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KEY TAKEAWAYS

- Post-operative recurrence (POR) is extremely common after Crohn’s disease (CD) surgery, and the severity of recurrence predicts future need for surgery, therefore POR monitoring is vital.
- The current gold standard for monitoring POR is ileocolonoscopy however there is poor patient compliance.
- Emerging data support combining intestinal ultrasound with fecal calprotectin as a new non-invasive tool for monitoring POR.
- Further research to fully elucidate the utility of non-invasive investigations in post-operative CD management is warranted.

CAN NON-INVASIVE MONITORING REPLACE ILEOCOLONOSCOPY FOR POSTOPERATIVE RECURRENCE OF CROHN’S DISEASE?

Introduction

The therapeutic landscape for Crohn’s disease (CD) has been reshaped by improvements in disease

management and medical therapy, leading to a decrease in the necessity for intestinal resection.¹ However, surgical intervention still plays a crucial role in treating medically refractory disease or

complications such as strictures or fistulae.² Recent biologic-era population studies have shown that the rate of CD-related abdominal surgery over 10 years is up to 49.9% in adult-onset CD and 37.7% in pediatric onset CD.³

Why is Postoperative Monitoring Important?

Although clinical remission is often achieved after surgery, endoscopic postoperative recurrence (POR) is detected in as many as 90% of cases within 3 years after surgery and up to 70% of patients require further surgery within 10 years if appropriate treatment is not instigated.⁴ Disease recurrence occurs in the neo-terminal ileum or anastomosis and it usually manifests with endoscopic findings prior to clinical symptoms.¹ The severity of endoscopic recurrence 1 year after surgery is often predictive of later clinical recurrence and the need for future surgery.⁴ Postoperative recurrence is thought to be triggered by the presence of intestinal contents and bacteria in the lumen that lead to mucosal invasion by inflammatory cells.¹

Current Surveillance for CD Recurrence

The current gold standard for monitoring CD postoperatively is ileocolonoscopy performed at 6-12 months post-surgery.⁵ (Figure 1) The landmark POCER trial supported the central role of endoscopy postoperatively. In this study, patients were randomized to either the 'active care' arm with a 6 month ileocolonoscopy and step-up therapy if there was endoscopic recurrence or the 'standard care' arm with symptom-based management and no ileocolonoscopy. At 18 months follow up, patients in the 'active care' endoscopy group exhibited significantly lower endoscopic recurrence rates compared to the 'standard care' group (49% vs 67% respectively, $p=0.03$).⁶ There is limited research to guide endoscopic surveillance beyond 12 months postoperatively but given high POR rates it has been suggested that repeat ileocolonoscopy could take place every 1-2 years to guide management.⁷ Endoscopic mucosal findings are graded using the Rutgeerts score, which predicts clinical recurrence and categorizes disease severity from i0 to i4 according to the presence and extent of aphthous ulcers in the neo-terminal ileum and anastomosis.¹ The modified Rutgeerts and REMIND scores were recently developed to separate aphthous lesions in the neo-terminal ileum from those confined to the anastomosis as questions remain about whether anastomotic lesions are related to post-surgical ischemic change rather than CD progression.⁸ These scores continue to be evaluated and may aid prediction of postoperative long-term outcomes.

Ileocolonoscopy cannot be replaced by non-invasive methods in all circumstances as endoscopic evaluation allows biopsies to assess histological activity and dysplasia. However, ileocolonoscopy is invasive and leads to high costs, procedural risks and logistical

issues such as operating room availability. Additionally, it cannot easily assess proximal small bowel disease, and the frequency of endoscopy is limited. It requires bowel preparation and it can be poorly tolerated by patients.⁹ As a result, patient compliance with recommended postoperative surveillance is poor with only 30-54% of patients undergoing ileocolonoscopy within 12 months of surgery. Given the importance of preventing and promptly treating POR to avoid bowel damage, non-invasive assessment methods for POR monitoring are warranted.

