Wireless capsule in Inflammatory Bowel Disease

Apports de la vidéocapsule endoscopique dans les maladies inflammatoires chroniques intestinales

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Summary
Capsule endoscopy (CE) is a safe, non-invasive diagnostic tool to evaluate small bowel lesions. CE, like conventional endoscopy, can detect focal and small-ulcerated lesions along the entire length of the small bowel, which are not identified by other imaging techniques. Meta-analysis has shown that CE is better than any other radiological technique to detect small bowel lesions in patients with suspected or known Crohn’s disease (CD). In unclassified colitis, CE is also useful in distinguishing CD and ulcerative colitis (UC). In established CD, CE may be used to detect post-operative recurrence, determine the extent of small bowel lesions and link ulcerated lesions with clinical symptoms. Although CE is well tolerated there is a theoretical risk of capsule impaction in general and in CD in particular. To avoid capsule impaction, a new option called the “patency capsule” is available especially in patients with symptoms suggesting small bowel obstruction. However, few data are available about this new device and its use in clinical practice needs to be clarified.

Résumé
L’exploration par vidéocapsule endoscopique (VCE) est un outil diagnostique non invasif, sûr, permettant de rechercher des lésions de l’intestin grêle. L’examen par VCE peut détecter des lésions ulcérées de petite taille et de localisation focale, que les techniques d’exploration conventionnelles ne mettent pas en évidence, tout le long de l’intestin grêle. Plusieurs méta-analyses ont montré que la VCE supérieure aux techniques radiologiques pour détecter des lésions de l’intestin grêle dans la maladie de Crohn. Dans les colites indéterminées, l’examen par VCE est également souvent utile pour distinguer maladie de Crohn et rectocolite hémorragique. Dans la maladie de Crohn connue, la VCE est un outil qui permet de rechercher une récidive endoscopique postopératoire, de déterminer l’extension de la maladie sur l’intestin grêle, et de relier des symptômes

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Crohn’s disease (CD) is a chronic inflammatory bowel disease that can involve any segment of the gastrointestinal tract. Ileocolonoscopy is considered the “gold standard” for detection of ulcerated lesions. Unfortunately, ileocolonoscopy is an invasive procedure and only a limited distal part of the small bowel can be explored. Despite many advances in conventional endoscopy, small bowel assessment remains a challenge because of its length. Except in tertiary centers, where push-enteroscopy or double-balloon enteroscopy is used, small bowel lesions are detected by radiological techniques i.e. small bowel follow-through, computerized tomography (CT) and magnetic resonance imaging (MRI).

Recently, a wireless capsule endoscope (CE) has been developed and is now available in routine practice. The CE has the following advantages over traditional endoscopic procedures: a) full-length visualization of the small bowel including the neoterminal ileum, b) ability to detect small lesions, c) no sedation or anesthesia required, d) well tolerated by patients. The superiority of this technique compared to traditional endoscopic or radiological procedures has been demonstrated in various situations. The PillCam SB (Given Imaging, Yoqneam, Israel) CE was approved by the Food and Drug Administration in 2001 for use in adults and children 10 years or older to evaluate undiagnosed gastrointestinal bleeding and suspected CD.

The disposable capsule is swallowed and passes naturally through the gastrointestinal tract. It is 11 mm in diameter x 26 mm long. Imaging features include a 140° field of view and images at a frequency of 2 frames per second for 7 hours until the battery expires. Images are transmitted to a data recorder via radio frequency and after the procedure, images are downloaded to a customized PC workstation with specialised software for review and interpretation by a gastroenterologist trained in capsule endoscopy.

Although classic bowel preparation includes administering 1 to 2 liters of polyethylene glycol (PEG) solution before the procedure [1], no studies have clearly demonstrated that bowel cleansing has a major impact on the quality of images. Swallowing is possible in almost all cases; in difficult cases, the capsule can be placed endoscopically in the duodenum [2] or ingested with an overtube [3] in particular in small children.

The indications and contraindications of CE in IBD are reported in Table 1. They are similar for children and adults. In the most cases, CE is safe and well tolerated.

A pacemaker is not a contraindication because there is no interference between CE and the radiofrequency of pacemaker [4, 5].

