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Updates in the diagnosis and management of small-bowel Crohn's disease

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1. Introduction

Crohn's disease (CD) can affect any part of the GI tract, but small bowel (SB) involvement is present in 80% of patients with CD; 30% have exclusive SB disease [1] presenting a diagnostic challenge due to the inaccessibility of standard endoscopic techniques.

Accurate assessment of treatment response [2] and regular monitoring are crucial to prevent surgery and to identify patients at risk of relapse and/or complications before the onset of clinical symptoms [3]. Ileocolonoscopy (IC) is considered the gold standard for evaluating mucosal healing (MH) in CD, but it is invasive and costly [4] and only allows visualization of the terminal ileum (TI). The CALM study has demonstrated that C-reactive protein (CRP) and faecal calprotectin (FCP) can be effective surrogate markers of MH and help guide treatment [5]. Nonetheless, their efficacy is limited [6] as approximately 30% of patients do not present with elevated CRP levels during relapse [7] and the correlation between FCP and active SB disease is weak [8].

Thus, CD requires a multidisciplinary approach. We aim to provide an overview of recent advances in the diagnosis and management of small bowel CD.

2. Suspected Crohn's disease

2.1. NON-ENDOSCOPIC tools

Although IC has traditionally been considered the gold standard for diagnosing CD [4], it has limitations in detecting SB involvement. Therefore, capsule endoscopy (CE) and non-endoscopic techniques such as computed tomography enterography (CTE), magnetic resonance enterography (MRE) and intestinal ultrasound (IUS) have emerged as valuable techniques and should be considered complementary tools in the diagnostic work-up [9]. CD diagnosis is based on a combination of clinical, biochemical, stool, endoscopic, and histological investigations. For this reason, new ECCO guidelines recommend a biochemical assessment (blood count, CRP, electrolytes, liver enzymes, and a stool sample for microbiological analysis, including *C. difficile* at diagnosis [10].

CRP and FCP are biomarkers of IBD [11]. CRP is non-specific for CD, whereas FCP is helpful for the initial diagnosis of IBD and it also correlates with endoscopic severity, therapeutic effect assessment, and relapse prediction [12]. In addition, CRP is meaningful for assessing acute inflammation [13] and can be easily measured in the blood [11]. Some studies suggest that normal CRP levels make it unlikely to have IBD, with less than 1% of patients with normal CRP levels ultimately receiving a diagnosis of IBD [14]. FCP is predominantly expressed by neutrophils. In individuals with IBD, FCP is thought to indicate granulocyte migration across the intestinal epithelium, which is associated with an inflammatory response [15].

FCP is relevant because of its ability to distinguish between IBD and functional disorders [16] with a sensitivity of 89% and 62% specificity [11]. Furthermore, in patients with chronic diarrhoea, the sensitivity and negative predictive value are 100% for detecting organic disease [17].

The correlation between FCP and endoscopic indices of disease

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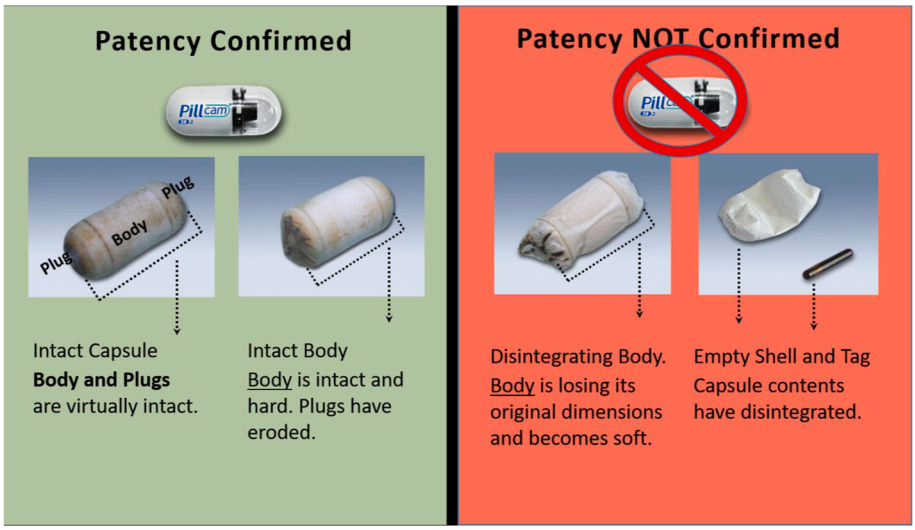

