

# Capsule Endoscopy: What We Know and What Is New in the Horizon

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## Abstract

### Keywords

- ▶ capsule endoscopy
- ▶ celiac disease
- ▶ Crohn's disease
- ▶ obscure gastrointestinal bleed
- ▶ small bowel

Capsule endoscopy (CE) is an advancing noninvasive technology primarily meant for small-bowel visualization, which has expanded its scope and has become a game changer in evaluation and management of various gastrointestinal (GI) diseases with special emphasis on obscure GI bleeding. The aim of this review is to know the basic aspects of CE and recent advances with clinical evidence.

## Introduction

Capsule endoscopy (CE) is a noninvasive technology to provide diagnostic imaging of the small bowel (SB). Gavriel Iddan, an Israeli electro-optical engineer, and Paul Swain, a British gastroenterologist, independently investigated the possibility of transmitting images from the digestive tract to an extracorporeal receiver by swallowing a wireless capsule camera.<sup>1</sup> In 1996, Paul Swain demonstrated that a wireless ingested capsule could transmit online images from a pig stomach to an outside receiver. In 1999, the internal review board of Royal Hospital London permitted the ingestion of a prototype capsule endoscope in a human. The first capsule endoscope introduced in 2001 by Iddan et al<sup>1</sup> was manufactured by Given Diagnostic Imaging Systems (Yokneam, Israel), called the mouth-to-anus (M2A) capsule later remarketed as the PillCam SB. Since then, newer capsules were introduced which have better operating time, field of view, frame rates, image sensor, and optical enhancements. Later on, the esophageal, colonic, and patency capsules were introduced.

### Technical Aspects of Capsule Endoscope

CE system consists of (1) capsule, (2) data recorder attached to aerial leads, and (3) dedicated computer with software for downloading and analyzing the images.

Capsule: It consists of (1) optical dome, (2) lens holder, (3) lens, (4) six LEDs, (5) complementary metal-oxide silicon sensor, (6) 2 silver-oxide batteries, (7) application-specific integrated circuit transmitter, and (8) antennae (▶ Fig. 1).

## Procedure

Capsule is stored in a case containing a magnet that inhibits its activation. Once taken out, the LEDs start to flash and the capsule transmits images which are recorded by data recorder connected to battery worn on a belt. Following capsule ingestion, clear liquids and food are allowed after 2 and 4 hours, respectively. The sensor arrays are removed after 8 to 12 hours, and the recorded images are downloaded and processed on workstation. The capsule is disposable and is excreted.

## Indications

Indications for CE are summarized ▶ Table 1.

### Small-Bowel Capsule Endoscopy

Small-bowel capsule endoscopy (SBCE) is a reliable, noninvasive procedure, which has revolutionized the study of SB. PillCam SB is a prototype capsule measuring 11 mm × 26 mm, weighed 3.7 g, and provides 140 degree field of view, 1:8 magnification, 30 mm depth of view, and a minimum size of detection of approximately 0.1 mm. The battery lasts 6 to 8 hours, and transmission occurs at two frames per second. Color images are composed of 256 × 256 pixels.<sup>2</sup> Various newer capsules which are Food and Drug Administration (FDA) approved, along with their technical specifications, are shown in ▶ Fig. 2 and ▶ Table 2.<sup>2</sup> CapsoCam SV is a new capsule with “360 degree panoramic view” and battery life of 15 hours.<sup>3</sup> It is equipped with four cameras with frame rate of

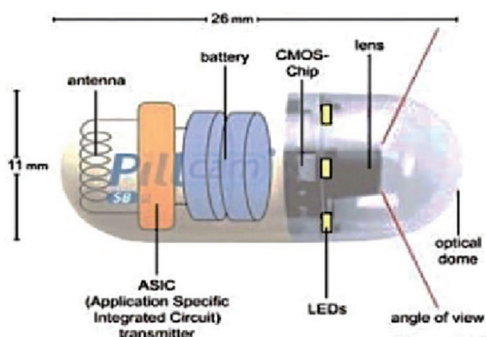


Fig. 1 Schematic structure of the capsule.

