The Role of Capsule Endoscopy in the Evaluation of Crohn's Disease

Zvi Fireman*, Yael Kopelman

Department of Gastroenterology; Hillel Yaffe Medical Center; P.O. Box 169, Hadera 38100, Israel
Correspondence: fireman@hy.health.gov.il

Crohn’s disease (CD) is a systemic granulomatous disorder that may involve any part of the alimentary tract: the small bowel is the affected site in 30–40% of cases. CD remains a clinical diagnosis based on a typical clinical history, physical examination, small-bowel radiography, and ileocolonoscopy with biopsy. Conventional endoscopic techniques are limited by the length and multiple, complex looped configurations of the small bowel, and mild lesions confined to the mucosa may be missed by barium-contrast radiographs and computerized tomographic (CT) scans. The diagnosis becomes even more difficult if symptoms are atypical, and a missed diagnosis can profoundly affect clinical care and patient outcome. Capsule endoscopy allows direct visualization of the entire small-bowel mucosa. A number of recently published studies report diagnostic yields of >70% for CD from capsule endoscopy in patients with negative or inconclusive findings on prior small-bowel series and ileocolonoscopy. Capsular endoscopy examination has been shown to be a very effective diagnostic tool in patients with a high clinical probability of having the disease, but whose classic endoscopic and radiographic studies have been negative. This review offers a brief introduction to capsule endoscopy, a recap of clinical studies on capsular endoscopy in evaluating CD, and a description of expectations for this technology in future clinical practice.

Introduction

Crohn’s disease (CD) is a chronic inflammatory disorder characterized by transmural intestinal inflammation with granuloma formation, which can affect any part of the gastrointestinal (GI) tract. It involves the small bowel, most commonly the terminal ileum, in around 30% to 40% of patients (7). The "gold standard" for the diagnosis of CD includes the presence of the following features: abdominal pain, weight loss, iron deficiency anemia, diarrhea, an elevated erythrocyte sedimentation rate (ESR), fever, elevated C-reactive protein (CRP) and typical evidence of pathological processes on conventional imaging techniques, i.e., small bowel X-ray, computerized tomography (CT) of the abdomen, endoscopy, and colonoscopy with ileoscopy.

Conventional Endoscopic Imaging

The conventional endoscopic imaging-endoscopic procedures, which can be used to evaluate the entire small bowel include colonoscopy with ileal intubation and push enteroscopy with mucosal biopsies, but they are limited by the length of the small bowel (2-4). These endoscopic procedures, although very useful in the evaluation of patients with suspected CD, leave a large area of the small bowel essentially unexplored. In addition, retrograde intubation of the terminal ileum (ileocolonoscopy) is not always technically feasible. Endoscopic methods that can potentially examine the small bowel in its entirety, such as sonde enteroscopy (now abandoned) (5) or intraoperative enteroscopy (3,4) and, recently, double-balloon enteroscopy (6) are invasive, time-consuming, and associated with a recognized risk of complications, and so have rarely been used for evaluating patients with suspected CD of the small bowel. Colonoscopy with ileal intubation and push enteroscopy is useful for diagnosing CD but is often limited by not being able to reach the entire length of the small bowel.

Ileocolonoscopy is highly informative but not always feasible. Other endoscopic methods that can potentially examine the small bowel in its entirety are too high-risk for routine use.
Radiological Imaging
Radiological imaging contrast radiographic studies, such as upper GI series with small-bowel follow-through (SBFT) and/or enteroclysis, were previously considered to represent the “gold standard” for evaluating CD of the small bowel (7), in spite of the fact that SBFT is unable to demonstrate flat lesions and has low sensitivity for raised lesions (8). CT enteroclysis was recently introduced as an alternative imaging method to overcome the individual deficiencies of CT (i.e., no distention of the small bowel) and conventional enteroclysis (i.e., no extra-luminal information) and to combine the advantages of both in one technique. This method has been described as highly accurate in depicting mucosal abnormalities and extra-intestinal complications in patients with CD (9). Magnetic resonance (MR) enteroclysis is a new technique that results in an excellent demonstration of the anatomy of the small bowel. It can also accurately assess luminal narrowing and extramural manifestations or complications of the disease. Imaging features, including the presence of deep ulcers, extensive wall thickening and mesenteric lymph nodes exhibiting marked gadolinium enhancement, correlate strongly with disease activity. Although the clinical utility of MR enteroclysis in CD has been widely recognized, its routine application is currently limited to academic centers (10).