Fig. 1. PC excretion may confirm SB patency.

activity has been established in several studies, however, no precise cut-off value distinguishes between IBD and functional bowel diseases. Nonetheless, a cut-off value of 150 μg/g has been suggested as it may offer good diagnostic accuracy [18].

Serological antibody tests are frequently used to diagnose CD and ulcerative colitis; however, ECCO guidelines do not recommend serological antibody testing for routine diagnosis of IBD [10].

Cross-sectional imaging techniques can assess the full thickness of the bowel wall and detect extra-enteric complications and extra-intestinal disease. For patients with clinical suspicion of CD and normal endoscopy, ECCO guidelines recommend SB exploration with small bowel CE or cross-sectional imaging [10] as IC may fail to detect CD in more than 50% of cases due to the disease can skip the TI or remain confined to the bowel wall and mesentery [19]. Since conventional imaging techniques like IUS and MRE may not entirely rule out SB involvement, individuals with suspected CD and normal radiological results should undergo CE [10]. Moreover, ECCO guidelines also recommend that all newly diagnosed CD patients undergo SB assessment [10].

IUS can provide information on CD's location, extent, and activity while detecting complications such as strictures, abscesses, and fistulas. Its sensitivity is 74%, with a specificity of 98% [20]; which is influenced by disease activity and location in less accessible areas, such as the rectum and upper SB [21].

While MRE and CTE accuracy are similar, the former is preferred as it does not involve radiation exposure [10]. The per-patient sensitivity and specificity of MRE for the diagnosis of CD are 78% (95% CI 67–84%) and 85% (95% CI 76–90%), respectively [22]. However, there are technical considerations that may impact the accuracy, such as bowel distension and the use of a luminal contrast, which can affect the assessment of changes associated with active disease, such as bowel wall thickening and enhancement following MRE contrast administration [22].

The election between IUS and MRE may depend on availability and expertise, as both techniques have a good correlation ($r = 0.63$; $P < 0.005$) [23]. In addition, they have similar diagnostic accuracy for detecting SB CD. The sensitivity is 94% for IUS and 96% for MRE, specificity values are 97% vs 94%, PPV 97% vs 94% and NPV 94% vs 96%, respectively. However, IUS is less accurate than MRE in defining the extent of CD, while the agreement between the two procedures regarding CD location is high ($r = 0.81$). In addition, MRE is better for detecting entero-enteric fistulas than IUS ($r = 0.67$) [24].

2.2. Endoscopic tools

Due to CD SB involvement, suspected CD warrants investigation of the SB, as has been widely documented by international guidelines [25–28].

Over the last two decades, SB CE and deep SB enteroscopy have been integrated into the diagnostic algorithm for CD. CE allows for SB inspection in a safe and well-tolerated manner, while device-assisted enteroscopy (DAE) provides direct visualization of the mucosa and tissue sampling when necessary [25].

Although IC is considered the gold standard, it cannot detect proximal SB lesions and thus explains the role of CE for direct non-invasive inspection of the SB mucosa [10,25]. Recent guidelines agree that CE has an important role in patients with suspected CD and normal IC [10,25,27] as it can determine the diagnosis, disease severity and extension.

Compared to radiological modalities, a meta-analysis reported that CE had shown similar diagnostic yield (DY) to CTE or MRE [29] whereas some studies report CE superiority, especially in the proximal SB [30,31]. Furthermore, compared to enteroscopy, a meta-analysis has reported similar pooled DY for inflammatory findings (18% and 16%) for CE and double-balloon enteroscopy (DBE), respectively [32].