Non-invasive Modalities for Monitoring CD Activity Postoperatively

Clinical Disease Indices

Clinical indices such as the Crohn's Disease Activity Index do not correlate well with the presence of recurrent endoscopic disease postoperatively.⁹ Endoscopically identified disease recurrence often occurs before clinical symptoms develop.¹ Moreover, there are many symptomatic confounders postoperatively such as bile-salt malabsorption, small bowel bacterial overgrowth, adhesions, dysmotility, and fat malabsorption that falsely elevate clinical indices.⁷

Serum Biomarkers and the Endoscopic Healing Index

Serum biomarkers such as C-reactive protein and erythrocyte sedimentation rate have been shown to be insensitive to detecting localized POR.^{1,10} However, the Endoscopic Healing Index, a score derived from a blood test analyzing 13 biomarkers postulated to reflect mucosal inflammation (ANG1, ANG2, CRP, SAA1, IL17, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGF- α , CEACAM1, and VCAM), has been developed and validated to identify patients in endoscopic remission. The accuracy of the Endoscopic Healing Index has been evaluated for the presence of postoperative endoscopic recurrence. After six months, both the Endoscopic Healing Index <20 and fecal calprotectin <100 $\mu\text{g/g}$ showed comparable sensitivity (81.8% and 90.9%, respectively) and negative predictive value (84.0% and 91.7%, respectively) for the detection of endoscopic recurrence. However, at 18 months, the Endoscopic Healing Index was unable to reliably distinguish between remission and recurrence, unlike fecal calprotectin, with a negative predictive value of 64.9% vs 89.7%, respectively.⁴ This was postulated to be attributed to the matrix remodelling markers being more prominent in the early postoperative phase. Although this test is promising, it currently has limited availability and further research validating its cost effectiveness and utility to predict POR in the real world is warranted.

Fecal Biomarkers

Growing evidence points to fecal calprotectin as a useful adjunctive tool for monitoring activity of CD

after surgery. Boschetti et al. studied 86 asymptomatic postoperative CD patients after a mean interval of 8.2 +/- 0.5 months. They reported that patients experiencing endoscopic recurrence had significantly elevated levels of fecal calprotectin compared to those in endoscopic remission (mean 473 µg/g vs 115 µg/g; $P < 0.0001$). Additionally, they observed a significant correlation between fecal calprotectin levels and Rutgeerts scores ($r = 0.65$, $P < 0.0001$).¹¹ Fecal calprotectin thresholds from 100 to 150 µg/g have demonstrated sensitivity of 70-89% and specificity of 58-69% in detecting endoscopic recurrence.¹² The high negative predictive value of fecal calprotectin >90% suggests that a threshold below 100 µg/g could avoid systematic ileocolonoscopies in 30% of asymptomatic postoperative CD patients. Moreover, existing literature indicates that serial fecal calprotectin trends over time can forecast early endoscopic and clinical recurrence in both pediatric and adult cohorts.¹³ Therefore, fecal calprotectin could play a role in perioperative risk assessment, proactive monitoring and evaluating treatment effectiveness in postoperative CD. European Crohn's and Colitis Organization (ECCO) guidelines recommend initiating fecal calprotectin measurements three months after surgery and consider subsequent endoscopic evaluation based on its levels and trends during follow-up.¹⁴ However, the optimal cutoff value to predict POR is still to be determined and adherence with stool tests can be challenging.⁴

Intestinal Ultrasound

Intestinal ultrasound (IUS) is emerging as a non-invasive alternative for ileocolonoscopy in diagnosing POR, defined as a Rutgeerts score ≥ 2 , with a sensitivity of 94% and specificity of 84%.^{15,16} (Figure 2). Scores

like the Simple Ultrasound Activity Score for Crohn's Disease (SUS-CD), the International Bowel Ultrasound Segmental Activity Score (IBUS-SAS) and the Simple Ultrasound Score demonstrate high accuracy in POR diagnosis with all three showing area under the curve of over 80%.¹⁷ Increased bowel wall thickness, bowel wall hyperemia and the presence of lymph nodes have all correlated with the endoscopic Rutgeerts score.^{9,18} The utility of IUS postoperatively to detect complications has not been studied. However, various studies have determined the role of IUS in detecting stenosis affecting the small bowel and by using surgery as a comparator they reported sensitivity of between 75-100% and specificity between 89-93%.¹⁸