- SBFT is the former “gold standard” imaging technique for evaluating the small bowel but it cannot demonstrate flat lesions and has low sensitivity for raised lesions.

- CT enteroclysis accurately reveals mucosal abnormalities and extra-intestinal complications in CD but with limited sensitivity and relatively high radiation exposure.

- MR enteroclysis provides excellent demonstration of small bowel anatomy and can accurately assess luminal narrowing and extramural manifestations/complications of CD but it is not always available and is relatively expensive.

Intraoperative Endoscopy
Another approach to small bowel imaging is examination of the entire small bowel by intraoperative endoscopy. The limitations of this option are the drawbacks inherently associated with exploratory laparotomy and with general anesthesia (11).

Intraoperative endoscopy exposes small bowel pathology but it is invasive surgery that should be the last resort for acquiring information.

Capsule Endoscopy
In this methodology, the capsule propels through the entire system by means of peristalsis and collects color images of the GI tract starting at the esophagus. These data are transmitted and stored in a recorder, and finally processed in a workstation. The authors’ experience (12,13) has been with a capsule that measures 11 mm x 26 mm, weighs 3.7 g and contains four light-emitting diodes, a lens, a color camera chip, two batteries, a radio frequency transmitter, and an antenna (Fig. 1). The camera uses a complementary metal oxide semiconductor (CMOS) chip, which requires less power than the charged coupled device (CCD) chips currently found in video endoscopes. It transmits continuous images at 2 frames per second; permitting the acquisition of more than 50,000 images during the 6- to 8-hour procedure, as it passes through the GI tract. Video images are transmitted from the capsule, using UHF-band radio telemetry, to sensor arrays taped to the patient's abdomen and stored on a portable solid-state recorder worn around the patient's waist. The recording allows physicians to locate lesions in the small intestine, as well as calculate gastric emptying time and small bowel transit time.

**Figure 1:** Composition of the capsule used in capsular endoscopy.

The CE Procedure
CE is a painless, noninvasive, diagnostic outpatient procedure. The patient fasts overnight and, on the morning of the procedure, swallows the capsule with a small amount of water. A trained nurse can instruct the patient and perform the procedure. Some physicians use an
oral purging solution and/or prokinetic drug prior to the swallowing of the capsule. The duration of the procedure is approximately 8 hours. It is ambulatory and the patient is free to continue his/her daily activities.

*The Procedure’s Limitations*
Despite the expected life span of ~8 hours, the capsule battery may run out before the entire small bowel is visualized, particularly in cases of delayed small-bowel transit time. A critical region of interest may remain unexamined, as in the terminal ileum in CD. Some lesions may be missed since the capsule direction and passage velocity are not controllable. Image quality is sometimes inferior to the quality of flexible video endoscopy, since the lesions cannot be washed or re-examined. The camera may be obscured by residual debris, such as bile, food, contrast barium or feces. The capsule’s inability to perform biopsies limits histopathological correlation and diagnostic accuracy. Capsule examination cost is still a limitation since it is generally not funded by most health insurance plans.

*Complications and Safety*
The capsule may be retained in the GI tract and may require endoscopic or surgical removal. Pathologies that may cause retention include benign strictures or adhesions, Crohn's strictures, and lesions (e.g., carcinoid tumor or adenomas) (14). Retention rarely occurs at Zenker’s or Meckel’s diverticula (15, 16). The overall incidence of capsule retention is low (0.1%-5%), and most of the cases are due to CD-related strictures (14). Capsule retention occurs in <1% of patients without evident CD (17), but retention rates of 4–6% are reported in patients with established CD (14).

