations and Adverse Events Associated With Capsule Endoscopy

The main limitation of capsule endoscopy is its miss rate for solitary small bowel lesions (11%), including tumors (19%).⁴⁸ Conversely, false-positive findings of mucosal erosions and submucosal bulges may lead to unnecessary procedures.^{49,50} Lesion localization based upon capsule transit time is another limiting factor.

The major adverse event is capsule retention, which occurs in 1.2% to 1.5% of patients with OGIB and increases with NSAID use, Crohn's disease, tumors, and prior small bowel radiation or surgery.^{51,52} Although retention may be minimized by the use of CTE, NSAID-induced diaphragms may be missed on imaging studies. A patency capsule prior to capsule endoscopy may be useful in high-risk patients to minimize retention.⁵³ A recent

study showed no benefit of “nonselective” patency capsule use in all patients with Crohn’s disease, and suggested that the test be used selectively in patients who have obstructive symptoms or prior abdominal surgery and are at high risk of capsule retention.⁵⁴

Summary

Capsule endoscopy is the initial diagnostic test for small bowel evaluation in patients with overt bleeding or unexplained IDA after negative bidirectional endoscopy results. The test is useful to guide further management with deep enteroscopy or surgery. In the absence of objective methods, capsule transit time is used to determine the insertion route of deep enteroscopy. There may be a role for repeat capsule endoscopy in select patients with recurrent bleeding. When there is a high clinical suspicion for a small bowel tumor or stricture, CTE and/or deep enteroscopy may be preferred over capsule endoscopy. In the future, newer technologies for capsule endoscopy, including maneuverable capsules, may allow better characterization and localization of small bowel lesions, a decrease in the miss rate, and the ability to perform therapeutic intervention.

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