Indications of capsule endoscopy in Crohn’s disease

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ABSTRACT

Capsule endoscopy currently plays a relevant role for Crohn’s disease. This manuscript will discuss the current indications and practical uses of capsule endoscopy in this disease. It is a non-invasive technique that represents a significant advance in the endoscopic diagnosis of small bowel conditions. These circumstances, together with its diagnostic yield and excellent tolerability, make it considerably acceptable by both patients and physicians. This paper discusses the current evidence on the specific circumstances where capsule endoscopy may be indicated for three specific scenarios: Suspected Crohn’s disease, indeterminate colitis, and established Crohn’s disease, where it plays an extensive role. Furthermore, the impact and implications of capsule endoscopy results for follow-up are reviewed. These recommendations must be interpreted and applied in the setting of the integral, individual management of these patients. Understanding its appropriate use in daily clinical practice and an analysis of results may define endoscopic scoring systems to assess activity and mucosal healing in this condition. The present role of capsule endoscopy for Crohn’s disease is subject to ongoing review, and appropriate usage uncovers novel applications likely to result in relevant changes for the future management of these patients.

Key words: Crohn’s disease. Capsule endoscopy. Inflammatory bowel disease.

INTRODUCTION

Early diagnosis in inflammatory bowel disease (IBD) currently remains a challenge given that inflammatory activity progression results in irreversible damage (1-4). Presently there is no reference test for the diagnosis of Crohn’s disease (CD) (5,6), hence techniques must be interpreted in an appropriate context (7). Until a decade ago endoscopic visualization of the small bowel (SB) mucosa was achieved by means of the limited reach of push enteroscopy or the invasive nature of intraoperative enteroscopy. Since receiving FDA approval in 2001, the use of capsule endoscopy (CE) has improved imaging diagnosis for SB diseases. It uses a small device that takes hundreds of photographs during its natural transit of the bowel, thus providing a direct, non-invasive view of the mucosa. This review discusses its primary indications for CD as based on currently available evidence (8-12). These publications highlight its value for the identification of superficial lesions usually overlooked by other endoscopic and radiographic techniques (7,9,12-15), and define it as the reference technique for SB assessment in the absence of strictures or fistulas (12,16). Today, following bleeding of uncertain origin, CD is the second most important indication of CE (17). This review discusses its role in three scenarios: suspected CD, indeterminate colitis, and established CD.

CD DIAGNOSTIC CRITERIA USING CAPSULE ENDOSCOPY

As with any endoscopic technique, the description of lesions consistent with CD uses a standardized terminology (18): Strictures, ulcers, erosions, aphthae, pseudopolyps, and fistulas (Fig. 1). In the presence of such lesions other conditions must be ruled out (infection, ischemia, vasculitis, iatrogenesis, tumors, lymphoma, and Behçet’s
disease, among others). Other lesions such as denudation, erythema or petechiae are considered nonspecific. Most studies have used the diagnostic criterion defined by Mow et al. (19) in 2004: Presence of diffuse or multiple –more than three– ulcerations in the absence of antiinflammatory drug ingestion. This criterion confers a sensitivity (S) of 77 %, a specificity (Sp) of 89 %, a positive predictive value (PPV) of 55 %, and a negative predictive value (NPV) of 96 % for clinical, endoscopic, radiographic, and histological findings, hence it is highly relevant for disease exclusion.

Similarly, albeit with a lower specificity, the presence of multiple aphthous or erosive lesions (> 10 similar to those shown in figure 2), either with continuous or segment-like distribution, has also been described as a diagnostic criterion for CD by other authors (20). In 2008, Gal et al. (21) reported on the capsule endoscopy-related CD activity index (Niv score or CECDAI), which defines ulcer size,
extension, and strictures in the proximal and distal segments of the SB, and has been prospectively validated of late (22) (Table I). As is the case with colonoscopy, SB activity shows no clinical correlation. Thus, in a symptomatic patient, CE will detect lesions on half occasions (23,24) and, vice versa, CE will identify lesions in 62% of patients in clinical remission (CDAI < 150) (25).

CE INDICATIONS IN CROHN’S DISEASE

The role of capsule endoscopy in CD varies depending on suspicion earliness and on disease extension, activity and distribution (26,27).