According to ECCO-ESGAR guidelines, the diagnosis of CD can be supported when three or more SB ulcers are identified at CE in the absence of non-steroidal anti-inflammatory drug use (>30 days) [10]. The combination of the "red-flag" questionnaire from The International Organization for Inflammatory Bowel Disease (IO-IBD) with elevated levels of FCP can identify patients with a high probability of CD [25]. FCP levels below 50 μg/g have been suggested as a negative predictive factor for CE findings [33] while a cut-off level of 95–100 μg/g seems a more accurate screening tool to select patients that should undergo CE [34,35]. Nevertheless, the correlation between diagnostic tools and CE findings remains inconclusive [36].

While SB CE has one camera recording 2–4 frames/second, novel models dedicated to CD patients, have been developed with two cameras (PillCam Crohn's -PCC-). This new capsule has a wider angle of view and adaptive frame rate (4–35 frames/second) to ensure adequate SB visualization regardless of bowel movement, increasing the detection of SB pathology without compromising the procedure's safety and tolerability [37] and allows complete evaluation of both SB and colon [38]. PCC can provide monitoring of CD activity in established CD patients and guide management [39] while for patients with suspected CD, PCC and IC findings have similar ileocolonic disease activity scores and additional scores regarding ulcer size, affected area and ulcerated surface [40]. Furthermore, PCC has a superior diagnostic sensitivity compared to

MRE for patients with suspected CD [41]. Therefore, PCC could be considered an alternative to IC as a first screening modality in suspected CD patients [42].

Artificial intelligence (AI) and machine learning algorithms are being integrated into CE, thus reducing reading time and enhancing accuracy [43,44]. AI identifies SB abnormalities with higher sensitivity than endoscopist interpretation (99.9% vs 74.6% per patient and 99.9% vs 76.9% per lesion) and in a shorter time frame [45]. The pooled sensitivity and specificity for the detection of SB ulcers are 95% and 94% respectively [46]. A dedicated AI algorithm for automatically detecting clinically significant SB CD findings has an 83% sensitivity and 98% specificity for ulcer detection and 91% sensitivity and 93% specificity for erosion detection [47].

Capsule retention is the main complication of CE and could lead to SB obstruction or perforation in sporadic cases [48]. When a capsule remains in the SB for more than 15 days after ingestion, it is considered as retained, sometimes needing endoscopic removal [49]. However, the development of the patency capsule (PC (Medtronic, Yoqneam, Israel)) has been revolutionary. The PC is a "faux" capsule of the same size as CE and is used to ensure SB patency; it has a radio frequency identification tag and barium that facilitates detection and precise localization of the capsule if retained [50]. It is ingested as a regular CE and expected to be excreted within 30 h. If the PC is excreted intact, thus the capsule can be administered; however, if the PC is not excreted or is excreted with a disintegrated body, capsule ingestion should be avoided (Fig. 1).

Capsule retention risk is similar in suspected CD and SB bleeding and is estimated to be around 0.5% [25]. Performing cross-sectional imaging or PC in suspected stricture patients reduces capsule retention risk [51]. However, cross-sectional imaging cannot accurately predict SB patency as capsule retention has been described after negative imaging [52], having MRE a low positive predictive value and specificity of 40% and 59%, respectively [52]. Hence, careful patient examination and clinical history are necessary to exclude obstructive symptoms [25].

European guidelines recommend using CTE or MRE initially and a PC before performing CE in patients with obstructive symptoms or known stenosis. Those patients without obstructive symptoms should be investigated with SB CE after normal IC without prior imaging or PC [25].

