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A Review on the Management of Postoperative Crohn's Disease


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Postoperative Crohn's disease recurrence often precedes the emergence of clinical symptomatology and requires detection and management strategies for early objective recurrence. A multidisciplinary approach to optimize patients for surgery via nutrition, smoking cessation, and immunosuppression management may not only prevent postoperative complications but also future Crohn's disease recurrence. Postoperatively, a strategy to provide pharmacologic prophylaxis prior to the detection of objective recurrence and/or intensive monitoring via fecal calprotectin and endoscopy may alter the natural history of the disease and prevent a future surgery for complicated Crohn's disease. In this review, the management of perioperative and postoperative Crohn's disease is outlined for providers on the multidisciplinary team caring for these patients.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disorder that often leads to stricturing and fistulizing complications requiring surgery. Prior to the advent of biologics, approximately 50% of CD patients underwent ileocolonic resection (ICR) within 10 years.[1] Despite advances in the pharmacologic armamentarium against CD, surgical resection is still required in nearly 30% of patients by 10 years.[2] Although surgery may be an initial option for ileal CD, it is not curative and requires consideration of pharmacologic prophylaxis and/or a close monitoring protocol to prevent recurrence of disease (Figure 1).[3–5]

Objective postoperative recurrence (POR) of CD (i.e. histologic, endoscopic, or imaging findings) is common and can be detected prior to the emergence of clinical symptomology.[6] Before evidence of macroscopic disease arises, histologic recurrence on endoscopic biopsy pathology can be seen as early as one week after surgery.[7–9] Endoscopic recurrence, preceding either clinical or surgical recurrences, is estimated to happen in up to 70-90% of patients within one year postoperatively.[6,9] Medical providers have an opportunity to prevent surgical recurrence for stricturing or fistulizing complications by optimizing peri-operative care, aggressively monitoring these patients postoperatively, and

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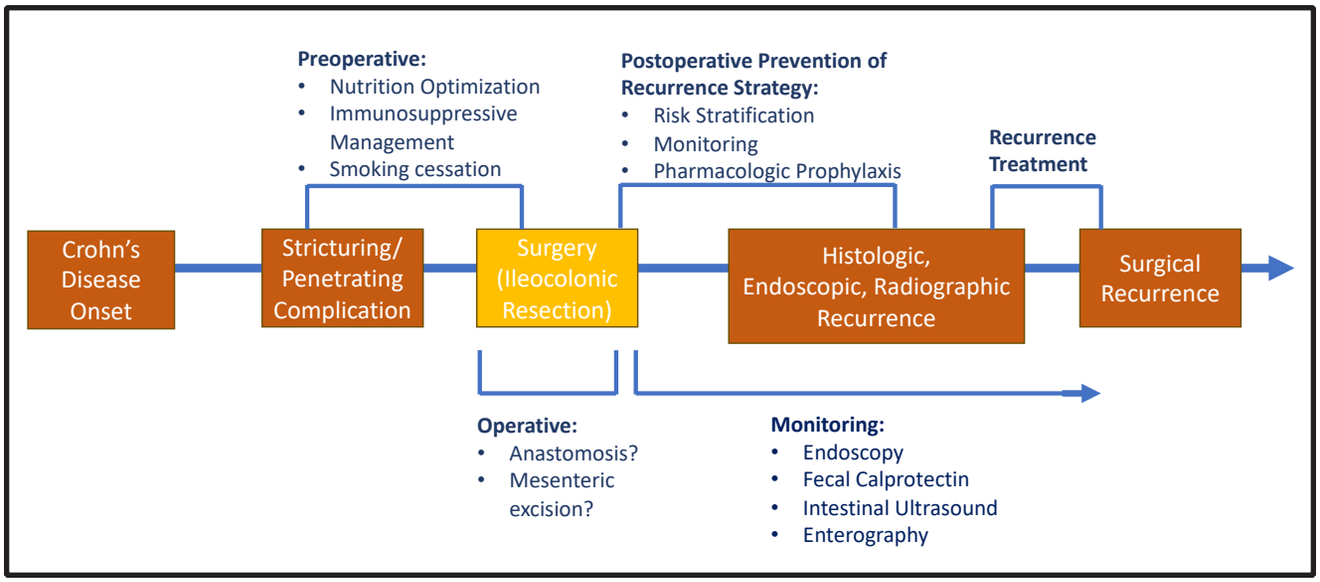

Figure 1.

providing pharmacologic prophylaxis in higher risk patients.