*Contraindications*
CE is contraindicated in pregnancy, in patients with known or suspected small bowel stricture, previous major abdominal surgery, dysphagia, or with implanted cardiac pacemakers, although Payeras et al. recently reported that patients with an implanted pacemaker underwent CE studies without any electrical interferences (18). Endoscopic delivery of the capsule in patients with dysphagia, anatomical abnormality, or gastroparesis has been reported as safe and effective (19) in pediatric patients as well. A biodegradable capsule (20), which has now become available, can be used for pretesting, in order to exclude significant luminal narrowing. This capsule may be retained in the stomach due to gastroparesis and delayed gastric emptying, a problem which may be overcome by the use of prokinetic agents. Clinical problems, such as difficulty or inability to swallow the capsule or incomplete small-bowel examination, may hamper or prevent the diagnosis in about 6% of cases.

*Initial Experience with CE*
Several series have been published on the utility of CE in diagnosing CD.

The initial report by Fireman et al. (21) reported a 71% yield in diagnosing small-bowel CD: 12 of 17 patients with a normal small bowel series and colonoscopy but with a high clinical suspicion of having CD were found to have lesions consistent with CD.

Eliakim et al. (22) studied 20 patients with suspected CD in whom the diagnosis was suspected based on abdominal pain (95%), diarrhea (75%), and weight loss (65%). Lesions that were felt to be medically significant or explained the patient’s reason for referral were found in 14 of 20 patients and they included ulcers and erosions (36%), erythema (22%), aphthae (17%), absent or blunted villi (14%), and nodular lymphoid hyperplasia (5.6%).

Herrerias et al. (23) studied 21 patients with suspected CD, all of whom had diarrhea and abdominal pain. Approximately half of them also had weight loss, anemia, or leukocytosis, and approximately one-third had either fever or an elevated CRP level. Colonoscopy and small bowel series had been unremarkable in all cases. Findings compatible with CD were identified by CE in 9 patients: these included aphthae, linear or irregular ulcers, and mucosal fissures. Based on this physical evidence of disease, the patients were started on standard therapy with prednisone and mesalazine and they were all in clinical remission 3 months later.

Ge et al. (24) evaluated 20 patients with suspected CD who had a normal small-bowel series and colonoscopy. Inflammatory lesions were identified by CE in 13 of them and were described as mucosal erosions (n = 2), aphthous ulcers (n = 5), nodular mucosa (n = 1), large ulcers (n = 2), and ulcerated stenoses (n = 3), mostly located in the distal jejenum and ileum. These patients were then treated with 5-ASA (4...
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g/d) and short-term steroids, with improvement in 11 of the 13.

Arguelles-Arias et al. (25) reported CE findings in 12 pediatric patients with suspected CD. They all had abdominal pain, weight loss, and fever, and 6 of them had diarrhea. Colonoscopy, esophagogastroduodenoscopy, and small-bowel series CE revealed abnormalities in 7 of these 12 patients: there were ulcerations in 4 and aphthous ulcerations in 3. The lesions were jejunal/ileal in 5 patients and purely ileal in 2. Each patient with abnormalities was then treated with prednisone and mesalamine, with clinical remission in them all after a mean follow-up of 3 months (Table 1).

Tabibzadeh et al. (28) described the utility of CE in identifying lesions proximal to the terminal ileum in patients previously thought to have only terminal ileum involvement: more than 50% of patients thought to have only ileitis were found to have small-bowel lesions proximal to the terminal ileum and approximately one-third of patients had lesions in the duodenum and/or jejunum.

Comparative Studies
Hara et al. (29) compared the findings of 4 diagnostic small-bowel imaging techniques in the same patients known to have or suspected of having CD. Each patient underwent CE, CT enterography, colonoscopy with ileoscopy, and SBFT. Seventeen patients completed the study out of 20 patients enrolled. CD was identified by CE in 12 patients (71%), ileoscopy in 11 (65%), CT enterography in 9 (53%), and SBFT in 4 (24%). This preliminary study demonstrated that CE and CT enterography may reveal nonobstructive CD.

