Abstract

Wireless capsule endoscopy (CE) is a technology developed for the endoscopic exploration of the small bowel. The first capsule model was approved by the Food and Drug Administration in 2001, and its first and essential indication was occult gastrointestinal (GI) bleeding. Over subsequent years, this technology has been refined to provide superior resolution, increased battery life, and capabilities to view different parts of the GI tract. Indeed, cases for which CE proved useful have increased significantly over the last few years, with new indications for the small bowel and technical improvements that have expanded its use to other parts of the GI tract, including the esophagus and colon. The main challenges in the development of CE are new devices with the ability to provide therapy, air inflation for a better vision of the small bowel, biopsy sampling systems attached to the capsule and the possibility to guide and move the capsule with an external motion control. In this article we review the current and new indications of CE, and the evolving technological changes shaping this technology, which has a promising potential in the coming future of gastroenterology.

INTRODUCTION

Before the development of capsule endoscopy (CE) the small bowel could be explored only by invasive procedures (intraoperative enteroscopy) or poorly effective methods, such as small bowel series. The widespread availability of CE, which allows a better mucosal visualization with few complications, has elicited a revolution in small bowel endoscopy, and a significant increase in...
the indications of CE.

The first CE indication was obscure gastrointestinal (GI) bleeding (OGIB), with two key reports published in 2001 and 2002[1]. Since then, technical improvements and increasing clinical experience have led to many studies that analyzed the efficacy of CE in this setting, and its role in the diagnostic algorithm for OGIB.

However, technical improvements and clinical considerations have broadened the range of applicability for CE, including examination of segments of the GI tract other than the small bowel, including the colon and esophagus, which are within reach of conventional endoscopy, but can benefit from increased safety and comfort with CE.

In this review article we will to evaluate the current and novel applications of CE, with focus on the likely expansion of this established but still promising technology to many other fields (Table 1).

## CE FOR THE SMALL BOWEL: TYPES AND DIFFERENCES

Actually, there are four different manufacturers for small bowel CE devices that have the following common technical features: (1) the capsule, which contains the camera, with differences in size, vision angle, battery life, etc.; (2) the reception system, which includes an antenna array capable of surrounding a body to receive the transmitted video output, a data recorder, and a battery. Everything is set on a belt attached to the patient that holds the entire device; and (3) the workstation, which is a computer used for processing and evaluation of the downloaded images, contained in the data recorder and transformed into a video datastream.

Improvements in these systems have led to better image quality and battery duration, which have increased the diagnostic yield. The currently available CE devices are described below:

**PillCam SB3** (Given Imagin Ltd. Yoqnean, Israel): It was the first CE device approved by the FDA, in August 2001 (M2A), and it was followed soon by its second version, M2A Plus, and by the PillCam SB series, its third version (PillCam SB3). This new version has a better resolution and an auto adjustable speed of frame acquisition depending on the capsule’s speed of progression in the small bowel. The associated software (Rapid Reader v8) offers improvements, such as the possibility of visualizing several different frames at the same time, the ability to measure lesion’s size, and a detector of bleeding lesions[5] the capability to apply digital light filters to perform electronic chromoendoscopy (FICE, Fuji Intelligent Chromo Endoscopy) for the better characterization of mucosal abnormalities, and an atlas for real-time comparisons.

**EndoCapsule** (Olympus Corporation, Allentown, PA): The FDA approved this new CE device in 2007. It is similar to PillCam SB and incorporates a blood indicator that marks suspicious bleeding points along the small bowel. It has an automatic control of reproduction speed, and four simultaneous different frames can be visualized at the same time on the screen.

**MiRo** (IntroMedic Co., Seoul, South Korea): This device was available in many countries between 2007 and 2009, and was approved by the FDA in 2013. This device has a different system of data transmission through the patient’s own tissues[6], allowing an increased battery life and time for frames acquisition. One trial showed similar diagnostic yield and complete small bowel examinations between EndoCapsule and MiRo in 50 patients[7].

**OMOM capsule** (M2A): The FDA approved this new CE device in 2007. This device was available in many countries between 2007 and 2009, and was approved by the FDA in 2013. This device has a different system of data transmission through the patient’s own tissues[6], allowing an increased battery life and time for frames acquisition. One trial showed similar diagnostic yield and complete small bowel examinations between EndoCapsule and MiRo in 50 patients[7].