Given that CD is transmural, it is more thoroughly evaluated by imaging which can assess the entire intestinal wall and extraluminal manifestations, unlike colonoscopy which can only assess mucosal damage. Moreover, imaging may be able to detect active inflammation in the proximal small bowel. An important advantage of non-invasive methods like IUS is the ability to be repeated multiple times, potentially improving accuracy for this test, as well as facilitating close patient monitoring and minimizing delays in diagnosis and treatment. Earlier treatment has the potential to reshape the trajectory of disease in postoperative CD patients and minimize risk of POR. Intestinal ultrasound is operator dependent and is more challenging with larger body habitus. However, it is inexpensive, non-irradiating, and provides valuable point of care information. Recent ECCO guidelines suggest IUS as an alternative method for detecting POR, especially after small bowel resection with an anastomosis that is beyond the accessibility of endoscopy.¹⁸ International CD postoperative consensus

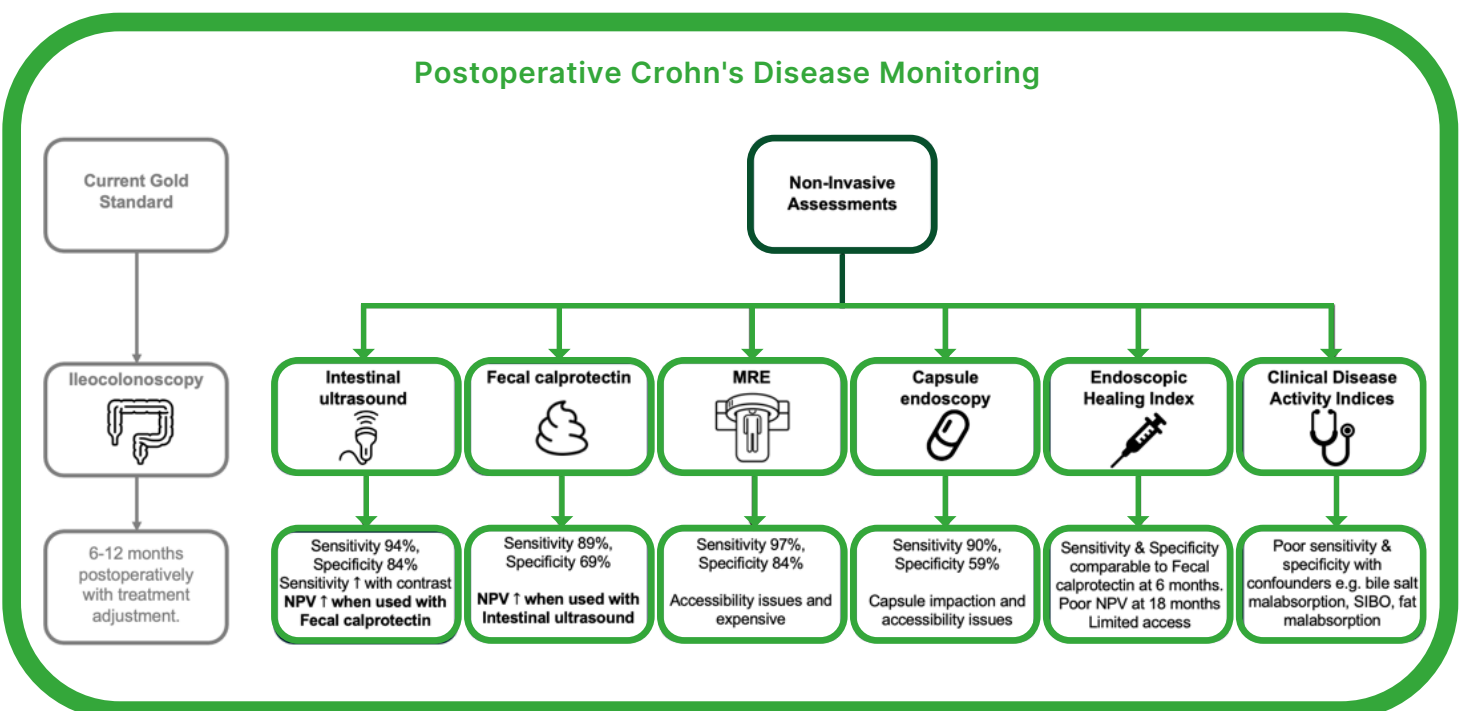


Figure 1: Postoperative Crohn's disease monitoring; courtesy of Dr. Shreya Kishore MD, Dr. Sally Lawrence MBChB, FRCPCH, FRCPC
Abbreviations: NPV: Negative predictive value; MRE: Magnetic resonance enterography; SIBO: Small intestinal bacterial overgrowth.

