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The why, when and how of small bowel and panenteric capsule endoscopy in Crohn's disease

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Abstract

Small bowel capsule endoscopy (SBCE) is a tool used for Crohn's disease (CD) diagnosis and monitorization, which aids in appropriate clinical decision-making, especially in the switch of treatment or withdrawal and influencing reclassification of unclassified inflammatory bowel disease. Compared to cross-sectional imaging, namely intestinal ultrasound and magnetic resonance enterography, SBCE has a superior diagnostic yield in proximal small bowel inflammatory activity, which has been associated with greater morbidity. The risk of capsule retention is higher in patients with established CD with suspected stenosis and those with suspected CD with obstructive symptoms, known stenosis or previous small bowel resection. In these situations, SBCE should be administered only after small bowel patency has been evaluated. There is evidence that the pan-enteric capsule (PEC) has a higher diagnostic yield than ileocolonoscopy in detecting terminal ileum mucosal defects. Future research should evaluate the PEC place in CD algorithms as it offers a non-invasive approach, which is especially important in a long-term follow-up, likely diminishing the disease burden.

Keywords: Crohn's disease, small bowel capsule endoscopy, pan-enteric capsule, Patency capsule

INTRODUCTION

The diagnosis of Crohn's disease (CD) can often be challenging due to the absence of a single reference standard. As a result, physicians are compelled to integrate the patient's clinical manifestations with their laboratory, imaging and histological data. CD is a pan-enteric, chronic inflammatory disease, with up to



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80% of patients exhibiting small bowel (SB) involvement. Therefore, the visualization of the small intestine can be considered an obligatory exploration^[1].

The most frequently used techniques to explore the small intestine in patients with CD are small bowel capsule endoscopy (SBCE), small bowel ultrasound (IUS) and MR enterography (MRE). These techniques have similar diagnostic yields except for proximal SB involvement, where SBCE has proven to be superior^[2,3]. Furthermore, proximal SB CD has been associated with poorer outcomes, highlighting the importance of an early diagnosis and selecting an appropriate initial treatment approach^[4].

ROLE OF SMALL BOWEL CAPSULE ENDOSCOPY IN SUSPECTED CROHN'S DISEASE

WHY? The typical endoscopic findings in CD are inflammatory lesions with a discontinuous distribution, strictures, fistulae, and perianal disease. Furthermore, it has been described that detecting at least three ulcers in SBCE highly suggests CD, provided the patient has not recently used non-steroidal anti-inflammatory drugs^[2]. Among the benefits of SBCE, its ability to detect SB mucosal defects, assess disease activity and location and translate these findings into indexes like the Lewis Score and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) are noteworthy. The use of indexes is highly recommended to help categorize the disease, monitor activity and aid in treatment selection^[1,5]. SB inflammatory activity was evaluated using the Lewis score in a small series of patients with unclassified inflammatory bowel disease (IBD-U). SBCE influenced reclassification to CD in approximately 25% of cases and after a mean follow-up of 42 months, only 28% of patients remained with IBD-U^[6].

Kopylov *et al.* conducted a meta-analysis of 13 studies comparing the diagnostic yield of SBCE to MRE and IUS in detecting SB inflammatory activity. The results suggest that there are no significant differences in the ability of each diagnostic modality to detect SB inflammation in suspected CD^[7].

WHEN? In most cases of suspected CD, positive findings on ileocolonoscopy (IC) help confirm the diagnosis. SBCE aids in establishing a CD diagnosis by describing disease extension and activity. It is also useful when IC is inconclusive and to determine SB involvement other than distal terminal ileum. Samuel *et al.* reported the endoscopic skipping of the distal terminal ileum in more than half of suspected CD patients when evaluated with a SBCE^[1,5,8].

MONITORING CROHN'S DISEASE WITH SMALL BOWEL CAPSULE ENDOSCOPY

WHY? Monitoring patients with established CD aims to achieve early recognition of disease flares, identify endoscopic or transmural response and guide treatment escalation, de-escalation or switch. The preferred treatment outcome is mucosal healing as it has been associated with less overall morbidity^[2,3]. Mucosal healing can be assessed indirectly through cross-sectional imaging and non-invasive fecal and serological markers or by direct mucosal visualization, where capsule endoscopy has a leading role. In a study by Gonzalez-Suarez *et al.*, SBCE showed higher sensitivity for detecting proximal and distal disease (77% vs. 45%) compared to MRE^[9]. Furthermore, the use of SBCE in monitoring established CD has been studied, and according to several studies, capsule findings may lead to a change in Montreal classification and affect management in more than half of the patients^[7,9,10]. Additionally, capsule endoscopy is deemed cost-effective, and can be perceived as more comfortable when compared to MRE, which is especially important for long-term follow-up^[11,12].

WHEN? The current ECCO-ESGAR guidelines suggest that 12 to 24 weeks after treatment initiation is the appropriate timing for mucosal healing reevaluation^[2]. It is also recommended to perform mucosal healing reevaluation when there is suspicion of treatment failure that may require a switch of therapy, when a

relapse is suspected or when new symptoms arise^[2].