In patients with suspected SB CD, direct mucosal examination and histological evaluation are important to set a diagnosis and exclude other diagnoses such as infection, malignancy etc. [10]. Most studies in this setting address the use of balloon-assisted enteroscopy (BAE) while motorized spiral enteroscopy (MSE) data are promising but still scarce. ESGE guidelines recommend using DAE after a negative IC when either SB CE or imaging provide evidence of suspected CD [25]. All DAE techniques have similar safety profiles and efficiency and should be used according to local expertise. MSE has a shorter insertion time, but real-time studies are needed to assess overall intra and post-procedural complications [53,54]. The MSE has a high DY and therapeutic success rate, with a complication rate of 17%, being the major complication rate of 1% [55]. The overall DY in patients with suspected SB CD is almost 80%, resulting in subsequent treatment decisions in 82% of the cases; even more DAE tissue sampling may assist in positive diagnosis in almost 40% of cases [56]. The advancement of AI can also benefit DAE procedures, with an actual accuracy of 98.7% for the automated detection of SB erosions and ulcers [57].

3. Established Crohn's disease

3.1. NON-ENDOSCOPIC tools

CD treatment goals have shifted towards sustained deep remission, including mucosal and transmural healing, instead of exclusive symptom control [58]. Hence, assessment of known SB CD should be directed to detect MH, as achieving MH is related to significant improvements in quality of life, and can decrease relapse rates, hospitalization rates, and the need for surgery [59].

Endoscopy is considered the gold standard for determining MH. However, its invasiveness limits its repeated use during disease monitoring, mainly due to patient preference [60]. Therefore, non-invasive tools, such as CRP, FCP, and cross-sectional imaging, are alternatives to endoscopic visualization of MH.

The correlation between CRP and MH is variable and thus not recommended [10]. However, the DY of FCP is significant for detecting active SB disease, with a NPV of 90% for the cut-off value of 50 μg/mL [61]. FCP levels correlate well with SES-CD, using a cut-off value of 215 mcg/g with a sensitivity of 82.8%, specificity of 71.4%, PPV of 74.3%, NPV of 80.6%, OR of 12.0, and area under the ROC curve value of 0.81 [62]. FCP correlates well with MRE assessment of ileal CD with MRE parameters associated with long-term biologic- and surgery-free remission [63].

Endoscopy is valuable for examining intestinal mucosa but is limited for transmural evaluation. Up to 50% of CD patients who appear normal on endoscopy have abnormal findings when evaluated with cross-sectional imaging techniques such as CTE, IUS, and MRE [19]. Extramural findings have recently emerged as better outcome predictors than endoscopic mucosal assessment, identifying more relevant therapeutic targets. Specifically, transmural healing has been proposed as a potential new treatment endpoint for patients with CD, as it is associated with lower rates of drug escalation, CD-related hospitalizations, and surgery [58]. Therefore, cross-sectional imaging should be incorporated into tight monitoring and treat-to-target strategies [64]. Due to CTE radiation safety concerns, MRE or IUS for monitoring disease activity are recommended [10] as they can monitor extramural complications (fistulae and abscesses) in combination with clinical and laboratory parameters.

MRE employs the Magnetic Resonance Index of Activity (MaRIA score), which has been proven to be a valid and reliable index for evaluating therapy response, with a 90% accuracy rate for ulcer healing and an 83% for endoscopic remission compared to IC [65].

IUS is highly sensitive in detecting endoscopic activity and correlates well with SES-CD and FCP. It can also determine treatment response, potentially reducing the number of ileocolonoscopies [66,67]. Furthermore, sonographic healing is associated with improved clinical outcomes, such as reduced risk of medication escalation, corticosteroid use, hospitalization, surgery, and clinical remission [68].

Surgical resection may be necessary for patients who do not respond to medical treatment or develop fibrotic strictures. However, recurrence is common, with endoscopic recurrence observed in nearly 90% within three years after surgery, even without symptoms [69]. MRE is valuable for predicting the risk of clinical recurrence in this setting [70]. An MRE index (the MONITOR index) is significantly associated with the Rutgeerts score and can be easily applicable in clinical practice, with an AUC of 0.85 for predicting postoperative recurrence [71]. Moreover, functional imaging techniques, such as diffusion-weighted imaging, MRE and ultrasound elastography to assess inflammation and disease activity in CD are gaining acceptability and have promising results [72,73]. Lastly, there is also a significant correlation between IUS findings and surgical recurrence [74].