Table 1 Indications for capsule endoscopy

Esophagus	Small bowel	Colon
Gastroesophageal reflux disease	Obscure gastrointestinal bleeding	Polyp screening
Barrett's esophagus	Suspected Crohn's disease	Monitoring of IBD
Esophageal varices	Suspected small-bowel tumor	Incomplete colonoscopy
	Evaluation of any abnormal small-bowel imaging	Unwilling to undergo colonoscopy
	Evaluation of partially responsive celiac disease	
	Surveillance of inherited polyposis syndromes	
	Evaluation of drug-induced small-bowel injury	

Abbreviation: IBD, inflammatory bowel disease

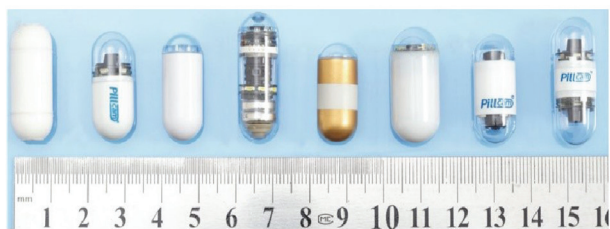


Fig. 2 Commercial capsule endoscopes. Left to right: Agile patency capsule, PillCam SB2, Endocapsule, CapsoCam, MiroCam, OMOM capsule, PillCam ESO, and PillCam COLON2.

12 to 20/s. Smart Motion Sense Technology enables the capsule to activate its cameras only during capsule motion. The images are captured by capsule itself and stored, so it has to be retrieved by the patient after expulsion. A study involving 172 patients showed that CapsoCam SV is easy to use, reliable, and has comparable diagnostic yield and safety profile to forward view SBCE.<sup>4</sup>

## Preparation

Patients should fast for at least 12 hours before. A purgative may help to eliminate food residue, air bubbles, and bile. A meta-analysis of 12 studies comparing CE with and without a purgative revealed better visualization and higher diagnostic yield using purgative bowel preparation over a clear liquid diet alone.<sup>5</sup> Studies comparing the amount of polyethylene glycol (PEG) to be used has shown that 2 liters of PEG is superior to no preparation, but 4 liters of PEG has not been found to be of any further benefit.<sup>6,7</sup> However, in a randomized controlled trial, no benefit was demonstrated in overall or distal SB visualization with active preparation using either PEG or sodium picosulfate plus magnesium sulfate compared with clear fluids only.<sup>8</sup> In an editorial, it was concluded that purgative preparations should not be routinely given to patients for CE except for selected situations particularly looking at the distal SB and conditions such as Crohn's disease (CD), who frequently have fecalization proximal to areas of the disease.<sup>9</sup>

## Clinical Evidence for Use

### Obscure Gastrointestinal Bleeding

Obscure gastrointestinal bleeding (OGIB) is the most common indication for CE. Conventionally, "OGIB" is defined as GI bleeding (overt or occult) who underwent normal upper and lower endoscopic examinations in addition to a SB series that did not reveal a source of bleeding. Second-look examinations using upper endoscopy, push enteroscopy, and/or colonoscopy can be performed if indicated before SB evaluation. However, in majority of these cases, bleeding source is localized to SB which accounts for 5 to 10% of all patients presenting with GI bleeding, so reclassified as SB bleeding. Therefore, now, the term "OGIB" is reserved for patients not found to have a source of bleeding after performance of standard upper, lower GI endoscopic examinations and SB evaluation with CE and/or enteroscopy and radiographic testing.<sup>10</sup> The detection rate of CE for potential culprit lesions in OGIB ranges from 35 to 77%, with performance dependent on various factors.<sup>11</sup> Variables associated with a higher detection rate includes earlier CE (within 1 week of bleeding), inpatient status, overt GI bleeding with transfusion requirement, male sex, increasing age, use of warfarin, and liver comorbidity. Three prospective randomized studies comparing different CE systems have shown comparable diagnostic yield and moderate interobserver agreement between PillCam (Given imaging, Yokneam, Israel) SB/Endocapsule (Olympus, Tokyo, Japan) ( $k = 0.48$ ) and PillCam/MiroCam (Intromedic, Seoul, South Korea) ( $k = 0.66$ ).<sup>12-14</sup> In a randomized trial involving 181 patients, CapsoCam SV1 detected more lesions than PillCam SB3; however, relevant bleeding sources were visualized by both capsules. Physician's as well as patient's satisfaction was high with both capsule systems. Serious adverse events were 0% with PillCam SB3 and 1.3% with CapsoCam SV-1.<sup>15</sup>

