Review Article on Current Applications and Future Concepts of Capsule Endoscopy

Helmut Neumann a  Lucía C. Fry b  Markus F. Neurath a

a Department of Medicine I, University of Erlangen-Nuremberg, Erlangen, and b Department of Internal Medicine, Gastroenterology and Infectious Diseases, Marienhospital Bottrop, Bottrop, Germany

Abstract
Since the advent of capsule endoscopy (CE) more than one decade has passed. During this time, extensive efforts have been made to proof the relevance of CE for diagnosis of various disease entities within the esophagus, small bowel, and colon. To date, the most common indications for CE are obscure gastrointestinal bleeding, Crohn’s disease, polyposis syndromes and evaluation of patients with complicated celiac disease. In this review we will focus on the current clinical applications of CE for imaging of the esophagus, small bowel and colon and will additionally give an outlook on future concepts and developments of CE.

Key Words
Capsule endoscopy · Small bowel · Advanced imaging · Endomicroscopy · Inflammatory bowel disease

Introduction
Since the introduction of capsule endoscopy (CE) in 2000, various studies have shown the potential of this minimally invasive technique to improve diagnostic outcomes among a variety of gastrointestinal (GI) conditions [1–58].

To date, multiple CE systems from different companies are available. Nevertheless, currently only the Given M2A video capsule system (Given Imaging Ltd., Yoqneam, Israel) and the Olympus Endocapsule (Olympus, Tokyo, Japan) are FDA and CE approved. Capsule systems are available for examination of the esophagus, small bowel and colon. While suspected small bowel stenosis is a contraindication for performing CE a patency capsule (Agile capsule, Given Imaging) was developed for these patients. This capsule is a self-dissolving capsule with the same size as the conventional CE and contains a radiofrequency identification tag that allows it to be detected by a scanning device placed on the abdominal wall. In addition, it has a radiopaque coating that permits its location within the bowel using fluoroscopy. When its passage is blocked by a stenosis or tumor, the patency capsule dissolves within 40–80 h after ingestion.

Although the capsule is easily ingested and swallowed by most individuals, patients with severe dysphagia, large Zenker’s diverticulum, pill phobia, significant gastropareses, and small children may have problems ingesting the device. For these situations, a capsule-loading device (Advance, US Endoscopy, Mentor, Ohio, USA) is available to directly deliver the capsule into the stomach or duodenum. The disposable device is a 2.5-mm single-sheathed device which is first preloaded through the working channel of a standard endoscope. The activated
CE is then loaded into the specialized capsule cup and afterwards the endoscope and the loading device are carefully advanced through the esophagus. After reaching the stomach or duodenum the CE is released and the endoscope is withdrawn.

Based on a recent systematic review, the following were identified as the most common indications for CE: obscure GI bleeding, accounting for 66% of interventions, clinical symptoms only (10.6%), Crohn’s disease (10.4%), others (7%), neoplastic lesions (3.5%), celiac disease (1.7%), and healthy subjects (0.8%) [2]. It is important to emphasize that CE has a low diagnostic yield in the evaluation of patients with abdominal pain or diarrhea in the absence of anemia or elevation of inflammatory markers [3].

**Technical Specifications**

At the time of writing this review, two FDA and CE-certified capsule devices are available consisting both of disposable plastic capsules. The Given small bowel capsule measures 11 × 26 mm and weights less than 4 g. The field of view is 140 degrees and the system can detect objects less than 0.1 mm. The SB2/4 capsule is capable of capturing four images per second. The operating time is between 6 and 8 h. The Given capsule for esophageal diseases (PillCam Eso) has the same size like the SB capsule but is capable to take up to 18 images per second as it passes down the esophagus. The Endocapsule system from Olympus has a maximum field of view of 145°, a depth of field between 0 and 20 mm and a sampling rate of 2 frames per second. The dimensions of the capsule are 11 mm in diameter and 26 mm in length. The operating time of the device is about 8 h.

**Relative and Absolute Contraindications**

It is recommended to use the CE with caution in patients with known or suspected GI obstruction, fistulas, or motility disorders [4]. Nonexcretion of the CE was reported to occur in less than 1% of patients [5]. In this context, retention only occurred in cases with localized pathology while no retention has been reported in normal subjects or those with small bowel diverticulosis or appendiceal orifices [6]. In patients with suspected Crohn’s disease and obscure GI bleeding capsule retention has been reported in between 1.5 and 5%. Although CE retention is usually clinically asymptomatic, it may require either endoscopic or surgical removal to avoid further complications [7]. While there has been concern about the use of defibrillators and cardiac pacemakers, recent evidence suggests that CE can be safely performed in these patients with appropriate monitoring. Moreover, it was shown that capsule-induced electromagnetic interference remains a possibility but is unlikely to be clinically important. Cardiac pacemaker-induced interference of CE is also possible, but is infrequent and does not result in loss of images transmitted by the capsule [8]. In contrast, patients should not undergo magnetic resonance imaging after having excreted the CE. Plain radiographs can easily identify the CE in case of suspicion of any retention.

**Patient Preparation**

Patient preparation for CE of the esophagus is performed after the patient has fasted for at least 2 h. For small bowel CE there are several accepted preparation methods, which include fasting since the day before, clear liquid diet, the ingestion of 2–4 liters of polyethylene glycol solution or the use of mannitol. In addition, some experts recommend the use of simethicone before the ingestion of the capsule to reduce intraluminal foam and bubbles. Bowel cleansing for colon CE is of paramount importance and it is still under development and improvement.

Because CE is a minimally invasive technology patient compliance is good in most cases. Only a minority of patients have problems to swallow the capsule and some patients experienced problems drinking the amount of fluid necessary for optimal colon CE examination.
Clinical Applications

**Esophagus**

GERD and Barrett’s Esophagus

Eliakim et al. [9] presented the results of a multicenter trial evaluating the diagnostic accuracy of PillCam ESO versus upper endoscopy in patients with chronic gastroesophageal reflux disease. Overall, 106 patients were included and of those 66 patients had positive esophageal findings. CE identified esophageal abnormalities with a sensitivity and specificity of 92 and 95%, respectively. The per-protocol sensitivity, specificity, positive predictive value, and negative predictive value of CE for Barrett’s esophagus were 97, 99, 97 and 99%, respectively, and for esophagitis 89, 99, 97 and 94%, respectively. In this study, CE was preferred over standard upper endoscopy by all patients.

In 2008, Gralnek et al. [10] presented the results of the second-generation CE (PillCam ESO 2) for the detection of esophageal diseases. Compared with upper endoscopy for detecting suspected Barrett’s esophagus and esophagitis, the PillCam ESO 2 had a sensitivity of 100% and a specificity of 74%, and a sensitivity of 80% and a specificity of 87%, respectively.

Another study compared the accuracy of upper endoscopy with esophageal CE in patients at risk of esophageal squamous cell cancer [11]. Overall, 68 patients were included. Sensitivity of CE for neoplasia diagnosis was 46%.
On a per-patient basis, the sensitivity, specificity and positive and negative predictive value of CE were 63, 86, 77 and 76%, respectively. Therefore, CE seemed not to be sensitive enough to diagnose neoplastic lesions in the esophagus.

In conclusion, CE of the esophagus seemed to be a convenient and sensitive method for visualization of Barrett’s esophagus and esophagitis but is not sensitive enough to diagnose SCC.

Esophageal Varices
Various studies have evaluated the potential of CE for diagnosis of esophageal varices. One recent meta-analysis included 9 studies with 631 patients [12]. The pooled sensitivity and specificity of CE for detecting esophageal varices were 83 and 85%, respectively. Nevertheless, CE was not comparable to upper endoscopy. It was therefore concluded that esophageal CE could be an acceptable alternative to conventional endoscopy in certain situations but could not be recommended to replace standard upper endoscopy.

Small Bowel
Obscure Gastrointestinal Bleeding
Obscure GI bleeding is defined as either occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including colonoscopy and EGD. Obscure GI bleeding accounts for most (about 66%) of CE interventions and CE has been recommended as the 3rd diagnostic test for patients with obscure GI bleeding (after at least one normal upper and lower endoscopy) [2, 13]. It was shown that about 20–38% of patients with normal upper and lower endoscopy have significant intestinal lesions [14, 15] (fig. 1). Previous studies have demonstrated that CE is superior to radiographic studies, including barium follow-through and CT enterography [16, 17]. Moreover, a pooled analysis of 7 prospective studies showed a CE yield of 71% for identification of a bleeding source compared to push enteroscopy [18]. In case of ongoing bleeding, CE detected the bleeding source in 92%. In case of heme-positive stool and anemia, CE detected the bleeding source in 44% and in patients with a prior overt bleeding in about 13% of patients.