3.2. Endoscopic tools

As stated before, IC is considered the gold standard, as it allows visualization of the TI and can predict clinical relapse and survey areas of concern in longstanding disease. Moreover, some patients may benefit from endoscopic treatment of complications that may arise in CD [75]. The endoscopic toolbox includes CE; however, its use in established CD has not been widely accepted by ECCO and ESGE until recently [10,76].

CE retention is a concern in suspected CD, but it is even more important for established CD patients. Using PC instead of MRE decreases the number of patients who would be denied a regular CE [47.5% denials in the MRE group vs 20.7% in the PC group) [77].

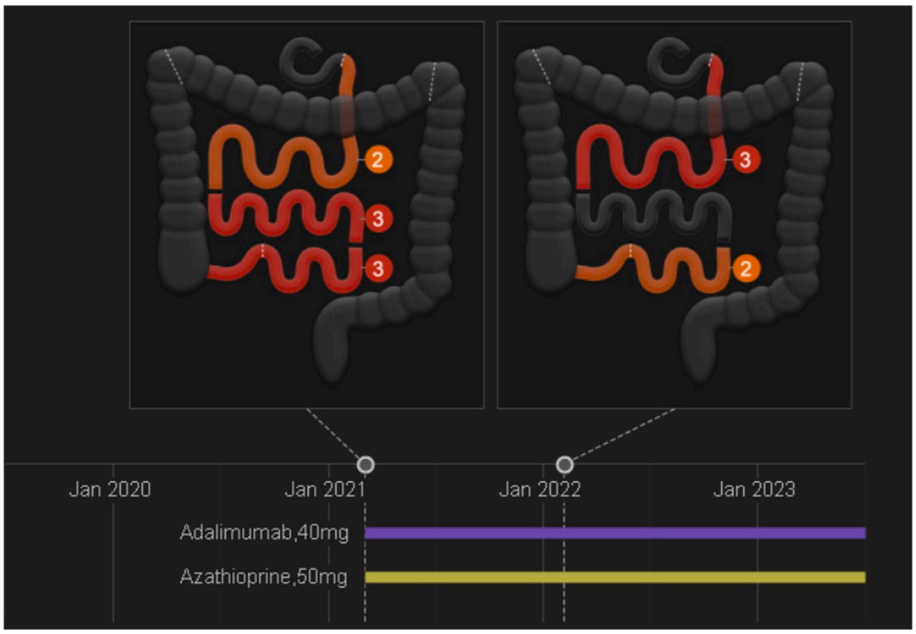

Fig. 2. GI map showing disease evolution over time.

Notwithstanding, patients with clinically stable CD and non-confirmed patency have worse long-term clinical outcomes than those with confirmed patency, irrespective of the disease phenotype. Thus, a standalone PC (without CE) may be a novel, safe, and cost-effective prognostic tool [78].

Being CD a pan-enteric disease, the new PCC might be useful for CD patients. Besides the capsule features, another difference with SB CE is within the software, which contains a GI table and map dedicated to CD, built according to the severity of the findings, as shown in Fig. 2, which helps compare patients' evolution over time.

Compared to IC, PCC has shown an improved performance in patients with active disease, with a substantial rate of active lesions detected only by PCC (18%), suggesting that PCC should complement the IC in CD patients [79]. Comparing PCC with the standard of care (IC and/or MRE), PCC demonstrated higher sensitivity and specificity in the proximal SB vs MRE, as well as TI vs MRE and/or IC, and equal performance in the colon vs IC. Even more, patient satisfaction was superior for the capsule, emphasizing PCC's great advantage in enabling reliable disease staging with a single procedure [80]. A patient satisfaction survey regarding the satisfaction and acceptability of both CE and MRE found that 85% of patients preferred CE for follow-up rather than MRE [81].