NON-INVASIVE DETECTION OF CROHN'S DISEASE POSTOPERATIVE RECURRENCE

WHY? Surgical resection and disease recurrence are common in many CD patients. Recurrence can occur at the anastomosis or in a proximal segment. Within three years after an ileocollectomy, up to 100% of patients may suffer from endoscopic recurrence without treatment, with at least 65% recurrence within the first year, according to Rutgeerts *et al.*^[13]

Although ileocolonoscopy is recommended in the first 12 months after ileocollectomy, CD recurrence in the small bowel can also occur after total proctocolectomy and ileostomy, with a 23.5% 10-year median cumulative rate^[14]. Capsule endoscopy may aid in early detection of endoscopic recurrence as there is a correlation between Rutgeerts score evaluated by ileocolonoscopy and capsule endoscopy findings^[15]. To detect endoscopic recurrence before symptoms arise and improve outcomes through optimized biologic therapy, Shiga *et al.* recommend postoperative repeated SBCE, starting within three months from surgery^[16]. Moreover, SBCE is recommended in the postoperative setting due to its lower morbidity and higher sensitivity, especially in detecting proximal SB activity.

ALTERNATIVES TO CAPSULE ENDOSCOPY

Local expertise and availability should guide study selection in both CD diagnosis and monitoring. Cross-sectional imaging techniques are alternatives to endoscopy for evaluating disease activity and monitoring. Growing evidence suggests MRE and IUS can be used as first-line investigations for diagnosing and monitoring CD^[17]. Since CD monitoring strategies demand repeated evaluation of disease activity, patients may prefer cross-sectional imaging over endoscopy in the long term due to its non-invasiveness^[18].

As previously mentioned, SBCE, MRE and IUS have similar diagnostic yields for detection of SB activity^[2,3,19]. Activity scoring systems are available for both MRE and IUS. MRE activity scores have been demonstrated to have a high correlation with endoscopic indexes like the Rutgeerts score, while few IUS scores have been validated against MRE or endoscopy scores^[17,18].

One advantage of cross-sectional imaging is the ability to evaluate transmural disease. If there is a clinical suspicion of a stricturing component, current guidelines recommend cross-sectional imaging over SBCE. MRE should be the first choice to evaluate transmural disease and its penetrating complications^[1,5,20]. Additionally, cross-sectional imaging is helpful for monitoring. MRE can identify disease activity well by measuring bowel wall thickness and T2 signal and classify therapeutic response into four categories: transmural remission, response, stable or progression. Likewise, IUS offers a rapid, on-site evaluation of treatment response, which can be determined as soon as 4 weeks after treatment initiation in CD^[18]. Moreover, the terminal ileum can have active inflammation confined to intramural portions with an overlying normal mucosa, which would not be detectable by endoscopy. Some studies have concluded that cross-sectional imaging findings predict clinical outcomes and disease progression better. Therefore, transmural response has been proposed as a better therapeutic target than endoscopic healing^[1,17,18,20].

Conversely, MRE performs poorly in early recognition of disease because of the minimal mucosal defect of aphthoid ulcerations^[7]. Hence, SBCE is recommended in patients with a strong suspicion of CD and non-diagnostic radiological tests (IUS and/or MRE) to exclude SB involvement^[2]. There is mounting evidence that performing SBCE in these patients can influence management and prognosis. Therefore, we should work to harmonize the findings and not consider these studies as contenders^[21,22]. SBCE and cross-sectional imaging should be considered complementary explorations in the CD evaluation.

CAPSULE RETENTION RISK

WHY? The use of capsule endoscopy in CD has expanded over the years for its capability of accurately visualizing the entire SB, aiding in detection of disease activity, endoscopic recurrence, treatment response and evaluation of mucosal healing through indexes^[23]. However, its use is hindered by the potential risk of retention, which excludes high-risk patients from the benefits of SBCE. Radiological tests can also be used to exclude stenosis, which would deter SBCE. Both patency capsules and cross-sectional imaging have similar high negative predictive values^[2]. Unlike patency capsules, MRE evaluation does not depend on intestinal motility, eliminating potential false-positive results but overestimating the risk of retention as it has a high sensitivity but a low specificity of around 60%^[1]. Therefore, if SB patency was evaluated only by MRE, fewer SBCE procedures would be performed due to MRE's overestimation of true stenosis^[24].

WHEN? Capsule retention occurs when the capsule remains in the gastrointestinal tract within two weeks after ingestion. Retention is mostly asymptomatic, and the capsule is naturally excreted after two weeks in about 30% of patients. Capsule retention can occur in any SB condition, not limited to CD. A high risk of retention has been associated with small bowel tumors, anastomoses, radiation and NSAID enteropathy. In these scenarios, capsule ingestion may result in perforation or acute obstruction requiring endoscopic retrieval or surgical intervention^[23].

In established CD, reported retention rates are high, ranging from 2% to 13%^[2,25]; Nemeth *et al.* designed a multicenter retrospective study of 406 patients with established CD to evaluate the appropriate utilization strategy of the patency capsule to reduce the risk of capsule retention. The authors compared a selective strategy, which was the use of the patency capsule in patients with high-risk features, with a non-selective strategy, the use of patency capsule in all patients with established CD. The study results concluded that both utilization strategies had similar risk retention (1.3% vs. 1.6%, $P = n.s$), but with a selective strategy, more capsules were performed, leading to an improved diagnostic yield and reduced costs^[24].

In suspected CD without obstructive symptoms, known stenosis or history of small bowel resection, the rate of capsule retention is approximately 1.5%^[5], similar to patients with obscure gastrointestinal bleeding. Therefore, it is not compulsory to evaluate small bowel patency prior to SBCE^[24].

A recent metaanalysis was performed to evaluate retention rates in the adult and pediatric CD, 3.49% in adults and 1.64% in children. The retention risk in adult established CD was 3.4 times higher than in suspected CD. When small bowel patency was evaluated, the retention rate of established CD was reduced to 2.8%^[23]. The retention rates are significantly lower in studies that systematically performed cross-sectional imaging or patency capsules before SBCE. If retention occurs, medical treatment for CD should be started or maintained to allow for spontaneous passing. Depending on the symptoms and localization, one should decide on endoscopic retrieval or surgical consultation^[5,26].

HOW? A patency capsule can be used to confirm intestinal patency, especially if small bowel stenosis is suspected and has not been firmly excluded. A patency capsule indicates a safe SBCE exploration can be done when the passage to the colon of an intact patency capsule has been radiologically confirmed, when it is excreted before 30 h or excreted after 30 h but intact^[5].

USE OF PAN-ENTERIC CAPSULE IN CROHN'S DISEASE

Considering the mouth to anus distribution of CD, it would be reasonable to use a study that allows inspection of the entire digestive tract. Exploring this idea, Leighton *et al.* conducted a feasibility study of the pan-enteric capsule (PEC) (PillCam CROHN'S, Medtronic, Yoqneam, Israel) comparing its diagnostic

yield to ileocolonoscopy. In this study, PEC showed better outcomes (83.3% *vs.* 69.7%) even when only the detection rate of terminal ileum lesions was taken into consideration (70% *vs.* 54%)^[27]. Bruining *et al.* published a multicenter, prospective study including 158 patients evaluating the overall sensitivity of PEC versus ileocolonoscopy plus MRE. They concluded that capsule endoscopy sensitivity had a similar diagnostic yield in the terminal ileum and colon and a better diagnostic yield than MRE for proximal small bowel activity (97% *vs.* 71%)^[28].

Several studies have demonstrated the feasibility of PEC in diagnosing and monitoring CD^[29]. Tai *et al.* studied the feasibility, safety and impact on management that PEC had on 93 patients (71 established and 22 with suspected CD), finding that half of the patients had active disease, 20% had proximal small bowel involvement leading to a change in management, with only a 2.8% capsule retention rate^[30].

Pediatric patients may benefit from using PEC by diminishing the invasiveness and number of procedures needed for diagnosis and monitoring the affected segments. Current guidelines recommend a full evaluation of the gastrointestinal tract at the time of CD diagnosis^[31-33]. Oliva *et al.* evaluated the feasibility of using PEC to evaluate mucosal response to treatment and guide therapeutic modifications compared to other testing modalities in a cohort of 48 pediatric patients with established CD. The overall diagnostic yield of PEC, MRE, and biomarkers were 54%, 37%, and 33%, respectively ($P < 0.05$)^[34]. The Capsule Endoscopy-Crohn's Disease (CE-CD) index and the Eliakim score have been developed to standardize image interpretation, taking into account the findings of the small and large intestines. The CE-CD was determined to be reliable in pediatric patients and correlated well with the Pediatric Crohn's Disease Activity Index (PCDAI) and the Eliakim score with the Lewis score^[35,36].

PEC may potentially reduce the burden of disease by diminishing the number and invasiveness of procedures and improving diagnosis in proximal segments when used in non-stricturing CD.

CONCLUSION

In conclusion, small bowel capsule endoscopy (SBCE) has emerged as a valuable tool for both diagnosing and monitoring Crohn's disease (CD). With a higher diagnostic yield in proximal small bowel compared to cross-sectional imaging, SBCE has the potential to lead to a change in management, ultimately reducing the burden of disease. Additionally, confirmation of small bowel patency through SBCE is essential for patients with obstructive symptoms, known stenosis, or a history of small bowel resection.

Looking to the future, further research is needed to explore the suitability of the pan-enteric capsule (PEC) in CD diagnosis and management. The potential for the PEC to provide a non-invasive and comprehensive approach to a panintestinal disease is an exciting prospect that warrants further investigation. By continuing to refine and innovate these techniques, it is expected to provide patients with more effective and efficient care, while minimizing the impact of this complex and challenging disease.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the review: Bojórquez A, Carretero C

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Not applicable.

Consent for publication

Not applicable.

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