When comparing CE with intraoperative enteroscopy, the sensitivity, specificity positive, and negative predictive value of CE was 95, 75, 95 and 86%, respectively [19]. These findings are in line with other published data [20–22].

Balloon-assisted endoscopy (e.g. double-balloon or single-balloon endoscopy) has the potential to visualize the whole small intestine. One recent study compared double-balloon endoscopy with CE and identified nearly concordant findings in 12 out of 13 bleeding patients. In 1 patient, CE missed an ulcer [23]. Sheibani et al. [24] evaluated the long-term impact of CE in patients referred

Fig. 8. Proposed algorithm for the diagnosis of obscure GI bleeding.
patients with polyposis syndromes, CE was shown to detect small and can therefore be missed with CE. In patients with suspected and established small bowel Crohn’s disease, CE was superior to small bowel radiography, CT enterography and magnetic resonance imaging in the evaluation of patients with suspected Crohn’s disease. In patients with established Crohn’s disease, CE was superior to small bowel radiography, CT enterography and magnetic resonance imaging for the detection of small bowel polyps, but not for duodenal neoplasia [33]. Also for other hereditary polyposis syndromes, including Peutz-Jeghers syndrome and Lynch syndrome, recent data indicate that CE is a safe and effective method for small bowel surveillance and even result in a better reproducibility than with CT enteroclysis [34–36] (fig. 4). Nevertheless, despite these promising results surveillance of the small bowel is currently mostly not recommended in Lynch syndrome [37],

Table 1. Indications for CE according to different locations (most common indications are underlined)

<table>
<thead>
<tr>
<th>Location</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Esophagus</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td></td>
<td>Barrett</td>
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<td></td>
<td>Esophageal varices</td>
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<td>Small bowel</td>
<td>Obstructive gastrointestinal bleeding</td>
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<td>Intestinal tumors</td>
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<td>Crohn’s disease</td>
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<td>Celiac disease</td>
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<td>Colon</td>
<td>Polyps</td>
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<td></td>
<td>Cancer</td>
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<tr>
<td>General</td>
<td>Diarrhea</td>
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<td></td>
<td>Abdominal pain</td>
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for iron deficiency anemia. CE had a diagnostic yield of 61% and the CE-based diagnosis led to a therapeutic intervention in about 26% of patients. Another study included 100 consecutive cases with recent negative upper and lower endoscopy [20]. In patients with ongoing overt GI bleeding CE yielded positive findings in about 92%. In contrast, in patients with guaiac-positive stool tests, iron deficiency anemia and previous overt GI bleeding, CE yielded positive findings in about 44 and 13%, respectively. Sensitivity, specificity and positive and negative predictive values of CE were 89, 95, 97 and 83%, respectively. Figure 8 highlights our proposed algorithm for the diagnosis of obscure GI bleeding.

Intestinal Tumors

The frequency of intestinal tumors among patients investigated using CE for obscure bleeding ranges from 6 to 12% [25]. The most common tumors in the small bowel include adenocarcinomas, lymphomas, GI stromal tumors, neuroendocrine tumors and metastasis [26]. Nevertheless, there are several cases of missed tumors of the small bowel using CE, probably because these lesions grow predominantly in the submucosa and extraluminally rather than into the small bowel lumen [27, 28]. Moreover, small bowel tumors are sometimes relatively small and can therefore easily be missed with CE. In patients with polyposis syndromes, CE was shown to detect more polyps in comparison to small bowel follow through [29]. Moreover, CE seemed to be more effective than positron emission tomography in the detection of malignant melanomas and metastases [30]. Detection rates between MRI and CE for identification of polyps larger than 15 mm were similar while CE was more sensitive to diagnose smaller intestinal polyps [31]. Nevertheless, one potential limitation of CE is the examination of the proximal duodenum and the periampullary region which could only be visualized in about 10% of examinations in one recent study [32]. In patients with familiar adenomatous polyposis, CE was superior to conventional white-light endoscopy for the detection of small bowel polyps, but not for duodenal neoplasia [33]. Also for other hereditary polyposis syndromes, including Peutz-Jeghers syndrome and Lynch syndrome, recent data indicate that CE is a safe and effective method for small bowel surveillance and even result in a better reproducibility than with CT enteroclysis [34–36] (fig. 4). Nevertheless, despite these promising results surveillance of the small bowel is currently mostly not recommended in Lynch syndrome [37],