In the absence of objective CD recurrence, a broad differential including small intestinal bacterial overgrowth, bile acid diarrhea, fat malabsorption, infectious diarrhea, abdominal wall pain, amongst others should be considered for symptomatic recurrence.

Peri-Operative Management of Crohn's disease

Opportunities to prevent postoperative complications begin in the perioperative period and include nutritional optimization, smoking cessation, immunosuppression management, and corticosteroid avoidance. Studies have found that postoperative intra-abdominal septic complications (IASC) are associated with POR.[10] Malnutrition has been found to be associated with IASC, and various studies have shown the utility of enteral or parenteral nutrition in the weeks prior to surgery to prevent postoperative complications.[11–15] Exclusive enteral nutrition has the ability to reduce the risk of intra-abdominal septic complications which may indirectly decrease the risk of recurrence.[13,14] In a cohort study, four weeks of preoperative exclusive enteral nutrition compared to placebo was also associated with reduced endoscopic recurrence (11.9% vs. 28.4%, p=0.003).[16] Multidisciplinary care to optimize nutrition and in some cases to delay surgery are required.

Tobacco use prior to ICR is also a known risk factor for postoperative complications and surgical recurrence.[17,18] Smoking cessation lowers this risk and may even have a role in altering specific microbiota that are associated with POR.[19,20] All efforts by clinicians caring for CD patients should make smoking cessation a priority in order to improve postoperative outcomes.

Multidisciplinary discussions to optimize immunosuppression management prior to surgery are necessary. Corticosteroid use has been found to be associated with IASC and surgical site infections. When possible, every attempt to avoid or taper corticosteroids prior to surgery is required.[21–23] In contrast, biologic utilization has not been found to be associated with IASC. In a prospective cohort study of inflammatory bowel disease patients undergoing surgery, anti-TNF exposed patients within twelve weeks of surgery had similar rates of infections postoperatively as patients who were not exposed (20.2% vs. 18.1%, p=0.47).[24] Importantly, detectable perioperative anti-TNF drug levels were not associated with infectious complications. Utilization of biologics in the peri-operative period should not delay surgical intervention.[24–28] If an indication for surgery such as a stricturing or fistulizing complication exists, a new start of a biologic is not indicated prior to surgery.