CE is superior to other techniques in diagnosing the source of bleeding. A pooled analysis of 14 studies including 396 patients showed a diagnostic yield of 56% for CE versus 26% ( $p = 0.00001$ ) for push enteroscopy.<sup>16</sup> Saurin et al showed that although CE detects more lesions than push enteroscopy,

**Table 2** Commercial capsule endoscopes

Device	Company	Frames per second	Battery life (h)	Dimension (mm)	Field of view (°)	Image sensor
PillCam SB	Given Imaging	2	6–8	11 × 26	140	CMOS
PillCam SB2		2	8	11 × 26	156	CMOS
PillCam SB3		2–6	12	11 × 26	156	CMOS
PillCam ESO		14	20 minute	11 × 26	169	CMOS
PillCam ESO2		18	20 minute	11 × 26	169	CMOS
PillCam Colon		4–35	10	11 × 31	172	CMOS
Endocapsule	Olympus	2	8–10	11 × 26	145	CCD
MiroCam	IntroMedic	3	10–12	10.8 × 24	170	CMOS
OMOM	Jinshan	2	7–9	10.8 × 24.5	140	CCD
CapsoCam SV1	CapsoVision	12–20	15	13 × 27.9	360	CMOS
NaviCam	Ankon Technologies	2	–	11 × 31	–	CMOS

Abbreviations: CMOS, complementary metal-oxide semiconductor; CCD, charge-coupled device.

only half of them have true bleeding potential (P2 lesions, Saurin et al classification).<sup>17</sup> Three meta-analyses showed that double-balloon enteroscopy has diagnostic yield similar to CE in OGIB.<sup>18–20</sup> However, recently, it was demonstrated that CE is better in detecting bleeding source and performing DBE after CE increases the diagnostic yield of vascular lesion by 7%.<sup>21</sup> The yield of CE in OGIB and spectrum of underlying etiology has varied from study to study.<sup>22–26</sup> A recent study showed the high diagnostic yield of 72.5% with common etiologies being vascular malformations, SB ulcerations of varied etiology with emphasis on SB tuberculosis, and CD and worm infestation being important causes of OGIB in the tropical countries such as India.<sup>27</sup>

### Crohn's Disease

CE is an important adjunctive tool to establish the diagnosis and assess disease extent, severity, and mucosal healing in SB CD.<sup>28,29</sup> A meta-analysis showed that in patients with suspected CD, CE had a superior diagnostic yield compared with SB follow through and enteroclysis and is comparable to CT or MR enterography. Whereas, in established CD cases, the diagnostic yield of CE compared with enteroclysis was greater and CE identified significantly more lesions in the terminal ileum as compared with ileoscopy.<sup>30</sup> The European Society of Gastrointestinal Endoscopy (ESGE) and European Crohn's and Colitis Organization guidelines advocate the use of validated endoscopic scoring indices for the classification of inflammatory activity in patients with CD undergoing SBCE, such as the Lewis score<sup>31</sup> or the Capsule Endoscopy Crohn's Disease Activity Index or Niv score.<sup>32</sup> With the new "treat-to-target" concept of achieving mucosal healing as the final goal of treatment, CE is presumed to have a central role in evaluating the SB mucosal healing.

### Celiac Disease

CE can detect endoscopic markers of celiac disease (loss of mucosal folds, mosaic mucosal pattern, scalloping of the duodenal folds, and nodularity of the mucosa).<sup>33</sup> In

a meta-analysis of six studies involving 166 patients of celiac disease, CE had a pooled sensitivity and specificity of 89% and 95%, respectively.<sup>34</sup> CE was able to detect the findings of celiac disease in 87% of cases, with unexpected findings in up to 45% of cases (neoplasms, ulcerations, and strictures).<sup>35</sup> These data suggest an additional role of CE in complicated celiac disease.