In established CD, monitoring disease activity is fundamental to disease management. PCC can detect active disease in 67.6% of patients with established CD, upstaging disease extent in 33% of patients (9 with newly upper involvement). Notably, PCC was superior to symptoms or

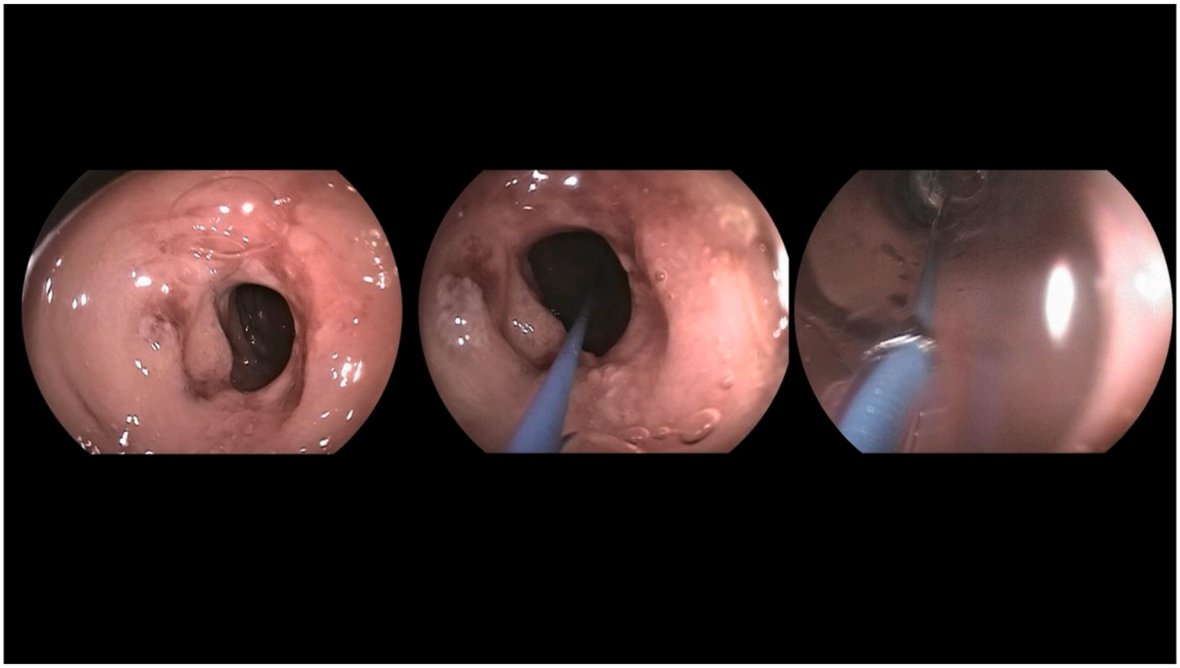

Fig. 3. DAE-assisted endoscopic balloon dilation.

biochemical/faecal markers in identifying active CD [82].

MH is one of the most critical long-term targets in established CD, as outlined in the STRIDE II paper [83]. Kopylov et al. conduct a prospective study following established CD patients who are given Vedolizumab with PCC (before treatment, at weeks 14 and 52). The interim analysis shows a 35–50% improvement in inflammatory scores (Lewis score and Eliakim score) and FCP at week 14 [84]. In addition, endoscopic response to infliximab using PillCam Colon2 as a PCC (given before, 8 & 12 weeks after treatment) has shown endoscopic remission in 27% of patients, with 50% having endoscopic response [85].

Improved monitoring could aid in identifying patients with an increased risk of flare or complications. For example, in a study of CD patients in clinical remission for two years, who underwent MRE, followed by a PC and CE every six months with regular laboratory tests every three months, 85% of patients in clinical remission exhibited mucosal inflammation (64% mild and 21% moderate-to-severe) and only 15% of patients achieved MH [6]. Furthermore, the combination of CE and MRE proved valuable in changing the disease phenotype of patients. In 60% of cases, using both imaging modalities led to changes in patient phenotype, with up to 51% presenting with proximal disease and 59% demonstrating a B2/B3 phenotype [86].