Crohn’s Disease

Various studies have shown the potential of CE for diagnosis of Crohn’s disease [38–42] (fig. 2). Eliakim et al. [38] compared CE to barium follow through and computed tomography (CT) in patients with suspected Crohn’s disease. CE yielded a diagnosis in 77% of patients, compared to 23 and 20% for barium follow through and CT, respectively. These results were also confirmed by other investigators [39, 40]. Notably, one recent small study including 39 patients reported on a sensitivity and specificity of 89 and 100%, respectively [41]. These results need to be critically discussed, because Crohn’s disease-associated mucosal changes are nonspecific for the disease and can also be observed in up to 14% of healthy volunteers and in patients taking nonsteroidal anti-inflammatory drugs [42] (fig. 5). Therefore, it is important for the endoscopist to read the CE findings with extensive knowledge about the patient’s history. One recent published meta-analysis evaluated the diagnostic yield of CE in patients with suspected and established small bowel Crohn’s disease in comparison to push enteroscopy, ileocolonoscopy, small bowel radiography, CT enterography and magnetic resonance tomography [43]. The meta-analysis revealed that CE was superior to small bowel radiography, CT enterography and ileocolonoscopy in the evaluation of patients with suspected Crohn’s disease. In patients with established Crohn’s disease, CE was superior to small bowel radiography, CT enterography and push enteroscopy. Similar results were shown in another recent meta-analysis from Leighton et al. [44]. In contrast to these data, Solem et al. [45] found that the sensitivity of CE for diagnosis of active small bowel Crohn’s disease was not sig-
significantly different from CT enterography, ileocolonoscopy, or small bowel follow through. The authors concluded that CE has only a limited value as the first-line test for small bowel Crohn’s disease. Importantly, the risk of capsule retention in patients with known Crohn’s disease must be considered and analyzed before the ingestion of CE. Although patients with suspected Crohn’s disease have the same risk of retention as compared with the general population (1.6%), in patients with known or established Crohn’s disease this risk of retention is up to 13%, with the consequent need of surgery in some cases [46]. Of note, balloon-assisted endoscopy is mostly successful to remove foreign bodies from the small bowel [47]. Figure 9 highlights our proposed algorithm for the diagnosis of Crohn’s disease.

Celiac Disease
Advanced celiac disease is characterized by villous atrophy which can be visualized using CE Figure 3. One recent published meta-analysis described an overall pooled sensitivity of 89% (95% CI 82–94) and specificity of 95% (95% CI 89–98) for CE in celiac disease [48]. In a subgroup analysis of patients with complicated or refractory disease, CE documented unexpected findings such as strictures, ulcerations and neoplasms in up to 45% of cases [49]. Of note, CE can only diagnose advanced stages of celiac disease, as early stages are only based on histological findings. The most important use of CE in celiac disease is the evaluation of patients with refractory celiac disease, investigating ulcerative changes or the development of T cell lymphomas. Besides, CE may also be sufficient to diagnose enteropathy-associated T cell lymphoma which is an intestinal tumor of intraepithelial lymphocytes [50] (fig. 6).

Colon
Polyps and Cancer
Colorectal cancer screening still remains a challenge because most patients decline to participate in screening programs due to anxiety directly related to the endoscopic procedure. In this context, the colon capsule has been proposed as an alternative minimally invasive tool for colorectal cancer screening (fig. 7).

In a prospective study, including 84 patients, CE was followed by standard white-light endoscopy on the same day [51]. 24% of patients had significant findings, defined as at least one polyp of 6 mm or more in size or three or more polyps of any size: 70% were identified with CE and 80% were identified by conventional colonoscopy. Polyps of any size were found in 45 patients, 76% found by CE and 80% by conventional colonoscopy. In comparison with conventional colonoscopy, false-positive findings on CE were recorded in 33%.

The second-generation colon capsule has several advantages when compared with the first colon capsule. It has an increased angle of view to 172° and an adaptive frame rate which alternates from 35 frames per second while in motion to 4 images when virtually stationary. This second-generation colon capsule was evaluated by the same group in a prospective, multicenter study [52]. Overall, data from 98 patients were analyzed. The capsule sensitivity for the detection of patients with polyps ≥6 mm was 89% (95% CI 70–97) and for those with polyps ≥10 mm 88% (95% CI 56–98). Specificity of CE for polyps ≥6 mm was 76% (95% CI 72–78) and for those with polyps ≥10 mm it was 89% (95% CI 86–90), respectively.