### Small-Bowel Tumors and Polyps

SB tumors constitute 1 to 3% of all primary GI tumors. They appear as masses or polyps in most and ulcer or stenoses in a minority of patients and can cause OGIB in up to 10% of patients. CE had resulted in doubling the rate of diagnosis of SB tumors to 6 to 9% of patients undergoing CE for various indications.<sup>36</sup> Adenocarcinoma and GI stromal tumors are the most frequent malignant and benign neoplasm, respectively.<sup>36</sup> CE is useful for the surveillance of small- and medium-sized polyps in patients with inherited GI polyposis syndromes. The duodenum is a potential pitfall as the capsule passes it very fast and may give false-negative results. CapsoCam has an advantage as this capsule has shown an increase in completeness of SB examination and detection of duodenal papilla in 71% of patients in a pilot study.<sup>3</sup>

### Other Indications

Unexplained iron-deficiency anemia, unexplained chronic abdominal pain, indeterminate colitis, protein-losing enteropathy, intestinal lymphangiectasia, Meckel's diverticulum, follow-up of SB transplantation, and graft versus host disease are the GI diseases in which CE is used rarely.

### Esophageal Capsule Endoscopy

The first esophageal capsule PillCam ESO (Given Imaging) was developed in 2004. The second-generation PillCam ESO2 was FDA approved for marketing in 2007. The size, shape, and weight of the capsule are similar to SB capsule

except for few modifications. The battery life is shortened to 20 minutes, and cameras are placed on both ends of the capsule which can take images at 18 frames/s with a wider angle (169 degree).

### Procedure

The patient should be fasting for over 2 hours. The patient ingests the capsule in the supine position with 10 mL of water. Two-minute recordings in the supine and 30 degree inclined position, followed by 1-minute recording at 60 degree. A subsequent 15-minute recording is acquired in the upright position. The images obtained are transmitted via three thoracic sensors to the recorder.

### Clinical Evidence for Use

#### Barrett's Esophagus

In a meta-analysis involving 618 patients of gastroesophageal reflux disease, the pooled sensitivity and specificity of ECE for the diagnosis of Barrett's esophagus (BE) were 77% and 86%, respectively, whereas using esophagogastroduodenoscopy (EGD) as the reference standard, were 78% and 90%, respectively.<sup>37</sup> However, it was suggested that EGD remains the modality of choice for evaluation of suspected BE.

#### Esophageal Varices

Grading of esophageal varices (EV) according to the CE is simpler than that of EGD. Three grades were evaluated: C0 = no varices, C1 = small and nontortuous varices <25% of the frame circumference, and C2 = large varices >25% of the frame circumference. In a meta-analysis of 17 studies involving 1,328 patients of portal hypertension, the diagnostic accuracy, sensitivity, and specificity of ECE in the diagnosis of EV were 90%, 83%, and 85%, respectively.<sup>38</sup> For the grading of varices, the diagnostic accuracy was 92% and pooled sensitivity and specificity were 72% and 91%, respectively. Based on these results, ECE was not considered capable of replacing EGD for diagnosing EV. However, it may be used in patients who have contraindication or those who refuse EGD.

### Colon Capsule Endoscopy

Colon capsule endoscopy (CCE) (Given Imaging) was introduced in 2006 for the diagnosis of colonic pathologies mainly polyps and tumors. CCE has great potential for colorectal cancer screening. The second-generation capsule (CCE-2) is slightly larger than the SBCE measuring 31 mm × 11 mm and has two camera domes with an adaptive frame rate of 4 to 35 frames/s, a 172 degree view angle for each camera and longer life of up to 11 hours due to the addition of a third battery.