- **Suspected Crohn’s disease.** CD suspicion is based on the occurrence of symptoms whether associated or otherwise with compatible extraintestinal manifestations, laboratory abnormalities, and/or radiographic findings (7). In such cases an ileocolonoscopy with biopsy taking should be performed, and an assessment of the proximal gastric and/or intestinal extension is advisable regardless of results (5,12,28). Therefore, this is the second most important indication of CE in the adult (17), and the first most important one in children from 10 to 18 years of age (29). Cost-effectiveness is greater when symptoms are accompanied by anemia, thrombocytosis, inflammation markers and/or fecal markers (30-33). Furthermore, this is a first-line technique when endoscopy and radiology results are negative or inconclusive, as it identifies subtle inflammatory changes usually overlooked by radiographic techniques (Fig. 2). Thus, two significant meta-analyses (34,35) show performance to be superior to that of ileocolonoscopy, barium small-bowel follow-through (SBFT), and computed tomography (CT) by 22%, 37%, and 42%, respectively. Interestingly, studies comparing all the techniques used for the diagnosis of CD obtain highly variable results depending on the reference technique considered. Thus, when ileoscopy is the reference test CE show a value superior to that of computed tomography enterography (CTE) or magnetic resonance enterography (MRE) (36). In contrast, when enteroscopy plus expert clinical assessment is the reference test chosen, MRE is slightly superior to CE (37).

- **Indeterminate colitis.** Population-based studies have shown that in 4-10% of patients with IBD and colonic involvement alone CD differentiation from ulcerative colitis is challenging. This condition is designated indeterminate colitis (IC) or IBD unclassified (IBDU) (38-40). In such cases CE may identify distal ileal lesions consistent with CD in 17-70% of patients (40), with performance being superior to that of SBFT or enteroscopy. No data comparing CTE or MRE are available. Furthermore, when CE is normal, a future diagnosis (12) may not be excluded and a repeat CE may be recommended in the mid-term (8).

**Table I. Capsule endoscopy Crohn’s disease activity index (CECDAI) (22)**

<table>
<thead>
<tr>
<th>1. Inflammation score:</th>
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<tbody>
<tr>
<td>0: None</td>
</tr>
<tr>
<td>1: Mild to moderate edema/hyperemia/denudation</td>
</tr>
<tr>
<td>2: Severe edema/hyperemia/denudation</td>
</tr>
<tr>
<td>3: Bleeding, exudate, aphtha, erosion, small ulcer (&lt; 0.5 cm)</td>
</tr>
<tr>
<td>4: Moderate ulcer (0.5-2 cm), pseudopolyp</td>
</tr>
<tr>
<td>5: Large ulcer (&gt; 2 cm)</td>
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<th>2. Disease extension score:</th>
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<tbody>
<tr>
<td>0: No disease - normal exploration</td>
</tr>
<tr>
<td>1: Focal disease (single segment involvement)</td>
</tr>
<tr>
<td>2: Patchy disease (2-3 segments involved)</td>
</tr>
<tr>
<td>3: Diffuse disease (&gt; 3 segments involved)</td>
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<th>3. Strictureing score:</th>
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<tr>
<td>0: None.</td>
</tr>
<tr>
<td>1: Single – passed</td>
</tr>
<tr>
<td>2: Multiple – passed</td>
</tr>
<tr>
<td>3: Obstructing (not passed)</td>
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Segmentary score (proximal or distal): \[(A \times B) + C\]
Total score: proximal \((A \times B) + C\) + distal \((A \times B) + C\)

- **Established Crohn’s disease.** CE should be mainly considered when a change in disease management is foreseen (6,8,9,28). Furthermore, given its high diagnostic yield for established disease (85.7%), its findings may influence management changes and clinical monitoring in 64% of these patients (41). Therefore, in the presence of symptoms or signs unexplained by a normal or inconclusive result from radiology and/or colonoscopy, CE may detect lesions accounting for manifestations beyond the duodenum and terminal ileum, otherwise inaccessible to conventional endoscopy (12,42). In addition, it may be advisable for unfavorable or normal ileocolonoscopies (28). In these indication, identification of mucosal lesions is superior versus SBFT (78 vs. 32%) and may be better than with CTE (68 vs. 38%) or MRE (93 vs. 79%), but the clinical significance of such differences remains undefined.

Assessment of extension in Crohn’s disease

Following full SB accessibility using CE, SB involvement was seen to potentially coexist with ileal and colonic disease. Because of this, the Vienna classification was replaced by the Montreal classification in 2005, adding the intestinal localization (L4) to the rest of sites when upper digestive tract involvement is detected to the proximal ileum (43). Half of patients with symptomatic ileal and/or colonic CD also have their proximal SB affected, with most common distributions including the proximal ileum (67%) followed by the jejunum (53%) and/
or duodenum (32 %) (23,44). Currently, an assessment of extension all along the GI tract is advisable at initial diagnosis (12,45). Furthermore, very recent studies show that proximal involvement is associated with younger age, nonsmoking status, coexistence of ileal involvement, and stenosing pattern. Specifically, jejunal involvement is associated with stenosing patterns requiring more surgery (46,47). Data are similar for CD with ileal involvement, which progresses towards stenosing and penetrating patterns more often than colonic CD (48). The association of stenosing behavior and jejunal CD may solely be the result of inflammatory response in the intestinal segment with the smallest lumen. In this respect the difference in stenosing complication rates between small-bowel and colonic CD seems logical.

Crohn’s disease in the small bowel

Diagnosing CD only in the SB is truly challenging and the condition may occur in up to one third of patients (49-51). Symptoms are usually nonspecific and, as with colonic involvement, bear little correlation to endoscopic activity. Screening modalities are currently considered supplementary, and their selection will depend upon experience in each individual site (52):

CE may provide early diagnosis for mucosal lesions and suggests the need for other exams (indication, biopsy, therapy, approach). Main benefits include absence of invasivity and radiation, direct study of the mucosa throughout the SB, and assessment of SB activity when ileocolonoscopy is normal. In the presence of stenosis CE is contraindicated. Given the low sensitivity of SBFT for stricture identification, its use is controversial (53). Thus, in most cases of capsule retention in patients with CD radiology was deemed inadequate to raise suspicion on potential stenoses (54). Therefore, when stenosis is suspected, some authors recommend that a biodegradable capsule be previously used to assess potential CE contraindication (as discussed under “Complications”).

Fecal calprotectin (FC) reveals in a noninvasive, direct manner activity or recurrence, and drives the need for other tests. It is well correlated to CE results, with S = 83 %, Sp = 100 %, PPV = 100 %, and NPV = 80 % (24). Therefore, in patients with clinically suspected CD and a normal ileocolonoscopy, an FC value around 200 µg/g is associated with a high diagnostic yield by CE (65 %) (55).

CTE and MrE assess the progression of transmural damage and complications (transmural extension, abscesses, fistulas, stenoses, and collections), hence they are used prior to CE when such lesions need to be identified (8). Mucosal lesion detection using radiographic techniques is limited (56), although some series comparing MRE and CE find similar sensitivities (75 % vs. 77.8 %, respectively) (57).

Assessing activity and severity

CE allows to assess the whole SB and is activity. It is carried out for anemia, thrombocytosis, weight loss, and fecal inflammatory markers not justified by ileocolonoscopy or radiography findings (26,28). Lesion severity is objectively assessed using reproducible scoring systems such as CECDAI (22) or Lewis score (58). CECDAI has no specific threshold but increased values indicate increased mucosal inflammation severity. Lewis score, in turn, assesses villous edema, ulcers, and strictures (Table II), with PPV = 82.6 %, NPV = 87.9 %, S = 82.6 %, and Sp = 87.9 % for the diagnosis of CD versus clinical, laboratory, radiographic, endoscopic, and histological assessment (59). Both scores are well correlated, with CECDAI levels of 3.8 and 5.8 corresponding to a Lewis score threshold of 135 and 790, respectively, the first values indicating mild activity and the second ones moderate-to-severe activity (60). Recently, other authors have identified a higher threshold of 23.5 in CECDAI for severe inflammation, which may be more useful for driving clinical management (61). These scores were initially developed to standardize capsule reports, but their use as a clinical tool needs prospective validation studies to assess CE-related lesion categorization systems (12). Hence, noninvasive studies such as radiology, FC, and CE must be considered supplementary (52).

Overall, the more suspicion criteria are available (clinical, laboratory, radiographic, endoscopic), the more likely will consistent lesions be found with CE. Thus, with 1 suspicion criterion CE reveals mild activity and diagnosis is confirmed in 20 % of cases; however, with 3 suspicion criteria activity will be severe and diagnosis will be confirmed in around 80 % of cases (59). Among healthy patients (no NSAID intake, intestinal resection, ankylosing spondylitis or digestive symptoms), only 9 % may have
mucosal lesions similar to those of CD; however, in all of them the Lewis score would suggest mild activity (62). These scores have shown a good correlation with FC, in such a way that LS is normal when FC ≤ 100 µg/g (60). Therefore, when CD is suspected and endoscopy is normal, FC > 100 mcg/g indicates CE (55), since FC elevation is similar for SB and colon inflammation (63).