Marmot et al. (30) studied 31 patients with endoscopically and histologically proven CD who had undergone enteroclysis as their initial examination, followed by CE. Abnormal findings were documented in 8 of 31 patients by the former and in 22 of 31 patients by the latter (25.8% vs. 71%, P<0.001). In 16 patients with known involvement of the terminal ileum, the diagnostic yield of CE compared to enteroclysis was significantly superior (89% vs. 37%, P<0.001). In 15 patients without lesions in the terminal ileum, abnormal findings in the proximal small bowel were detected in 7 (46%) patients by CE and in only 2 (13%) patients by enteroclysis (P<0.001).

Dubcenco et al. (31) described 39 patients, 28 with proven CD and 11 with suspected CD. The diagnostic yield of enteroclysis for identifying CD was 20.5% (8/39), and the diagnostic yield of CE was 66.6% (26/39), with normal or nonspecific findings in 13/39 (33.4%). The difference in diagnostic yields of the two tests was significant (P<0.0001).

Albert et al. (32) studied 52 consecutive patients who were investigated by MRI, fluoroscopy and, if bowel obstruction could be excluded, by CE. CD was newly suspected in 25 cases, while the diagnosis of CD (non-small bowel) had been previously established in 27 others. Small-bowel CD was diagnosed in 41 of the 52-patient cohort (79%). CE was not carried out in 14 patients due to bowel strictures. Of the remaining 27 patients, CE, MRI, and fluoroscopy detected small-bowel CD in 25 (93%), 21 (78%), and 7 (of 21; 33%) cases, respectively.

Chong et al. (33) described 22 patients who were known to have CD and 21 who were suspected to have small-bowel CD. Mucosal

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Positive Findings</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Fireman et al. (20)</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Eliakim et al. (21)</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Herrerias et al. (22)</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Ge et al. (23)</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Arguelles-Arias et al. (24)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>90</td>
<td>55</td>
</tr>
</tbody>
</table>

All the cited patients had a high clinical suspicion of CD but their small-bowel series and colonoscopy results were normal.
changes consistent with CD were seen on CE in 17 (77%) of the former group and in 4 (23.5%) of the latter group. Evidence of small-bowel CD was noted at push enteroscopy in 3 patients (P<0.001 compared with the 17 by CE). In the 21 patients who underwent enteroclysis, a mucosal abnormality was detected in 4 (P<0.001 compared with the 17 by CE). Management was changed for 13 of the 17 patients with small-bowel findings. CE was performed in the 21 patients with suspected CD, but the examination was complete to the cecum in only 17 of them. CE detected erosions or ulcers in 4 of these 17 patients. Push enteroscopy was performed (including proximal jejunal biopsies) in all 21 patients in this group and was normal in all cases. Enteroclysis was successfully performed in 16 patients. Three studies were reported as abnormal, but none were interpreted.

Voderholzer et al. (34) studied 56 consecutive CD patients who underwent CT enteroclysis: CE was carried out if stenosis >10 mm was excluded. CE could not be performed due to strictures detected by CT enteroclysis in 15 patients (27%). Of the remaining 41 patients, jejunal or ileal lesions were found in 25 patients by CE compared with 12 by CT enteroclysis (P=0.004).

Eliakim et al. (35) compared CE to small bowel series and CT enterography in patients with suspected CD. Thirty-five consecutive patients with abdominal pain (89%), diarrhea (63%), or significant weight loss (45%) underwent small-bowel series followed by CE and CT enterography if a stricture was ruled out. Diagnostic findings were identified in 27 of these 35 (77%) patients: they included erosions (36%), aphthous ulcerations (22%), erythema (22%), and nodular lymphoid hyperplasia (20%). The diagnostic yield of SBFT was 23% and that of CT enterography was 20%.