**CapsoCam SV1** (CapsoVision Inc. Saratoga, CA): This device offers a novel concept, with 4 cameras, a peak acquisition speed of 5 frames/s and a 360o view of the small bowel. The images are loaded into the capsule, without the requirement of an external receptor; however the capsule has to be recovered by the patient and connected to the workstation. In a multicenter trial[8] with 73 patients that compared this capsule with PillCam SB2, a strong diagnostic concordance was reported; however CapsoCam required a longer video analysis time. Nevertheless, this device offers a better vision of the ampullar area, with good visualization of this particular area reported in 70% patients in a study[9].

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**Table 1  Current capsule endoscopy devices**

<table>
<thead>
<tr>
<th></th>
<th>PillCam SB3</th>
<th>EndoCapsule</th>
<th>MiroCam</th>
<th>OMOM capsule</th>
<th>CapsoCam SV-1</th>
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<tr>
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<td>11</td>
<td>13</td>
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<td>3</td>
<td>2</td>
<td>12-20 (3-5 per camera)</td>
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<td>CCD</td>
<td>CMOS</td>
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<tr>
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<td>130°</td>
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<tr>
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<td>14</td>
<td>NA</td>
<td>-</td>
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<td>RT view</td>
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<td>VE-1 viewer</td>
<td>Miro Viewer</td>
<td>Real-time monitoring</td>
<td>-</td>
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<td>11</td>
<td>6-8</td>
<td>15</td>
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<tr>
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<td>RF</td>
<td>RF</td>
<td>HBC</td>
<td>RF</td>
<td>CapsoView</td>
</tr>
</tbody>
</table>

RT: Real-time; RF: Radio frequency; HBC: Human body communication.
INDICATIONS FOR SMALL BOWEL CE

OGIB
OGIB (Figure 1) is the first and most common indication for small bowel CE, and shows a better yield. The global diagnostic yield of CE for OGIB ranges between 30% and 70%, which is higher than that of push enteroscopy, double balloon enteroscopy, and small bowel series, with sensitivities of 31%, 23% and 5% respectively. In a 2007 study,[7] CE showed its superiority over computed tomography (CT) and angiography in the detection of bleeding lesions, and detected a suspected bleeding source in patients with negative results for two other procedures. CE seems to impact OGIB management and outcomes. In a retrospective study of 75 patients,[8], CE diagnosed relevant lesions in 66.7% patients, and 49 (50.7%) of these patients, underwent confirmatory tests and subsequently received specific therapy [surgery, medical therapy, nonsteroidal anti-inflammatory drug (NSAID) withdrawal].

The diagnostic yield of CE for OGIB increases when the procedure is performed in the first 48 h after bleeding onset.[9,10] Other recognized factors related to a higher diagnostic yield include: advanced age, male sex, hospital admission and increased transfusion requirements.[11]

The most frequent finding of OGIB is intestinal angiodysplasia (22%). Other causative lesions include: (1) small bowel ulcer (10%); (2) esophago-gastric benign lesions (i.e., esophagitis or gastritis) (11%); (3) blood in the small bowel in the absence an identified lesion (8%); (4) small bowel tumors (7%); and (5) small bowel varices (3%).

Iron deficiency anemia
Iron deficiency anemia (IDA) is usually determined by blood loss through the GI tract. Therefore, CE is a good method to identify causative lesions, once other common potential bleeding sources located within the reach of upper or lower endoscopy have been ruled out. CE proved its superiority over enteroclysis in a previous study, with a causative lesion identification rate of 57% with the former and 11.8% with the latter.[12]

Crohn’s disease
CE plays a role in diagnosing suspected Crohn’s disease (CD) (Figure 2) when the clinical history is compatible with its findings after a normal examination by conventional endoscopy. It also plays a role in small bowel evaluation in patients with indeterminate colitis and disease extension assessment in patients with known CD.[13] The diagnostic yield in this setting is 66%-71% for known CD and 33%-68% for suspected CD.[14]

In a 2010 meta-analysis,[15], the diagnostic yield for small bowel CD was higher (50%-70%) with CE than with other procedures such as small bowel series (22%), colonoscopy (48%), push enteroscopy (8%), and enteroclysis/CT enterography (31%). In another study,[16], CE was compared with magnetic resonance imaging (MRI) enterography and CT enterography, and showed a clearly higher sensitivity and specificity.