Gastroparesia could be a limiting factor because the CE could stagnate in the stomach for several hours. To limit gastric transit time metoclopramid and erythromycin have been tested: metoclopramid decreased gastric transit time and increased the likelihood of successful examination [6], while the efficacy of erythromycin was controversial [7].

For ethical reason, no studies have evaluated the risk of CE in pregnancy. Thus pregnancy should be considered a relative contra-indication for CE.

The presence of an intestinal stricture is a contraindication for conventional capsule endoscopy because of the risk of impaction. The rate of capsule retention varies widely in the literature, from 0% to 13%, and appears to be dependent on the indication for this examination. Studies have shown higher impaction rates in patients with established than suspected Crohn’s disease [8]. In trials evaluating patients with suspected Crohn’s disease, one capsule was retained in a total of 71 patients (1.4%) [9-12] whereas Mow et al. reported an incidence of 4% in patients with established CD. However, most CE studies in CD patients excluded patients at risk of bowel strictures so the real incidence of capsule impaction is unknown. To avoid capsule impaction, certain specialists have recommended systematic enteroclysis or CT scan prior to CE. But another option includes the use of a “patency capsule”, especially in patients with symptoms suggesting small bowel obstruction [13]. The patency agile is the same size as the CE, with a body of lactose and barium, it is biodegradable and covers a small radiofrequency identification (RFID) tag. The capsule disintegrates into small fragments after 40 hours and is completely dissolved after 80-100 hours. If the intact capsule is excreted intact, if the scanner does not detect the RFID tag or if the capsule is undetectable on an abdominal X-ray after 30-40 hours, then CE can be done safely.

Table 1 Indications and contraindications of capsule endoscopy in IBD.

<table>
<thead>
<tr>
<th>Indications and contraindications of capsule endoscopy in IBD.</th>
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<tbody>
<tr>
<td>Indications</td>
</tr>
<tr>
<td>Suspected Crohn’s disease (with normal upper and lower endoscopy)</td>
</tr>
<tr>
<td>Iron deficiency with chronic anemia in Crohn’s disease patients</td>
</tr>
<tr>
<td>Inflammatory bowel disease unclassified type evaluation</td>
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<td>Evaluation of small bowel lesions</td>
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<td>Persistence of atypical symptoms despite treatment</td>
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Finally in case of capsule retention, surgery for extraction is not always necessary, because the capsule can be extracted by endoscopy after dilatation.

**CE Findings in Crohn’s Disease**

Mucosal lesions observed during CD with CE were described by different authors with no standardisation. It should be noted that many lesions described in studies of suspected CD were not specific and could explain the variability of the diagnostic results of CE. Indeed, CE may reveal small alterations such as lymphangiectasia, villous denudation or nodular lymphoid hyperplasia. Although these lesions are not specific, they were considered early manifestations of CD in some series and not in others. For instance, mucosal breaks were frequently described in CD, but up to 23% of normal asymptomatic individuals may also have mucosal breaks detected by CE [14]. Moreover, non steroid anti-inflammatory drugs (NSAIDs) have been shown to induce small bowel lesions similar to lesions in CD patients [14]. Therefore, the high sensitivity of CE has revealed unknown and unspecific small bowel injuries. The diagnostic criteria of CD need to be established based on CE findings in the near future to discriminate between specific and non-specific lesions.

CE can reveal typical lesions such as aphthae, fissural ulcers, crater-like ulcers and fistulas (Figure 1). These lesions are usually discontinuous with large segments of normal mucosa surrounding altered mucosa. Although they seem to be more specific for CD the severity cannot be assessed without a prospective and validated index of severity, such as the Crohn’s Disease Index of Severity (CDEIS) for ileo-colonoscopy.

Another difficulty for CE is to localize the capsule, and thus the small bowel lesions in the gut. This depends on small bowel motility, the progression of CE through the gastrointestinal tract and any stagnation. Because there is no physical separation between the jejunum and the ileum, the small bowel is divided into two equal parts in time between the first image of the duodenum and the first image of the colon, the first segment corresponding to the jejunum and the second to the ileum.

**Comparison of CE with Radiological and Endoscopic Methods in IBD**

Diagnosis of IBD can be quite difficult when inflammation is mild and located in the small bowel. There is no gold standard and the gastroenterologist must consider the patient’s clinical symptoms, history and digestive lesions. In most cases, radiological and endoscopic imaging is necessary to confirm the diagnosis. Current techniques to explore the small bowel include conventional endoscopy and radiological techniques such as barium small-bowel follow-through (SBFT), computed tomographic (CT) enterography, small-bowel magnetic resonance imaging (MRI). Conventional endoscopy is limited to the proximal small bowel or the distal terminal ileum, which cannot always be seen because the caecum cannot be reached or the ileum cannot be intubated during colonoscopy. Barium small-bowel follow-through (SBFT) may lack precision and sensitivity, notably in mild disease.

CE, CT and MRI provide complete small-bowel evaluation. Initial retrospective studies compared, CE to different radiological techniques in suspected CD patients with negative conventional endoscopic results. The patients were included in these studies for many reasons including chronic pain or diarrhoea, anaemia or elevated biological markers of inflammation. In most studies, even if CE was compared to SBFT, patients with stenosis detected by initial SBFT were excluded [9, 11,15-19]. The definite diagnosis of CD was based on CE findings which were obviously limited by the lack of validated diagnostic score. Despite these biases, the data suggest that CE is better than all these techniques to detect CD in the small bowel.

Recently, a meta-analysis by Triester et al. [20] performed a literature search of prospective and comparative studies.

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**Figure 1** Capsule endoscopy findings in Crohn’s disease. A-erythema, B-denudation, C-erosion, D-ulceration, E-aspect of nodular lymphoid hyperplasia, F-small aphtous ulceration.

Comparing the results of CE to other modalities in patients with suspected or established CD (Table 2 and 3).

### Table 2 Diagnostic yield of capsule endoscopy (CE) and barium small-bowel follow-through (SBFT) in Crohn’s disease (CD) [9, 11, 15, 16, 19, 21, 22, 25, 29].

<table>
<thead>
<tr>
<th>n</th>
<th>Indication</th>
<th>CE (%)</th>
<th>SBFT (%)</th>
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<tbody>
<tr>
<td></td>
<td>Suspected CD</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fireman et al., 2003</td>
<td>71</td>
<td>0</td>
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<td></td>
<td>17</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Herrera et al, 2003</td>
<td>43</td>
<td>0</td>
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<tr>
<td></td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eliakim et al., 2004</td>
<td>77</td>
<td>23</td>
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<tr>
<td></td>
<td>35</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ge et al., 2004</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Arguelles-Arias et al., 2004</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albert et al., 2005</td>
<td>92</td>
<td>28</td>
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<td></td>
<td>25</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Chong et al., 2005</td>
<td>93</td>
<td>59</td>
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<td></td>
<td>27</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dubcenco et al., 2005</td>
<td>67</td>
<td>20</td>
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<td></td>
<td>39</td>
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</tbody>
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### Table 3 Diagnostic yield of capsule endoscopy (CE), computed tomography (CT) and magnetic resonance imaging (MRI) in Crohn’s disease (CD) [10, 17, 22-25].

<table>
<thead>
<tr>
<th>n</th>
<th>Indication</th>
<th>Diagnosis by CE (%)</th>
<th>Diagnosis by CT/MRI (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Suspected CD</td>
<td>70</td>
<td>35/ND</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eliakim et al., 2004</td>
<td>77</td>
<td>26/ND</td>
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<td></td>
<td>35</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Golder et al, 2005</td>
<td>72</td>
<td>ND/50</td>
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<tr>
<td></td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albert et al., 2005</td>
<td>92</td>
<td>ND/77</td>
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<td>25</td>
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<td></td>
<td>27</td>
<td>93</td>
<td>ND/81</td>
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<tr>
<td></td>
<td>Hara et al., 2006</td>
<td>50</td>
<td>38/ND</td>
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<td></td>
<td>8</td>
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<td></td>
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<tr>
<td></td>
<td>Volderholzer et al., 2005</td>
<td>89</td>
<td>67/ND</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>89</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Small bowel ileum 61</td>
<td>29/ND</td>
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<td></td>
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<td>43</td>
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</table>

Studies comparing CE and barium radiography in patients with suspected or established CD (9 studies, 250 patients) confirm that CE is more effective. The diagnostic results of CE versus barium radiography in all patients was 64% and 24%, respectively (P=0.001). In patients with suspected CD, diagnostic results with CE were 43% compared to 13% for barium radiography (P=0.09) and in patients evaluated for recurrent CD, diagnostic results with CE were 78% compared to 32% for barium radiography (P=0.001). However, interpretation of these results is difficult for the reasons described above. Barium radiography was performed before CE and patients with a stricture (with or without symptoms) were excluded from the study. Clinical and biochemical data before patient inclusion were heterogeneous from one study to the other and finally, diagnosis of CD with CE depended on the authors.

Three studies (n = 93) have compared CE with CT enterography or CT enteroclysis. These techniques are more useful than SBFT because the intestinal wall is evaluated and extraintestinal abnormalities such as, fistulas, abscesses or fat wrapping can be detected. Diagnostic accuracy with CE was 69% versus 30% for CT (P=0.001). Two of the three studies included patients with suspected CD (n = 43) and two included patients with established CD (n = 50). In patients with suspected CD, results with CE were 70% compared to 21% with CT enterography/enteroclysis (P=0.07). In patients with established CD, CE was significantly more effective 68% compared to 38% for CT (P=0.001).

One trial [24] compared CE to small bowel MRI in a small number of patients and there was no significant difference between the two methods (18 patients, P=0.16). In another study, CE was compared to MRI enterography in 27 patients with established CD and 25 with suspected CD. Results for diagnosis with CE and MRI were 93% and 79% respectively in the group with established CD. In the group with suspected CD, CE was more sensitive than MRI (92% versus 77% respectively) and more specific (100% versus 80% respectively) [25].

Four trials have compared CE to colonoscopy with ileoscopy (n=114) in the diagnosis of CD. Results of CE versus ileoscopy in all patients was 61% and 46%, respectively (P=0.02).

Two trials have compared CE to push enteroscopy in patients with suspected and established CD (84 patients, 46% versus 8%, P<0.001).

Recently, the Mayo Clinic has updated this meta-analysis by adding 5 additional studies [26]. Whatever the group evaluated (established or suspected CD) CE was found to be significantly more effective than other modalities (SBFT, CT, MRI, ileocolonoscopy, push enteroscopy).

In summary, in CD patients, CE is more effective and can be recommended as a first line diagnostic test compared to small bowel barium radiography, CT enterography, colonoscopy with ileoscopy, and push enteroscopy for small bowel CD without strictures. However, the diagnostic results of CE are also highly dependent upon the initial screening and therefore the symptoms described by the patients. In a recent consensus statement [27], the authors have recommended that before performing CE, patients should have at least two of the following symptoms: a family history of IBD, chronic abdominal pain, weight loss, extra-digestive symptoms of CD, peri-
neal disease, iron deficiency anemia or elevated markers of inflammation (Figure 2).

The impact of CE on therapeutical management needs to be determined. In the presence of lesions suggesting CD a change in management strategy was estimated to have occurred in 57% to 100% of patients depending on the study [9, 18, 28, 29]. However, no criteria for modification was determined previously according to the findings.

Finally, with diagnostic results of 64% or more, Goldfarb et al. has performed a cost-analysis suggesting that CE may be less expensive than first-line test compared to conventional radiological techniques in suspected CD patients [30].

**Role of CE in Inflammatory Bowel Disease**

**Inflammatory bowel disease of unclassified type**

The term “Inflammatory Bowel Disease of Unclassified type” (IBDU) is used when a diagnosis of ulcerative colitis or Crohn’s disease with pure colonic involvement cannot be confirmed at colonoscopy, or after colectomy [31]. A definite diagnosis of CD or UC is obtained in about 50% of patients during follow-up. However, it is important to classify IBD since the natural history, and the outcome after surgical resection is different. CE could play an important diagnostic role in the evaluation of patients with inflammatory bowel disease of unclassified type.

**Recurrence after surgery**

Despite the removal of all macroscopic lesions after ileocolonic resection, the disease typically recurs at the site of resection and extends to the neoterminal ileum in the same pattern as initially. Before clinical relapse, early features of endoscopic recurrence in the neoterminal ileum have been reported in 73 to 93% at one year post-surgery [35, 36]. Moreover, the severity of endoscopic lesions detected within the first year after surgery is the best predictor of the postoperative course of the disease. Even if the clinical importance of early endoscopic recurrence has not been evaluated in prospective controlled studies, it has been suggested that postoperative endoscopic examination of the neoterminal ileum 6 months after surgery may help determine the therapeutic management of CD patients after surgery. As a result of better diagnostic results and the detection of small lesions, CE may detect early recurrence and thus identify patients at a higher risk of symptomatic relapse. Two studies have reported the results of CE in detecting recurrence in CD patients after surgery. These studies evaluated the proportion of recurrence in these patients and compared CE and colonoscopy in this indication.
Bourreille et al. [37] (31 patients prospectively included) evaluated recurrence of CD 6 months after. Recurrence, defined by a Rutgeert’s score ≥ i2 [36], occurred in 21 patients (68%) and was detected by ileocolonoscopy in 19. The sensitivity (Se) was 90% and specificity (Sp) 100%. The Se of CE was 62% (lower estimate) and 76% (upper estimate) and the Sp was 100% and 90% respectively. There was a correlation between the severity of the lesions measured by both methods (p=0.05). The following values were obtained using a cut-off value of i2 for the definition of endoscopic recurrence: 14 patients (45%) had recurrence in the distal ileum. The Se and the Sp of ileocolonoscopy was 86% and 100%. The sensitivity of WCE was 50% (lower estimate) and 79% (upper estimate). Corresponding specificity was 100% and 94%.

Twenty-four patients with CD who had undergone ileocolonic anastomosis 6 to 12 months before were prospectively included in another study [38]. All patients were asymptomatic and were not taking any postoperative maintenance therapy. Recurrence (Rutgeert’s score ≥ i2) was visualized with ileo-colonoscopy in 25% of patients and 62% with CE. Moreover, CE detected proximal involvement in 13 patients. The authors concluded that CE was more effective than colonoscopy. However, as mentioned by Katz [39], the high rate of recurrence assessed by a Rutgeert’s score ≥ i2, seen by CE suggests that CE overestimates the lesions in the neo-terminal ileum. On the other hand, despite the correlation between lesions seen by CE and ileo-colonoscopy in the study by Bourreille et al., CE tended to underestimate the severity of recurrence. In summary, CE can detect lesions in the neo-terminal ileum after surgical resection. Although the Rutgeert’s score has been adapted to ileo-colonoscopy, it may not be adapted to CE. However, these two studies suggest that a new endoscopic score suitable for CE may be needed.

Pediatric applications

Data are limited on the use of CE in the diagnosis of IBD in children. Three studies have evaluated the efficacy of CE in suspected CD [12, 19, 40]. Arguelles-Arias et al. assessed the efficacy of CE in 12 patients from 12 to 16 years old. Lesions suggesting CD were identified by CE in 7 of the 12 patients (58%). In another prospective study [12] lesions suggesting CD were only found by CE in 10 of 20 patients with suspected CD (50%). The study by Antao included 18 patients and found lesions suggesting CD in 13 (72%). Finally an abstract published in 2007 reported the impact of CE on the diagnosis and management of pediatric inflammatory bowel disease (18 children) [41]. CE was useful for diagnosis in 83% of cases and for disease management in 75%.

Thus, CE is a safe and non-invasive tool for investigation of the small intestine in children, which can be routinely integrated as part of the diagnostic work-up of small bowel disease.

Conclusion

CE is clearly a suitable diagnostic tool for exploring the small intestine, especially in patients with CD and IBD. Many retrospective and prospective studies had shown that CE is more effective than other radiological and endoscopic techniques to diagnose suspected CD and evaluate the extent of lesions in the small intestine. Moreover, in the near future CE could become a standard technique to evaluate post-operative recurrence of CD and is already used in IBDU. Clearly, the risk of impaction of CE in an intestinal stricture remains limitation of this technique in known CD patients. Conventional radiological studies are not sensitive enough to detect all strictures and CE should not be performed in patients with clinical symptoms of intestinal obstruction. The use of the patency capsule before conventional CE can detect strictures and its systematic use is under investigation in CD patients. The other limitations of CE are the absence of a diagnostic score and severity index of small bowel lesions, but studies are ongoing in part by the GETAID group.

Conflict of interest:

Mathurin Flamand, Caroline Trang and Arnaud Bourreille have no conflict of interest.

References

Capsule endoscopy in IBD