Buchman et al. (36) compared CE findings to those of small-bowel series in 42 patients with established small-intestinal CD who had symptomatically active disease. Every patient underwent small bowel series, followed by CE if stricture was ruled out. Twelve patients (28%) were excluded from capsule ingestion due to obstructive findings on small-bowel series. In the remaining 30 patients, CE identified inflammatory lesions in 21 of them while

Table 2: Comparison of Different Imaging Modalities Vs. Capsule Endoscopy in Known or Suspected (Susp.) Crohn’s Disease Patients.

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>No. Patients</th>
<th>Positive Findings</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>CE Follow-Through</td>
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<tr>
<td>Hara et al. (29)</td>
<td>19</td>
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<td>Marmo et al. (30)</td>
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<td>Albert et al. (32)</td>
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<tr>
<td>Chong et al. (33) (Known CD)</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Chong et al. (33) (Susp. CD)</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Voderholzer et al. (34)</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>Eliakim et al. (35)</td>
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<td>27</td>
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<tr>
<td>Buchman et al. (36)</td>
<td>30</td>
<td>21</td>
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CT, computerized tomography; MRI, magnetic resonance imaging
small-bowel series identified inflammatory changes in 20 of them. Overall, there was general agreement in severity of findings between CE and small-bowel series ($r = 0.65$). The authors concluded that CE did not alter the previously known extent or severity of disease based upon small-bowel series, but that it provided complementary information on mucosal inflammatory changes (Table 2).

**Hypothetic Problem-Solving in CE**

Contemporary CE, like radiology, gives results that can only be read, unlike conventional endoscopic procedures, which enable concomitant biopsy when indicated. In the future, CE should be capable of performing a tissue biopsy or even an optical biopsy. It would also be highly desirable for CE to have the capability to stop bleeding in the same way and in real-time as is possible with therapeutic endoscopy by adrenaline injection, heat probe, argon plasma coagulation, and so forth. Zooming or magnification capabilities would be of considerable benefit in clarifying diagnosis, as would chromo-endoscopy, the ultimate aspiration for CE.

In addition, we want to be able to pinpoint drug delivery sites in special GI diseases, such as CD. The problem here is that it would have to be done daily over a long period of time and that would be time consuming and costly. Although a pre-programmed non-viewing (i.e., no camera) capsule for drug delivery would be much cheaper, the ability to check on the healing process of the disease (or lack of it) would be lost. A combination of viewing and non-viewing capsules would make this treatment efficient and cost-effective.

Small-bowel motility (and, for that matter, stomach and large bowel motility) is another area where the CE can help the clinician. The motility application in the small bowel may open a window to study the pathophysiology of relatively elusive medical entities, such as irritable bowel syndrome. The optimal capsule needs to contain an automatic computerized system for automatic detection of pathologies, such as that present in the ECG Holter recording, in order to overcome the drawback of time-consuming viewing.

We envision a system in which endoscopists will be able to “control and steer” the CE, as they are able to do in standard endoscopy. This would mean being able to maintain the capsule steady in a selected area and hold the view in order to have more time to examine the opposite wall of the bowel. Future gastroenterologists will have a variety of CEs from which to choose, according to the purpose of the evaluation, i.e., diagnostic and/or therapeutic. Just as the idea of a swallowed capsule’s taking images as it travels along the human anatomy was once in the realm of sheer fantasy, we have every
reason to believe that the ultimate CE will become a reality and not in the far distant future.

In Conclusion
It can be said that the invention of CE marked the dawning of a new age of diagnostic imaging and opened up the "final frontier" of endoscopy. CE is a more sensitive examination than traditional radiography, although the specificity and positive predictive values remain to be established. CE has been proven as being an effective tool in the diagnosis and follow-up of patients with CD. Refinement of the technology by prospective comparative studies with adequate control groups and predefined clinical endpoints can be expected to establish CE as invaluable in the diagnosis and treatment of CD.

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References: