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# POST-OPERATIVE CROHN'S DISEASE: CURRENT AND EMERGING MANAGEMENT TECHNIQUES

## Introduction

Numerous treatment options for Crohn's disease (CD) have been developed since infliximab was approved in 1998. Treatment practices for CD have also evolved: therapeutic drug monitoring and a treat-to-target approach have replaced symptom control. Despite a decline in surgery rates in Canada and elsewhere in the world, bowel resection is still required for patients with refractory, fistulizing or fibrostenosing CD. Unfortunately, postoperative recurrence (POR) is common; endoscopic recurrence affected 70%-90% of patients at the five-year point.<sup>5</sup> However, it is important to note that variations in recurrence were observed between randomized clinical trials (RCTs), referral centre studies and population-based studies. This article will provide an overview of the current monitoring strategies and therapies for CD patients who have undergone a bowel resection.

## Post-operative Monitoring Strategies

Endoscopy is currently the cornerstone of post-operative follow-up care. Its usefulness has been demonstrated in the landmark prospective study by Rutgeerts et al.<sup>6</sup> In their study, the authors monitored the natural clinical and endoscopic course of CD after an ileal resection. The study revealed the now established discordance between symptoms and endoscopic activity, as 20% of patients experienced symptoms and 73% had macroscopic inflammation. In addition, the authors reported the prognostic value of endoscopic activity. Since then, endoscopy and use of the Rutgeerts score (RS) (Table 1) have been recommended 6 to 12 months following bowel

resection to determine optimal management. A modified Rutgeerts score has also been developed to distinguish patients with a score of i2. (Table 2). A score of i2a indicates lesions confined to the anastomosis; i2b indicates more than five aphthous lesions in the neoterminal ileum, or which skip areas of larger lesions with normal mucosa between the lesions.

Determining which patients are high risk and deserve treatment post-surgery and prior to the recommended endoscopy continues to represent a challenge for physicians.

Several clinical studies have evaluated the association between a patient's pre-operative clinical profile and their post-operative endoscopic findings. In the pivotal prospective REMIND trial, a bivariate analysis reported three predictors of an increased risk of post-operative endoscopic recurrence (RS  $\geq$  i2): male gender, active smoking at surgery and previous intestinal resection.<sup>7</sup> A multivariate analysis was performed after adjustment for gender; age; pre-operative anti-TNF treatment; post-operative immunosuppressants; post-operative anti-TNF treatment; previous intestinal resection; penetrating behaviour; perianal disease; and active smoking at surgery. Male gender (OR = 2.48 [CI 95% 1.40-4.46]) active smoking at surgery (OR = 2.65 [CI 95% 1.44-4.97]) and previous intestinal resection (OR = 3.03 [CI 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence, while post-operative anti-TNF treatment was associated with a lower risk (OR = 0.50 [CI 95% 0.25-0.96]). There were no interactions between the gender and other variables.<sup>7</sup>

Rutgeerts score	
i0	No lesions
i1	Less than 5 aphthous lesions
i2	More than 5 aphthous lesions with normal mucosa between the lesions; skip areas of larger lesions; or lesions confined to the anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse ileitis with large ulcers, nodules and/or narrowing

Table 1. Rutgeerts score<sup>6</sup>

Modified Rutgeerts score	
i0	No lesions
i1	Less than 5 aphthous lesions
i2a	Lesions confined to the anastomosis
i2b	More than 5 aphthous lesions; skip areas of larger lesions with normal mucosa between the lesions
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse ileitis with large ulcers, nodules and/or narrowing

Table 2. Modified Rutgeerts score<sup>7</sup>

The current American Gastroenterological Association (AGA), European Crohn's and Colitis Organisation (ECCO) and British Society of Gastroenterology (BSG) guidelines list comparable but not identical high-risk clinical features, such as active smoking, prior intestinal surgery, and penetrating and perianal disease.<sup>8-10</sup> The above-mentioned determination is not an ideal solution and the risk of overtreatment or undertreatment remains. This was demonstrated in a recent retrospective study in which high-risk profiles defined by these association did not correlate with increased endoscopic POR (ePOR).<sup>11</sup>

Non-invasive diagnostic modalities are gaining momentum in POR monitoring. They allow accurate, safe and repeatable assessment of inflammatory activity. They provide critical information since pre-operative factors alone are not always accurate in predicting post-operative recurrence and since clinical symptoms are absent in up to 46%-67% of patients with ePOR.<sup>12</sup>

Fecal calprotectin (FC) is of particular interest. In a meta-analysis, FC showed a sensitivity of 82% and a specificity of 61% for the detection of ePOR, defined as  $RS \geq 2$ .<sup>13</sup> FC thresholds used in this study were variable. Although the ideal thresholds are unknown, FC remains a reliable, repeatable and safe indicator. Its suitability for identifying recurrence prior to the 6-12-month colonoscopy has been demonstrated. In a prospective study,  $FC < 65 \mu\text{g/g}$  at 3 months was associated with subsequent endoscopic remission at 6-12 months (OR 12.2, 95% CI [1.32-113.2]).<sup>14</sup> In another multicentre study, serial FC were collected and coloscopy was performed at six months.<sup>15</sup> An increase of  $\geq 10\%$  within the first three months predicted an ePOR, with a positive predictive value of 79%. Therefore, although additional studies are needed, the data support the use of FC, which ideally should be performed repeatedly.

In addition, imaging may have a place in monitoring for POR, particularly for 1) Patients who want to avoid invasive procedures, or 2) Patients who have a resection site out of reach of a standard colonoscopy.

Computed tomography (CT) and magnetic resonance (MR) enterography are alternatives to endoscopy. In a meta-analysis, MR enterography demonstrated a pooled sensitivity of 97% and a pooled specificity of 84% to detect  $RS \geq 1$  recurrences.<sup>16</sup> Only three studies including 76 patients were analyzed. Since then, a prospective study has demonstrated that postoperative inflammatory changes were sometimes subtle, and that the use of single parameters, such as bowel wall thickness, appeared limited.<sup>17</sup> To overcome

this problem, the MaRIA, Clermont and MR scoring systems have been developed for the detection of disease activity. Their clinical use remains limited.

Intestinal ultrasound (IUS) is a potential alternative to endoscopy. Previously limited to teaching centres, the use of IUS is growing steadily in Canada and around the world. Additionally, its potential for assessing Crohn's disease activity is supported by a growing body of literature.<sup>18</sup> Its low cost, accuracy, safety, and repeatability make it an attractive imaging option. In the above-mentioned meta-analysis, IUS demonstrated a pooled sensitivity of 89% and a pooled specificity of 86%.

Video capsule endoscopy also allows the detection of POR, particularly prior to the recommended endoscopic evaluation. In a recent prospective study, 86% of patients showed inflammatory lesions within three months of surgery.<sup>19</sup> Notably, half of the lesions were distant from the anastomosis. Despite its respectable performance, access remains limited. Capsule retention is another obvious limitation. In the above-mentioned study, 6 of the 48 patients were excluded due to patency capsule retention.

### Post-operative Therapeutic Strategies

At a time when proactive care is becoming the norm, opting for a more aggressive approach appears to be promising for POR.