In patients with SB disease, CE is a more effective diagnostic tool for detecting proximal SB disease and mild inflammation than MRE, with poor correlation between the MRE's MaRIA score and the capsule's Lewis inflammatory score (LS) for mild and moderate disease, being better in severe inflammatory cases [87].

The LS of CE is the most reliable predictor of both short and long-term relapse: a LS $<$ 350 is associated with remission, with a NPV of 92%. In contrast, a score $>$350 has a hazard ratio of 10.7 for relapse, with over 50% of patients exhibiting relapse [88].

Regarding the efficacy of PCC in monitoring the recurrence of CD post-surgery, significant disease can be detected in 19% at the early stage and 50% at the late stage (Ruttgeerts$>$2). Conversely, IC reveals significant inflammation in 33% of patients [89].

Another endoscopic option for the small bowel is the use of DAE. Recently, the small intestine research group of the Korean Association for the Study of Intestinal Diseases (KASID) Investigated changes in DAE use in CD over different periods and its role in clinical outcomes [90]. The main indications were initial diagnosis 50% and treatment of strictures in 21%. The DY in suspected CD was high 91%, as was the procedure's success. Therapeutic plans were adjusted in 61% of patients [90].

A recent meta-analysis has proven the efficiency and security of DAE-assisted EBD (Fig. 3) for CD SB strictures [91], including 463 patients and 1189 EBD. They describe a technical success of 95% (86.7%–98.1%), with short-term clinical efficacy in 82.3% of patients (68.1%–91%, and a symptomatic recurrence in the long term (20 months of follow-up) around 48% (33.2%–63.7%). The overall complication rate described is 3.11% in the per-patient analysis [91].

Lastly, consensus guidelines regarding the endoscopic evaluation of surgically altered bowel in IBD [91] suggest evaluating the neo-terminal ileum anastomosis 6–12 months after surgery, assessing stricture sites via DAE and evaluating SB resection and entero-enteric anastomosis using DAE. Similarly, surveillance for the recurrence of SB neoplasia should be done within a year of surgery and every 1–3 years [92].

4. Summary

Accurate diagnosis of Crohn's disease is critical, but traditional methods have limitations in detecting small bowel involvement. Biomarkers are useful in distinguishing IBD from functional bowel disorders, with FCP having a sensitivity of 89% and specificity of 62%. However, SB evaluation is mandatory in patients with suspected CD, where IC is the gold standard but cannot evaluate proximal SB. For this purpose, both CE and cross-sectional techniques may be considered. Moreover, all newly diagnosed CD patients undergo SB assessment.

Treatment goals have shifted towards sustained deep remission, including mucosal and transmural healing. Endoscopy is the gold standard for determining mucosal healing, but its invasiveness limits its use. Non-invasive tools like FCP and cross-sectional imaging are useful alternatives. In addition, CE has proven to be a safe and useful tool for monitoring the disease, being more accepted than MRE among patients.

4.1. Practice points

- Patients newly diagnosed with Crohn's disease should undergo small bowel assessment.
- Capsule endoscopy and cross-sectional studies should be considered complementary for the study of disease extension.
- CE is superior for proximal small bowel and for mucosal healing.
- Patency capsule should be administered in patients with known stenosis or obstructive symptoms, irrespective of being patients with suspected or established Crohn's disease.

4.2. Research agenda

- The role of artificial intelligence in cross-sectional and endoscopic techniques.
- Compare monitoring patients with the standard of care (ileocolonoscopy + MRE) with pan-enteric capsule.

Declaration of competing interest

Cristina Carretero has received speaker/consultation fees from Medtronic.

Alejandro Bojorquez discloses no conflict of interest.

Rami Eliakim has received research grants and speaker/consultation fees from Medtronic.

Nikolaos Lazaridis discloses no conflict of interest.

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[*] Most interesting references.To note they are the most interesting. But all of the * are followed by the reference