Operative Management

Various surgical techniques have been assessed

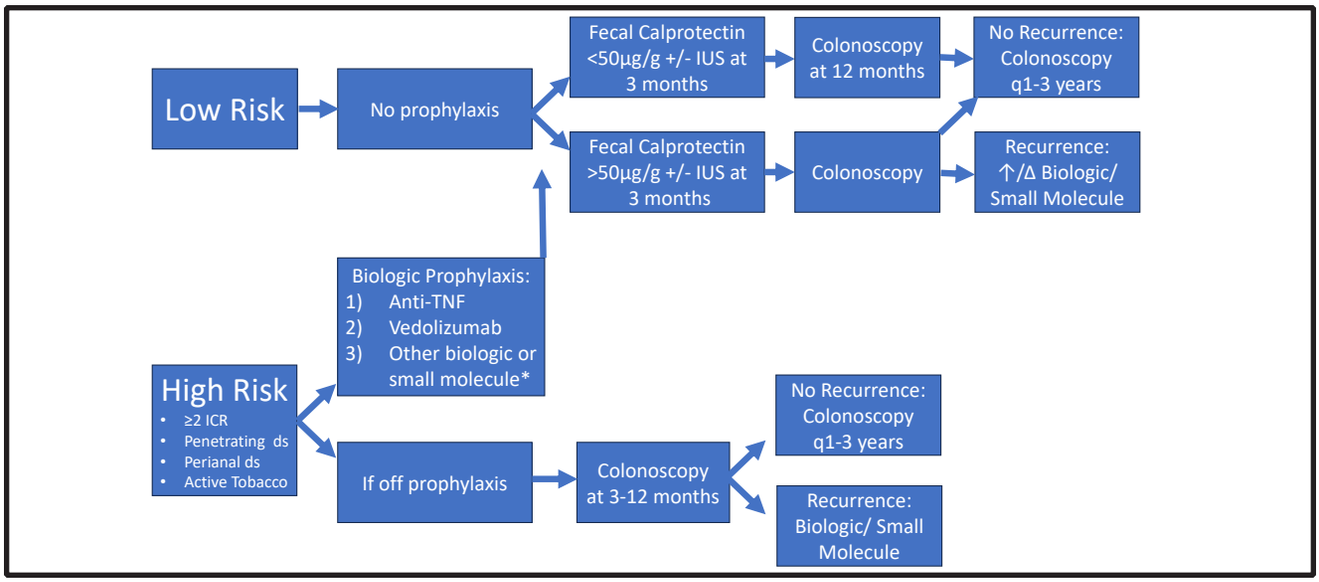

Figure 2.

to prevent POR. Although some anastomosis types were thought to be associated with reduced POR (end-end, side-side, end-side), the Kono-S anastomosis which provides limited mesenteric excision and reduced fecal stasis has been found to be associated with reduced POR.[29,30] In a randomized controlled trial (SuPREMe-CD), Kono-S compared to side-side anastomosis had a significantly lower rate of endoscopic recurrence (22.2% vs. 62.8%), clinical recurrence (8% vs. 18%), and surgical recurrence (0% vs. 4.6%).[29] However, the association between Kono-S and lower rates of endoscopic recurrence remains controversial.[31,32] There is growing interest and ongoing studies to surgically alter neural innervation, vasculature, and the mesentery, an active immune organ, to prevent POR.[33,3]

Postoperative Crohn's Disease Management Strategies: Intensive Monitoring versus Biologic Prophylaxis

Although surgery is not a cure for CD, early ICR as a first-line therapy for inflammatory ileitis has been shown be an effective management strategy. Up-front surgical resection for non-stricturing ileocecal CD compared to infliximab has a comparable quality of life (IBDQ score 178.1 vs. 172.0, p=0.25) and duration of treatment effect (33 vs. 34 months, p=0.52).[3,4] In a long-term follow up of the LIR!C study comparing laparoscopic ICR and anti-TNF (infliximab), a lower rate of anti-TNF use postoperatively (26% vs. 38%) and need for repeat surgery (0% vs. 48%) after five years was observed.[3,4] Similarly, a multicenter Danish study found that the risk of a composite outcome including: hospitalization, steroid use, surgery, and perianal disease was 33% lower with surgery compared to anti-TNF[5] In this cohort study, approximately 50% of patients did not require any therapy five years after surgery.[5] These studies may suggest that there is a subpopulation of postoperative CD patients who may not experience recurrence at rates that have previously been reported. It will be important to identify patients who experience surgical remission for an extended period of time in future studies.

Awareness and selection of a management strategy is imperative to prevent recurrence in patients who have undergone prior surgical resection. Current guidelines recommend considering either pharmacologic prophylaxis in patients who exhibit high-risk features or performing intensive monitoring in those who do not (Figure 2).[35,36] However, further research is ongoing to determine the optimal patient population benefiting from prophylaxis.

Risk-Stratification

Multiple risk factors associated with POR have been identified. These include patient, disease, operative, histologic, microbiome, genetic, and metabolomic risk factors. Current guidelines

Table 1. Modified Rutgeerts' Score: Endoscopic Recurrence

Rutgeerts' Score	Definition
i0	No lesions in neoterminal ileum
i1	<5 Aphthous ulcers in the neoterminal ileum
i2a	Lesions confined to ileocolonic anastomosis
i2b	≥5 aphthous ulcer with normal intervening mucosa in the neoterminal ileum +/- anastomotic lesions
i3	Diffuse aphthous ileitis with inflamed intervening mucosa
i4	Stenosis or large ulcers with inflamed or nodular mucosa in the neoterminal ileum

suggest dichotomizing patients into higher or lower illustrative risk profiles based on clinical risk factors. Higher risk features associated with surgical recurrence, including ≥2 surgeries, penetrating +/- perianal disease, and smoking, benefit from pharmacologic prophylaxis.[18,35] In a prospective cohort study, male gender, non-white race, and active smoking, but not penetrating disease or prior surgeries, were associated with endoscopic recurrence.[37] Broadening of risk factors associated with endoscopic recurrence and individualizing postoperative risk may further refine patients benefiting from prophylaxis.[18,37,38] Various real-world studies assessing risk stratification have suggested that prophylaxis may benefit patients irrespective of risk group, however this remains controversial and future prospective studies are required.[18,38,39]