Apart from allowing diagnostic confirmation and evaluation of CD extension, CE can be used to appraise disease activity and severity, facilitating therapeutic modifications with the intention to achieve mucosal healing, which has a direct impact on disease prognosis.[17]

On the other hand, CE has been shown to identify patients with a higher likelihood of a flare, with some authors observing that the presence of lesions in the jejunum in otherwise asymptomatic patients predicts a higher risk of a clinical exacerbation in the following two years.[18] CE was also proved to be superior to colonoscopy in the detection of postsurgical recurrence of CD (65% vs 25%), with better patient acceptance and tolerability, and it also even allowed the exploration of the neo-ileum that was not accessible by colonoscopy.[19]
The most common presentation of small bowel tumors is OGIB\textsuperscript{[22]}. The most common histopathological type is adenocarcinoma, followed by carcinoid, lymphoma, sarcoma and hamartoma. The most common location is the jejunum (40%-60%), followed by the ileum (25%-40%) and duodenum (15%-25%).

The most commonly occurring benign tumors in the small bowel are inflammatory polyps, lymphangioma, hemangioma, adenoma and lipoma. The most frequent metastatic tumor is melanoma\textsuperscript{[23]}, but there also some case reports of metastatic colorectal cancer (CRC) and hepatocellular carcinoma\textsuperscript{[24]}. The main known complication of CE in patients with CD is capsule retention in strictures, which has been observed in up to 5% patients. Therefore, when a stricture is suspected, a patency capsule should be administered before conventional CE. The other option is to select alternative procedures to study the small intestine, such as CT enterography and MRI enterography\textsuperscript{[20]}. 

**Small bowel tumors and polyps**

CE is an outstanding method for the detection of small bowel tumors and polyps (Figure 3), and the study of polyps in polyposis syndromes, such as familial adenomatous polyposis (FAP) and Peutz Jeghers syndrome\textsuperscript{[21]} (Figure 4).

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**Figure 2** Ulcers in the small bowel. A: Ulcer with erythematous and edematous edges; B: Serpiginous ulceration and stenosis affecting the entire colon circumference.

**Figure 3** Tumors in the small bowel. A: Dark tumor (arrows) confirming metastases from melanoma after surgery; B: Subepithelial white lesion compatible with lipoma.

**Figure 4** Enlarged gastric areas in a patient with Peutz Jeghers syndrome.
Vanishing visceral compression that protrudes to the small bowel lumen can confound an inexperienced physician who may misdiagnose it as a subepithelial mass. Some signs, such as well-defined margins, or visualization of the lesion for more than 10 min, increase the likelihood of a true subepithelial mass\(^3\) (Figure 3B).

With regard to small bowel tumors, CE has improved the diagnostic yield of previous procedures\(^2\), allowing an early diagnosis at a lower cost\(^1\). However, its impact on the management and prognosis of these patients has yet to be proven.

Hereditary polyposis syndromes also affect the small bowel, and the sensitivity and small bowel polyp detection rate are higher with CE than with X-ray series\(^3\), can be considered as an alternative follow-up\(^29,30\). However, CE tends to underestimate the number of polyps and exhibits poor performance while exploring the ampulla. In a prospective study\(^31\), CE was successful in identifying jejunal or ileal polyps; however it missed the ampullary area in all patients. Therefore, the role of CE in polyposis syndromes has yet to be established.

Other important applications of CE include the diagnosis of patients with suspected B-cell lymphoma; in such cases it can diagnose the condition, assess disease extension, and evaluate the response to chemotherapy\(^32,33\).

**Celiac disease**

Histology is the gold standard for the diagnosis of celiac disease. Therefore, CE cannot be the primary diagnostic tool in this setting, because of its inability to take biopsies. Nevertheless, CE can identify typical mucosal changes observed in this disease\(^34\), similar to upper endoscopy but with the advantages of the lack of insufflation and the higher image magnification. When compared with histology, CE has a sensitivity of 70% and specificity of 100% for the diagnosis of celiac disease\(^34\). Therefore, the role of CE is to assess mucosal abnormalities in patients with positive serology but normal histology\(^35,36\), keeping in mind that a normal CE examination does not rule out celiac disease, given its somewhat low negative predictive value (77%\(^34\).

CE also plays an important role in refractory or complicated celiac disease, allowing the diagnosis of T-cell lymphoma, ulcerative jejunoileitis and adenocarcinoma\(^37,38\).