In the multicentre POCER study, patients were assigned to a proactive approach, with a six-month post-operative colonoscopy, or a more reactive approach.<sup>20</sup> In this study, all patients were administered metronidazole for three months. Then, patients were categorized as high or low risk. High risk features were: active smoking, penetrating disease, or previous bowel resection. Finally, high risk patients received prophylactic azathioprine. Thiopurine intolerant patients received prophylactic adalimumab. Low risk patients were immunosuppression free. Patients were randomly assigned to parallel groups: colonoscopy at six months (active care) or no colonoscopy (standard care). At 18 months, 49% of patients in the proactive group and 67% in the reactive group experienced ePOR, defined as  $RS \geq 2$ . Also, despite prophylactic medications, high risk patients experienced more POR. In a recent retrospective study, a top-down strategy was compared to the down-top strategy to prevent endoscopic POR. Strategies were selected according to physician judgment. Top-down patients received anti-TNF and anti-IL12/23 therapies within the first month post-surgery; down-top patients received thiopurines, 5-ASA, or no medication.<sup>21</sup> At six months, 66% of patients in the top-down cohort and 47% in the step-up cohort experienced POR.

In this context, again, questions remain unanswered. Treating an RS i3 or RS i4 recurrence is consensual because of the poor clinical outcome. The practice of following rather than treating an RS i1 recurrence is also common. Opinions differ on the management of lesions confined to the anastomosis and lesions without ileitis (RS i2). In a recent systematic review, similar clinical and surgical outcome were observed in the two cohorts.<sup>22</sup> A recent retrospective study reported opposite results, demonstrating that severe endoscopic progression was observed in a greater number of RS i2b patients.<sup>23</sup> The risk of progression was similar in RS i0, RS i1 and RS i2a patients, which suggests that RS i2 patients do not share the same outcome.

To date, only three clinical trials have been dedicated to POR. The first trial, conducted in 2009, compared infliximab and placebo for the prevention of ePOR, defined as  $RS \geq i2$ .<sup>24</sup> At one year, 9% of patients on infliximab had endoscopic activity vs 85% of those on placebo. In 2016, the landmark PREVENT trial, a large multicentre study using the same medication, reached a similar conclusion regarding ePOR (22% vs 51%).<sup>25</sup> It should be noted that clinical recurrence, the primary endpoint, was not statistically different. Recently, the REPREVIO trial compared vedolizumab and placebo. Initiated four weeks post-surgery, vedolizumab 300 mg IV at Weeks 0, 8, 16 and 24 was superior to placebo for the prevention of ePOR at six months. Despite its positive results, the trial has not yet been published. In the absence of RCTs, real-world studies including bio-experienced patients, have confirmed the value of adalimumab and ustekinumab for the same indication.<sup>26</sup> Additional advanced therapies may prove effective, as well. Evidence-based data also supports azathioprine use.<sup>27</sup>

In 1995, Rutgeerts et al demonstrated the potential role of antibiotics for the prevention of POR. Since then, several studies supported the use of low-dose metronidazole for three months. In a recent retrospective study, 20% of the antibiotic-exposed patients had POR at one year, vs 54% of those receiving placebo.<sup>28</sup> Of note, 23% of patients experienced adverse event with the antibiotics. Unfortunately, antibiotics are only effective while being taken; it is unclear if their effects continue following cessation of therapy; therefore, it is not known whether or not they will have long-term impact on outcomes. For this reason, the routine use of antibiotics for POR has not been widely adopted in clinical practice.

Despite the availability of effective medications, determining which patients to treat can be challenging, as individual risk is not always

crystal clear. Preventive treatments are therefore administered on a case-by-case basis.<sup>29</sup> Without preventive treatments, therapies are administered in the presence of a POR.

### Summary

POR in CD is common. Evidence-based management includes endoscopy at 6-12 months to guide therapeutic management. Preventive treatments are available. However, their use must be individualized. The role of non-invasive modalities is likely to increase, particularly for the evaluation of patients with early or late disease recurrence. Additional clinical studies are necessary to determine the optimal management for the greatest number of patients.

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### Financial Disclosures:

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**Grants :** Abbvie, Advanz, Amgen, Mckesson, Organon, Pfizer, Sandoz, Takeda

**Consulting fees:** Abbvie, Bristol Myers Squibb, McKesson, Pendopharm, Takeda

**Honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events:**

Abbvie, Amgen, Fresenius Kabi, Janssen, Pendopharm, Pfizer, Takeda

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