Non-clinical risk factors for recurrence are being explored. Histologic features such as positive resection margins, plexitis, and transmural inflammation are associated with POR.[40] Microbiome analysis is not widespread but dysbiosis, including recolonization and depletion of various bacteria, is increasingly being recognized as a risk factor.[20,41,42] Serologic markers and metabolomics may play a role in the identification of high risk patients.[43–45] Furthermore, as precision medicine advances, important genetic features such as NOD2/CARD15 and CARD8 expression may identify higher risk patients.[46,47] Ultimately, efforts for precision medicine to identify patients who are highest risk based on all of these potential risk factors are necessary.

Intensive Monitoring Irrespective of Risk Profile

Irrespective of risk profile, monitoring of disease activity is the cornerstone of postoperative management. It is imperative for clinicians to understand that objective recurrence precedes the rise of symptoms in patients. In the first year postoperatively, it is recommended to incorporate fecal calprotectin and colonoscopy into a monitoring strategy. Emerging evidence may soon support the use of cross-sectional imaging and intestinal ultrasound (IUS) as well.

Endoscopy

Ileocolonoscopy remains the gold standard test to identify early POR prior to the onset of symptoms. The modified Rutgeerts' score is an endoscopic score of the neoterminal ileum graded from i0-i4 that correlates to future clinical and surgical recurrence (Table 1).[48] Endoscopic recurrence is determined based on a modified Rutgeerts' score of ≥i2b. A score of i2b correlates to 19% surgical and 40-80% clinical recurrence. Severe recurrence scores of i3 and i4 correlate to 28-50% surgical and 60-100% clinical recurrence in 2 years from surgery. In contrast, low-grade mucosal inflammation defined as i0 and i1 correlate to only 5-8% surgical and 10-50% clinical recurrence.[9,48] Refinement of this score to delineate the significance of i2a versus i2b disease is ongoing and a subset of patients with i2a recurrence may benefit from treatment.[49]

Active endoscopic management to step-up therapy has been well supported by the pivotal Postoperative Crohn's Endoscopic Recurrence (POCER) trial. In this multicenter randomized controlled trial, patients in the active (colonoscopy at 6 months with opportunity to step up therapy) versus standard (no colonoscopy) care groups had lower rates of endoscopic recurrence at 18 months (49% vs. 67%; p=0.03)[50] In another study, the risk of developing late endoscopic recurrence past one year is up to 40% despite initial

monitoring at 6 months, and therefore ongoing active monitoring with colonoscopy after the initial assessment approximately every one to two years may be reasonable.[51] Endoscopy at 3-12 months postoperatively is recommended and especially for those not receiving prophylaxis.

Fecal Calprotectin

Fecal calprotectin is a fast, reliable, and noninvasive tool that should be used to monitor for CD recurrence after ICR.[52,53] In a prospective, multicenter, randomized, controlled trial, fecal calprotectin at 6 and 18 months postoperatively correlated to the presence ($r=0.42$; $p<0.001$) and severity ($r=0.44$; $p<0.001$) of CD recurrence.[54] With escalation of therapy, fecal calprotectin responds similarly to endoscopic disease activity. Various studies have found that fecal calprotectin has a high sensitivity and negative predictive value for detecting recurrence.[54–56] Recent guidelines suggest that a fecal calprotectin <50 µg/g in asymptomatic patients with CD who are considered low risk or on prophylaxis and are in surgically induced remission within 12 months are unlikely to have recurrence of CD. Patients may therefore consider avoiding a colonoscopy within the first year from surgery. In patients with an elevated fecal calprotectin or with high-risk features not on prophylaxis, colonoscopy should be used as a screening method to detect early recurrence within 3-12 months postoperatively.[53]

Intestinal Ultrasound

In addition to fecal calprotectin, intestinal ultrasound is a newer, adjunctive, and noninvasive tool that assesses transmural inflammation and can detect recurrence. In regards to postoperative disease assessment, the combination of the presence of lymph nodes or bowel wall thickness ≥3mm plus a fecal calprotectin ≥50 mcg/g correctly classified 56% and 75% of patients as having endoscopic recurrence.[57] The sensitivity and specificity of IUS is >85% for detecting POR[58,59] Contrast-enhanced ultrasound of the neoterminal ileum has also correlated to the Rutgeerts' score indicating that this modality may be used as an early and noninvasive method to detect recurrence.[60] Though prospective studies are needed, in centers where intestinal ultrasound is available, monitoring for neoterminal disease at 3-6 months postoperatively in combination with fecal calprotectin with confirmatory endoscopy may be an effective strategy.