In addition, one recent study evaluated the feasibility, accuracy, and safety of the second-generation CE in a head-to-head comparison with colonoscopy [53]. Data from 109 patients were analyzed. The per-patient CE sensitivity for polyps ≥6 mm and ≥10 mm was 84 and 88%, with specificities of 64 and 95%, respectively. All 3 invasive carcinomas in the study population were detected by CE.

One large multicenter study included 328 patients and analyzed CE versus conventional colonoscopy for the detection of polyps and cancer [54]. The CE was excreted within 10 h after ingestion and before the end of the lifetime of the battery in about 93% of patients. CE yielded a
sensitivity and specificity for detecting polyps ≥ 6 mm of
64% (95% CI 59–72) and 84% (95% CI 81–87), respective-
ly. For the detection of advanced adenoma, the sensitivity
and specificity were 73% (95% CI 61–83) and 79% (95%
CI 77–81), respectively. Of 19 cancers which were detect-
ed by colonoscopy, 14 were also detected by CE (sensitiv-
ity 74%; 95% CI 52–88). Mild-to-moderate adverse events
were reported in about 8% of patients and were mostly
related to the colon preparation.

It is still under debate if patients should undergo same-
day colonoscopy in the setting of positive CE findings. In
our opinion, it would be useful that the patient sign the
informed consent for colonoscopy together with the in-
formed consent for the capsule. The colonoscopy could
then be performed on the same day, given the fact that the
patient is good prepared for the colonoscopy, and does
not have to undergo another preparation.

Future Concepts of Capsule Endoscopy

Small bowel imaging still remains the major indica-
tion for CE. Comparative studies between the Given Im-
ageing and the Olympus CE have demonstrated similar
efficacies of both systems [55]. Currently, new capsule de-
vices are under development in order to enable targeted
drug administration or even direct hemostatic therapy.
The results of the respective pilot studies are highly an-
ticipated as they will open new applications for CE.

In its current form, the colon capsule is no real alterna-
tive to conventional colonoscopy. CE procedure-related
costs are extremely high and an exhaustive bowel prep-
aration is needed to obtain reasonable polyp detection
rates. Moreover, CE is not sensitive enough to predict his-
tology of colorectal polyps so that every positive CE find-
ing needs to be clarified by conventional endoscopy.

Nevertheless, new capsule devices may improve both,
polyp detection and characterization rates. In this con-
text, externally rechargeable batteries (using RF, micro-
wave, ultrasound or electric induction) or even ‘battery
free’ CE are developed. Moreover, integration of virtual
chromoendoscopy techniques, like FICE or i-scan, will
further improve image resolution and will help to better
characterize colorectal lesions [56, 57]. Other devices
such as capsules which will enable confocal imaging with
near infrared light are also under development thereby
allowing obtaining an optical biopsy during the CE pro-
cedure. The NEMO (nano-based CE with molecular im-
aging and optical biopsy) project tends to develop a new
capsule that will combine optical and nano technologies,
biosensing, and maneuvering technologies in order to
further improve diagnostic and therapeutic possibilities
of the capsule system [56, 57]. Additionally, pilot studies
have already demonstrated the feasibility of new capsule
devices to obtain mucosal biopsies and to apply clips or
coagulation for hemostasis. In order to actively control
the CE, recently the prototype of a magnetically guided
capsule endoscope (MGCE) system from Siemens and
Olympus was introduced. The study demonstrated that
the new technology appears to be feasible and sufficient-
ly accurate for gastric examination and may permit endo-
scopic examinations that are more patient-friendly and
without sedation [58].

Conclusion

CE has proven its efficacy in multiple trials since its
introduction nearly 12 years ago. The main indications
for CE interventions are still obscure GI bleeding, fol-
lowed by clinical symptoms only and suspected Crohn’s
disease. Multiple studies have shown that CE for these
interventions is superior to radiologic interventions and
push enteroscopy. In case of positive CE findings bal-
loon-assisted endoscopy (i.e. single- and double-balloon
enteroscopy) offers the potential to apply targeted biop-
sies or therapy.

In the past, CE was only a diagnostic test and capsule
movement was passive according to the gut movement.
In the future, new capsule devices may offer a great po-
tential for minimally invasive diagnosis and targeted
therapy. Moreover, capsule movement will be actively
controllable thereby opening new avenues for advanced
specific diagnosis and targeted therapy.

Disclosure Statement

None.

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