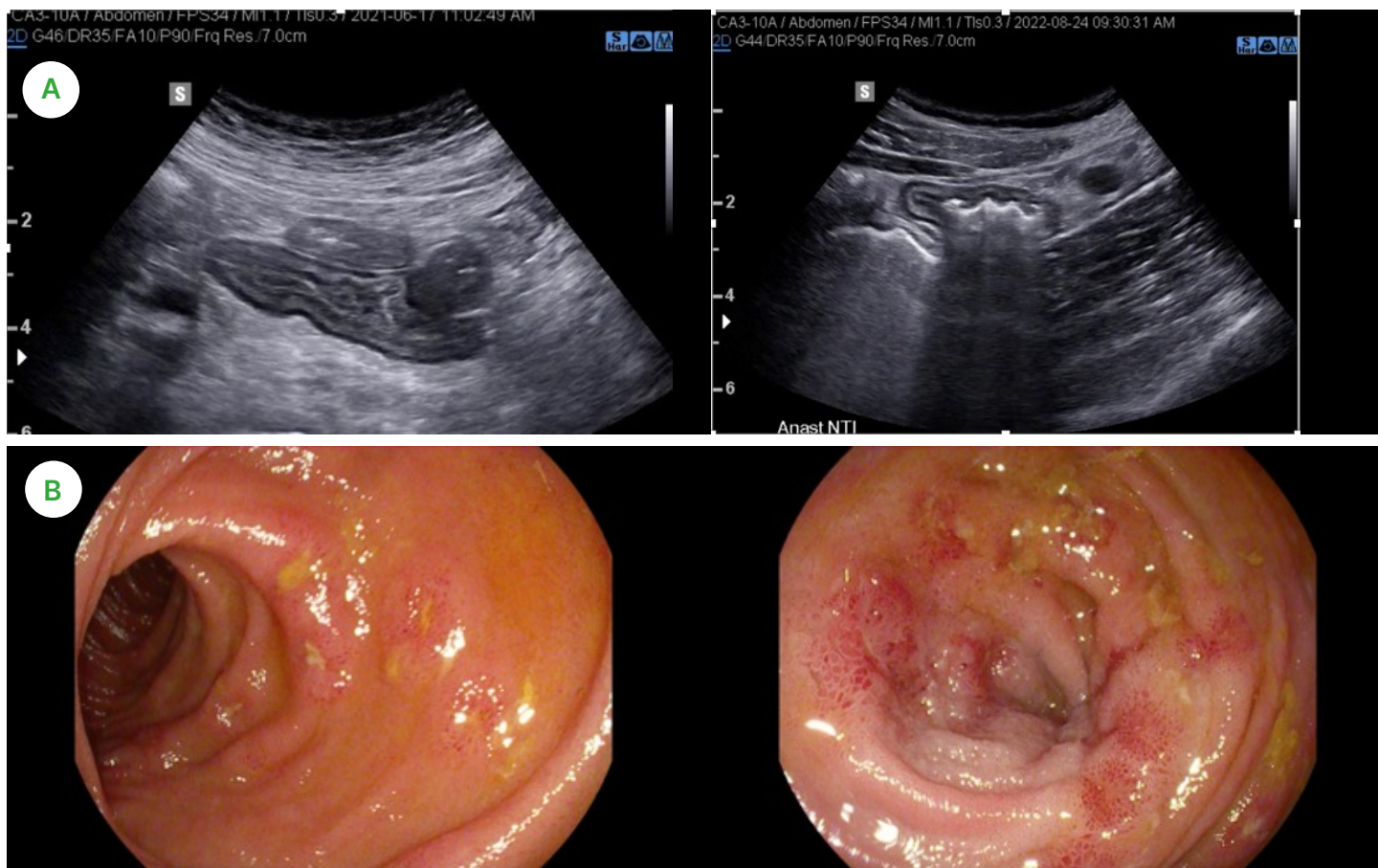


Figure 2: Postoperative Crohn's disease assessment 6 months post-ileocecal resection with side-to-side anastomosis in high-risk patient on postoperative prophylactic biologic therapy. **A.** Intestinal ultrasound showing side-to-side anastomosis with normal colonic mucosa and increased bowel wall thickness on the ileal side with surrounding bright inflammatory fat. **B.** Endoscopic images confirmed Rutgeerts score i3 recurrence in the neo-terminal ileum; *courtesy of Dr. Kerri Novak.*

guidelines for IUS parameters are currently underway and they will further bolster the use of this modality in the postoperative setting.