**Small bowel graft vs host disease after bone marrow transplantation**

Graft vs host disease (GVHD) is a severe complication of bone marrow transplantation, and usually requires quick intervention. In most patients, upper endoscopy or colonoscopy with biopsy is required for diagnosis. The role of CE has been evaluated in several studies, with two of them\(^39,40\) reporting relevant findings in regard to acute GVHD. These studies showed a high positive predictive value for CE in patients with suspected GVHD, given that patients with no findings did not develop the disease at the 2 mo follow up.

In conclusion, CE can be as useful as conventional endoscopy and biopsy for the diagnosis of GVHD\(^31,42\).

**NSAID induced enteropathy**

The real clinical impact of CE in this group of patients remains unknown, because up to 44% patients receiving NSAIDs have small bowel lesions. Its role is clearer in patients with OGIB after negative results are obtained in conventional endoscopy. The most common lesions are superficial erosions, petechiae, denuded mucosa, bleeding lesions, and ulcers, etc. Maiden et al\(^43\) showed that CE performed after 2 wk of treatment with NSAIDs and a proton pump inhibitor (PPI) for 40 healthy volunteers detected abnormalities in 65.5% patients, including reddened folds, active bleeding, angiodysplasia, and lymphangiectasia (Figure 5).

**Abdominal pain of unknown origin**

CE has shown a low diagnostic yield in patients with abdominal pain (13%) or chronic diarrhea (9%).

From the first few studies, researchers have tried to accurately select cases where CE can demonstrate and improved diagnostic yield. The DEDAP-Plus study\(^44\) comprised 50 patients with abdominal pain and chronic diarrhea. Two independent researchers found relevant findings in 36% and 40% patients, and potentially relevant findings in 14% and 24% patients. In this study patients were classified according to the presence of symptoms or “plus signs” such as weight loss, serum inflammatory markers, chronic anemia, and suspected GI bleeding. Researchers observed an increased diagnostic yield in patients with elevated inflammatory markers (OR
In a 2011 multicenter Greek study,[45] 72 patients with chronic abdominal pain were evaluated using CE. The global diagnostic yield was 44.4%, ranging from 21.4% in patients with abdominal pain without elevated serum inflammatory markers (CRP, ESR) to 66.7% in patients with altered parameters and 90.1% in patient who also presented with diarrhea. They concluded that elevated serum inflammatory markers are associated with a higher diagnostic yield for CE.

Other indications
Apart from the abovementioned indications, CE can be useful in other settings with small bowel involvement. Nevertheless, the rarity of those conditions prevents researchers from making general statements on its possible role. Specifically, CE can be useful in diagnosing systemic diseases and vasculitis[46] with small bowel involvement, such as Henoch-Schonlein purpura, Churg-Strauss syndrome and Behçet disease[47-49].

CE has also been evaluated for use in recipients of small bowel transplantation, for whom ileoscopy is the standard procedure to evaluate rejection. In a 2003 study[50] CE and ileoscopy were used in 5 patients with a prior bowel transplant. CE was better tolerated and provided high quality images of the small bowel in four patients. When the terminal ileum showed no abnormalities with both techniques, CE detected mucosal changes in segments inaccessible by ileoscopy in three patients.

INDICATIONS OUTSIDE THE SMALL BOWEL

In 2004, Given Imagin Ltd. developed a video capsule (PillCam ESO) for the esophagus, and its third version (PillCam ESO 3) was approved by the FDA in 2011. It has dual cameras that capture 35 frames/s for 30 min. Although its role remains unclear it has been proposed as a minimally invasive procedure for esophageal diseases[50,51] (Figures 6 and 7).

The first pillCam ESO study[52] included 73 patients with gastroesophageal reflux disease and 9 patients with known Barrett’s esophagus who underwent CE followed by standard upper endoscopy. The sensitivity and specificity of CE were 97% and 100% for Barrett’s esophagus and 98% and 100%, respectively for diagnosing esophagitis. However, further cost-effectiveness analyses showed that Barrett’s esophagus screening using PillCam ESO was not cost-effective compared with that using conventional upper endoscopy[53].

On the other hand, some studies point to a role for this capsule as an alternative to the conventional approach in special cases: (1) Patients with gastroesophageal reflux disease[54]; (2) Detection of esophageal varices in patients with cirrhosis. A multicenter study[55] showed its ability to discriminate small and big varices, which may facilitate a specific therapy. Indeed, cost-effectiveness analyses do not support the use of this capsule as a conventional method, which can be reserved for special
cases\cite{56}; and (3) In the emergency room, CE showed better performance compared with a nasogastric tube and similar performance compared with upper endoscopy while determining the presence of an active bleeding, thus demonstrating no therapeutic abilities. Therefore, it is not a true alternative to upper endoscopy in this setting\cite{55-58}.