**Assessing post-surgical recurrence**

Currently, the reference technique for this indication is ileoscopy using the Rutgeerts score (64). CE may identify proximal lesions out of ileoscopy’s reach (28,45,65), which may be classified using Buchmann’s activity index (66). The management of recurrence (endoscopic follow-up and treatment) is determined by risk factors, among which extension in the SB stands out (67). It is recommended at 6 months or 1 year after surgery according to other associated risk factors (68). While the clinical relevance of findings has not been studied, CE has a sensitivity of 62-76 % and specificity of 100 % as compared to ileoscopy (8). It is indicated when endoscopy is contraindicated or unsatisfactory (28), and represents the test of choice for difficult-to-access anastomoses and to suit patient preferences (8).

**Mucosal healing**

Achieving deep remission (clinical, biological, mucosal healing) (3) improves prognosis in this disease. Mucosal healing is the initial event of suppressing inflammation in the deeper layers of the intestinal wall (69). Specifically, mucosal healing in the SN has been scarcely studied because of a lack of adequate research tools. The use of CE for (non-fistulizing or penetrating) CD has shown ulcer improvement at 1 month after treatment (70). As is the case with colonic lesions, such healing does not correlate with clinical manifestations (71).

**Perianal disease**

Among patients with perianal disease who have a normal ileocolonoscopy, CE detects SB involvement in 24 % of cases, prompting a change in management for them all. A positive CE is not associated with laboratory abnormalities, IBD family history, or age (72).

**Differential diagnosis with other intestinal conditions**

Other CE indications include intestinal tumor suspicion—as the relative risk for tumors is higher in IBD versus the general population (73,74)—and malabsorption syndromes such as celiac disease and its complications (17). In uncertain celiac disease cases (negative antibodies and atrophy in the duodenal biopsy) CE has revealed lesions consistent with CD in 6 % of patients (75).

**IMPA CT OF CAPSULE ENDOSCOPY ON CROHN’S DISEASE**

Treatment changes brought about by CE include onset of a new therapy, medication changes or withdrawal, and surgery indication (41,76,77). At a practical level this impact on CD management will depend on the reason why CE was indicated. Overall, CE performance for the diagnosis of CD in current publications is 60-85 % (41,78). Similarly, CE results will result in changed decision-making for 90 % of patients when ordered for suspected CD, for 88 % of indeterminate colitis cases, and in 73 % of subjects with known CD.

This impact is particularly relevant at pediatric ages since CE reclassifies as CD 50 % of ulcerative colitis and IC cases, detects proximal lesions unnoticed by other techniques in 50 % of subjects, and changes therapeutic decisions for 78 % of patients (76).

Regarding established CD, therapeutic management will be modified in 64 % of patients (41). In studies with over 900 patients with CD (77), 61.6 % had their medication changed within 3 months following CE, and 39.5 % received a new treatment. Disease findings by CE, versus no or minimal findings, resulted in significant differences regarding therapy changes (73.2 % vs. 51.1 %, p = 0.04), added medications (58.5 % vs. 22.2 %, p < 0.01), and surgery indication (21.9 % vs. 4.4 %, p = 0.01). On the other hand, these patients had their therapies changed (in the above percentages) when CE was indicated for anemia (60 %) and when disease extension needs to be assessed throughout the SB (58 %). However, when CE is ordered for discrepancies between clinical status and other (endoscopic, radiographic) testing, our attitude will only change for 20 % of cases (27,78).

**COMPLICATIONS**

The most relevant complication of CE, virtually the only one, is capsule retention, which is rare in this disease—the whole SB can be examined in 85.4 % (79-90.8 %) of patients (79). In patients with suspected CD the risk for retention is comparable to that of other indications, including occult bleeding (1.6 %); in subjects with established CD it is slightly higher (1.8-13 %), particularly in the presence of known intestinal strictures. Should intestinal stricturing be suspected, CE must be preceded by an intestinal patency test with the Patency biodegradable capsule (PC) (Given Imaging, Yoqneam, Israel), approved to this end by the FDA in 2006, or using radiology, according to local availability and site...
monitoring expulsion and medical or endoscopic treatment in the absence of complete obstruction, with surgery being indicated for the latter. Medical therapy includes laxative or steroid administration depending on retention etiology. Enteroscopy will be indicated for capsule recovery, stricture biopsy taking, and stricture dilation.

**CONCLUSIONS**

In summary, CE is a noninvasive technique with a widespread role in CD. Its main utility is well defined in the early diagnosis of mucosal lesions when this disease is suspected, to assess disease extension, and in the study of indeterminate colitis, particularly when management changes are involved. Endoscopic scoring systems exist that indicate disease activity in the SB, although their use should be extended in future prospective studies to define activity and mucosal healing criteria that might represent therapeutic guidelines. As with other diagnostic studies and current therapies, the role of all these CE applications in the modification of the natural history of this disease remains to be established.

**REFERENCES**


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