### Bowel Preparation

Bowel cleansing is the prerequisite, as in absence of air inflation and suction, clinical success of CCE is dependent on appropriateness of bowel cleansing. Various regimens including split-dose regimen of at least 4 l of PEG in the evening before and during the morning of the study or PEG with booster regimens containing sodium phosphate or

magnesium citrate with prokinetics and bisacodyl have been employed with variable success.<sup>39-41</sup>

### Clinical Evidence for Use

#### Polyp Detection

CCE is indicated for colonic polyp detection in high-risk individuals in whom colonoscopy is not feasible or who have an incomplete colonoscopy without stenosis. Morphological criteria (polyp/mass ≥6 mm in size or ≥3 polyps) are accepted as surrogate markers of advanced neoplasia while screening for polyps. In studies with CCE-2, the reported sensitivities and specificities for detection of any polyp were 82% and 86% and for the detection of significant polyps (≥6 mm) were 84 to 89% and 64 to 88%, respectively.<sup>42-44</sup>

#### Inflammatory Bowel Disease

The role of CCE as a primary diagnostic modality is limited because biopsy and histological diagnosis are mandatory for the diagnosis. ESGE guidelines recommended that CCE may facilitate the monitoring of mucosal inflammation in patients with UC.<sup>45</sup> In a prospective study, CCE-2 had reported a sensitivity of 97% and 94% to detect mucosal inflammation (Mayo endoscopic subscore >0) and moderate-to-severe inflammation (Mayo endoscopic subscore >1), respectively, with negative predictive values to detect mucosal inflammation reaching 94 to 95%, respectively.<sup>46</sup> Advantages of CCE is that no sedation is needed and radiation, intubation, and insufflation are not involved. Contraindications for CCE are similar to that of CE. The CCE may become the first-line examination of the colon, particularly when there is a contraindication or patient is refusing colonoscopy, failed colonoscopy, and for screening colitis patients.

### Limitations of Capsule Endoscopy

The CE cannot be controlled, biopsies cannot be taken, and therapy cannot be delivered. There is limited battery life and inability to size and accurately localize the lesion. Interpretation of a CE study is time-consuming and requires concentrated attention, as abnormalities may be present in only a few frames.<sup>47</sup> On average, it takes approximately 1 hour to visualize all of the images (usually more than 50,000).

### Contraindications of Capsule Endoscopy

Contraindications of capsule endoscopy are summarized in ►Table 3.

**Table 3** Contraindications of capsule endoscopy

Absolute	Relative
Bowel obstruction	Cardiac pacemakers
Extensive and active Crohn's disease	Implanted electromedical devices
Bowel strictures	Dysphagia
Intestinal pseudo-obstruction	Previous abdominal surgery
Young children (<10 y)	Pregnancy



## Complications of Capsule Endoscopy

### Capsule Retention

It is defined as the capsule remaining in the digestive tract for a minimum of 1 or 2 weeks that requires therapy to aid its passage. Risk factors include CD, radiation enteritis, partial bowel obstruction, motility disorders, or Zenker's diverticulum. In a review, CE retention rates were 2% of patients undergoing evaluation for OGIB and are mostly due to SB strictures. Retention rates in patients with suspected or known inflammatory bowel disease were approximately 4% and 8%, respectively.<sup>48</sup> These rates get decreased by half when patency capsule or computed tomography enterography was used before performing CE. Retained capsules may be removed by endoscopy or surgery.

### Aspiration

Aspiration is an extremely rare event in elderly patients having comorbidities or swallowing disorder. In a review, 25 cases of capsule aspiration have been reported.<sup>38,49</sup>

## Advances in Capsule Endoscopy

### Technical Advances in Software

- Suspected blood indicator (Given Imaging, Israel) identifies frames containing several red pixels leading to focused examination.
- Quick View (Given Imaging, Israel) samples frames at a rate determined by the reader and selects images based on their pattern and color. A study validated the quick-view algorithm of the Given Imaging SBCE and showed a 93% sensitivity for significant lesions in a setting of OGIB with a mean reading time of 11.6 minute versus 60 minute.<sup>50</sup> The IntroMedic company recently proposed a new algorithm named "express view" reading mode and in a prospective study involving 83 patients with OGIB showed 94.2% sensitivity for the detection of significant lesions with a reduced mean reading time of 19.7 versus 39.7 minutes ( $P < 0.0001$ )<sup>51</sup>
- Fuji Intelligent Color Enhancement (Fujinon, Japan) technology appears to improve the definition and surface texture of SB lesions
- Real-time imaging—The data recorder (DR3 by Given Imaging, Israel) accompanies a screen which can show real-time images during ongoing examination. Rapid 6 systems by Given Imaging have made successful attempts in localization of capsule and estimation of size of the lesion.