A recent multicentre prospective study assessed a non-invasive approach combining IUS and fecal calprotectin. It demonstrated that bowel wall thickness (BWT) ≥ 3 mm and fecal calprotectin ≥ 50 $\mu\text{g/g}$ correctly identified 75% of POR patients, with a false positive rate of 2.5%.⁹ Conversely, the combination of BWT < 3 mm and fecal calprotectin < 50 $\mu\text{g/g}$ correctly classified 74% patients with just 4.5% of patients falsely classified as not having POR. This suggests that there is potential for patients with evidence of POR on IUS and elevated fecal calprotectin to initiate biologic therapy without undergoing ileocolonoscopy. Similarly, patients with normal calprotectin values and without IUS abnormalities could potentially continue their follow-up without undergoing endoscopic evaluation.

Ultrasound with Contrast

Small intestine contrast ultrasonography (SICUS) and contrast-enhanced ultrasound (CEUS) have also been used to assess POR in CD. SICUS utilizes an oral contrast (polyethylene glycol) to assess bowel wall changes and complications. CEUS requires intravenous contrast, enabling detailed evaluation of the intestinal wall vasculature. A recent meta-analysis found that SICUS is more sensitive than IUS (99%

vs 82%, respectively) but less specific (74% vs 88%, respectively).¹ A recent study reported that the already high sensitivity of 89.7% in detecting POR by IUS could be increased to 98% using CEUS.¹⁸ However, the modest gain in sensitivity must be balanced with the increased invasiveness, additional time required and lack of access. Therefore, both contrast-enhanced ultrasound methods currently do not appear to offer significant advantages over IUS.¹⁶

Capsule Endoscopy

The value of capsule endoscopy (CE) for POR in CD has been evaluated in several studies. It has been reported that the sensitivity of CE in detecting recurrence in the neo-terminal ileum is inferior to that of ileocolonoscopy, although it is able to detect lesions outside the scope of ileocolonoscopy in up to two-thirds of patients.¹ Nonetheless, CE carries a risk of capsule impaction, and it is more expensive than traditional endoscopy. CE may be useful as a non-invasive technique for POR in CD, but further studies are required.¹

Magnetic Resonance Enterography

Magnetic resonance enterography (MRE) has the potential for evaluating CD disease activity without the radiation exposure associated with computed tomography scans. The MONITOR index was recently

validated to predict POR in patients with CD using MRE. The score is calculated using seven criteria: bowel wall thickness, contrast enhancement, T2 signal increase, diffusion-weighted signal increase, edema, ulcers, and the length of the diseased segment. It has been found to be efficient and easy to use, demonstrating an area under the curve of 0.80 in predicting POR.¹⁹

A meta-analysis by Yung et al. evaluated the diagnostic accuracy of CE, MRE, and IUS in detecting endoscopic recurrence in postoperative CD. Both MRE and IUS demonstrated comparable accuracy in predicting POR, with area under the curve values of 0.98 and 0.93, respectively.²⁰ A significant advantage of IUS is that it can be performed by gastroenterologists, providing immediate information and guiding therapeutic decisions. In contrast, MRE requires evaluation by radiologists, leading to longer wait times for both the procedure and reporting. In addition, the examination is expensive, and the use of intravenous gadolinium contrast has been linked to long-term contrast retention in the brain.¹⁸ The use of MRE is limited by accessibility challenges, poor patient acceptance due to claustrophobia and the need for bowel preparation.

Conclusion

POR remains one of the most challenging aspects in the management of CD. Preventing and promptly treating POR is crucial to avoid bowel damage. Non-invasive monitoring could play a fundamental role in reducing the number of endoscopic procedures postoperatively in CD, decreasing the burden on patients. Fecal calprotectin, IUS plus other imaging modalities, and the Endoscopic Healing Index are minimally invasive monitoring methods emerging for identifying POR. Moreover, combining non-invasive assessments such as IUS and fecal calprotectin holds promise as it has been shown to be accurate and reliable for monitoring POR in CD, facilitating close patient monitoring and minimizing delays in diagnosis and treatment. Larger prospective trials are required to determine how IUS and fecal calprotectin can be integrated into the monitoring of POR in CD. However, these tests add to the diagnostic armamentarium after CD surgery and may reduce the need for invasive endoscopies in routine surveillance in the near future.

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