Another important goal for CE developers is the colon. Given Imagin produced the colon capsule (PillCam Colon), and they now have manufactured the second generation of this device. It has dual cameras, enabling it to acquire images from both ends. The angle of view from each imager is 172º. It has been approved in Europe because of its potential role in CCR screening although this remains to be clarified\cite{59-61}. In a 2010 meta-analysis\cite{62} sensitivity and specificity for adenoma and carcinoma detection were 69% and 86%, respectively. A further study\cite{63} observed improved sensitivity and specificity of 88% and 95%, respectively, for polyps measuring ≥ 10 mm, suggesting that CE may be a promising tool for screening, although it needs improvements before becoming an alternative to colonoscopy for CCR screening. This device can also be an alternative when colonoscopy is incomplete, when the patient rejects colonoscopy or when colonoscopy is associated with substantial risks derived from the patient's condition or comorbidities\cite{64}.

In 2012 the European Society of Gastrointestinal Endoscopy (ESGE) introduced guidelines\cite{65} to homogenize clinical practice. Patients with average CRC risk: CE is an alternative for the screening. Patients that a high risk of CRC ( alarming symptoms with a family or personal history of CRC): CE is not an alternative, because the probability of finding lesions requiring biopsies or polypectomy is high. Every patient with polyps measuring > 6 mm or with more than three polyps should undergo colonoscopy\cite{66}. Patients without findings on CE should repeat the procedure in 5 years, unless they have poor bowel cleansing. In situations where colonoscopy is not an option, CE can be an alternative, although further studies comparing CE with radiological methods are required.

Finally, CE can be useful for the detection of colonic diverticular disease or mucosal inflammatory changes\cite{67}, but no studies have addressed its role in non-neoplastic diseases. There are no objective data to support the use of CE for the diagnosis or follow-up of inflammatory bowel disease. Colon CE has been tested in patients with inflammatory bowel disease, and it exhibited a performance similar to that of colonoscopy\cite{68-71}, albeit without the ability to take biopsy samples.

**FUTURE OF CE**

CE has undergone continuous improvements since its first description including better image resolution, an increased number of frames obtained from the explored areas, a longer battery life, and better software for the visualization and management of images.

**Improvement in the angle of vision**

Apart from the abovementioned CapsoCam SV1, which widened the angle of view to 360°, there is another device, the Sayaka Capsule (RF Systems Lab Company, Nagano, Japan), which has described in 2005, and has a side camera that rotates, obtaining 30 frames/s. These frames are processed into an extensive series of overlap mosaicing, offering a map of the entire GI tract. The same company designed the Norika capsule, with a lens angled at 75º and a magnetic field based propulsion system.

**Capsule with therapeutic capabilities**

Capsules with anchoring devices have been developed, allowing for a precise drug delivery into the tract. Various systems are available, such as the one described by Woods\cite{72}, with a stopping mechanism that unfolds in 1.8 s and the ability to deliver 1 mL of medication to a target within the small intestines via a 1.5 mm needle.

**Active, operator controlled, CE**

Two CE systems with remote motion control are under study: (1) External systems, such as magnetic fields that can guide and move the capsule\cite{73-75}, and (2) Internal systems, within the capsule itself, which can move it through the small bowel\cite{76-78}.

**Capsules with air inflation ability**

Peristalsis is a common difficulty faced during exploration of some segments of the small bowel using CE. Inflation in some situations can significantly improve the visualization of these areas. Certain devices are under development, such as the one published by Gorlewicz et al\cite{79}, which has, in different compartments, chemical substances that release carbon dioxide when mixed, allowing distension and better small bowel exploration.

**CONCLUSION**

CE is a safe and acceptable method for GI tract exploration, and its use is widespread. Although the most common indication for CE is OGIB with suspected origin in the small bowel, there are other situations where it has been used, in other parts of the GI tract that are accessible by standard endoscopy. However, its use should be restricted to patients with risk levels or characteristics that make CE safe and more acceptable.

CE still has two major drawbacks compared with conventional endoscopy: the possibility of external motion control and the inability to treat lesions. Despite this, technological advances in the field may, in the near future, drive CE to become the first choice of modality for the diagnosis, treatment and follow-up of GI tract diseases.

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P- Reviewer: Leitman M, Sakata N S- Editor: Ma Y L- Editor: A E- Editor: Wang CH