### Technological Advances in Hardware

#### Maneuverable Capsules

Maneuverability is based on the principle that external magnetic field created by a permanent magnet or electromagnet interacts with an internal magnet component integrated into the capsule for active control of the capsule.<sup>52</sup> Given Imaging has incorporated a magnet inside one of the domes of a standard PillCam colon capsule, which can be manipulated with an external handheld magnet moved on the patient's

abdomen.<sup>53,54</sup> Similarly, NaviCam (ANKON) is a capsule remotely controlled by magnetic guidance hardware. Using such capsule, one study reported >75% of gastric mucosa visualization without any adverse events.<sup>54</sup> A study involving 350 patients with upper abdominal complaints concluded that magnetically controlled CE (MCCE) detects focal lesions in the stomach with comparable accuracy to gastroscopy and can be considered to screen gastric diseases without sedation.<sup>55</sup>

In a pilot study of MCCE in human colon, 57 volunteers underwent both MCCE and colonoscopy procedures.<sup>56</sup> The position of the capsule was monitored, and on reaching the cecum, it was controlled by the magnetic manipulator to observe the colonic mucosa under real-time monitoring by colonoscopy. Maneuverability was graded as good in 94% subjects.

### Tissue Acquisition

Several biopsy devices such as Crosby capsule and similar spring-loaded devices guided by real-time imaging and radiofrequency-controlled remote manipulation have been successfully tested in animals.<sup>57</sup> The Nano-Based Capsule Endoscopy With Molecular Imaging and Optical Biopsy (NEMO) and Versatile Endoscopic Capsule for Gastrointestinal Tumor Recognition and Therapy (VECTOR) projects aim to develop capsules with diagnostic and therapeutic capabilities, particularly for use in early GI cancer screening.<sup>58,59</sup>

### Therapeutic Drug Delivery Capsules

Capsules are under development to enable drug delivery in specific diseased areas of the GI tract. Coagulation capsule employs an exothermic chemical reaction to generate heat using the interaction of calcium oxide and water.<sup>60</sup> Enterion capsule a 32-mm long capsule device contains a drug reservoir and can deliver through a 9-mm opening any type of drug formulation when the spring is released.<sup>61</sup> Capsules that can deliver drugs with a pH or temperature-activated release mechanism have also been evaluated,<sup>62</sup> although not transformed into real clinical practice. The major constraints which have hindered the development of therapeutic capsules include limited size and energy budget. Considering dimensions of a typical human digestive system, the capsule must be limited to approximately 1 cm in diameter and 3 cm in length. This imposes a challenging restriction to the system and renders the integration of advanced functional units, particularly mechanical components, impractical due to their relatively large dimensions. Second, it is highly desirable to upgrade energy capacity to extend the capsule lifetime and to allow integration of functional modules with higher power consumptions such as motors and shape-memory alloy actuators, which requires energy-efficient, ultra-low power circuit design techniques, and effective power management strategies. The wireless communication through the human also poses a great challenge due to high signal attenuation, distortion, and uneven signal absorption rate of the body which restricts the usable operational frequency bands and thus the effective data rates. Hence, the need of the hour is to overcome these challenges with new technological advances in the field of therapeutic CE.

## Conclusion

CE has become a first-line investigation for OGIB and has extended its scope to evaluate SB and even beyond. Despite having good safety profile and patient tolerability, CE beyond the SB is currently not equivalent to gastroscopy or colonoscopy in terms of cost-effectiveness and diagnostic yield, therefore not used routinely in clinical practice. However, with the ongoing research, the future is not far when new CE devices will be developed that can evaluate the whole GI tract with capabilities for tissue sampling and goal-directed therapy.

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### Conflicts of Interest

None.

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