Enterography

Although enterography (CT or MR) is not recommended to screen for recurrence, it may have a role in detecting recurrence (intestinal wall thickening, luminal narrowing, mural hyperenhancement, and length of disease) in symptomatic patients even in the absence of endoscopic activity.[61] Enterography has also been found to be associated with subsequent endoscopic recurrence even in the absence of activity on the index endoscopy.[61]

Medical Prophylaxis in Patients with High Risk Profile

A multidisciplinary approach perioperatively is necessary to determine if initiation of pharmacologic prophylaxis is indicated after surgery. High risk patients benefit from prophylaxis ideally within one month of surgery.[62] Anti-TNF and vedolizumab, an anti-integrin, specifically have been found to reduce recurrence in prospective randomized control trials.[63,64] In the seminal PREVENT trial, infliximab compared to placebo reduced endoscopic but not clinical recurrence (30.6% vs. 60.0%; $P<0.001$).[64] Even in patients who have been on anti-TNFs prior to surgery, reutilization of anti-TNF prophylaxis after surgery may still be a viable option as long as they did not develop antibodies.[65,66] Adalimumab, another anti-TNF, likely has a similar effect in the prevention of recurrence.[67] Anti-TNF drug level and antibody monitoring may be indicated to achieve adequately therapeutic levels to optimize prevention of recurrence.[68,69] Vedolizumab within four weeks of surgery is also effective in reducing POR based on a prospective randomized trial.[63] Although these two agents have the strongest evidence behind them, it is also reasonable to utilize other biologics (interleukin 12/23 and 23 inhibitors) and presumably small molecules if there had been true failure or adverse events from anti-TNF and vedolizumab.[70,71] While on prophylaxis, it is imperative to continue to monitor with noninvasive tools as well as performing an ileocolonoscopy every 1-2 years.

Alternatives to advanced therapies for postoperative Crohn's Disease prevention

Alternatives to biologics and small molecules to prevent recurrence have been explored, however many of these agents are hindered by tolerability, adverse events, or a paucity of data.

Thiopurines have been shown to reduce postoperative recurrence. In a Cochrane meta-analysis, thiopurines were more effective than placebo in preventing clinical POR at 12-36 months [51% vs. 64%, RR 0.79, 95% CI 0.67-0.92] but not endoscopic POR.[72] Compared to mesalazine, azathioprine seems more effective in preventing endoscopic POR. Biologics are favored over thiopurines due to better efficacy and more favorable safety profiles.

Microbiome dysbiosis in the neoterminal ileum has a role in the development of CD at this site. Therefore, the utility of either probiotics or antibiotics has been postulated. Of these, nitroimidazoles have been shown to reduce endoscopic recurrence. Metronidazole 20 mg/kg (13% vs. 43%, p=0.02) and ornidazole 1g/day (OR 0.31, 95% CI 0.10-0.94, p=0.04) compared to placebo reduced endoscopic recurrence at 3 months and 1 year, respectively.[73,74] Despite the obvious efficacy, the utility of these agents are limited by their adverse effects including neuropathies and dysgeusia.[75] Probiotics, including Lactobacillus and VSL#3, to modify the microbiome as a method to prevent POR have been fraught with disappointing evidence thus far and future studies to alter the microbiome are required.[24,76,77]

Modulation of the microbiome via nutritional means has also been explored. Although not standard of practice, there is promising data to support the use of enteral nutrition as a means to prevent recurrence. Postoperative enteral nutrition plus a low fat diet compared to placebo has been found to be associated with a decrease in recurrence rate (10% vs. 45%, p=0.03).[12] An inherent barrier to adopting enteral nutrition as a means to reduce recurrence is the adherence to this modality of therapy. Future studies to assess methods of partial enteral nutrition and other nutritional studies are required.

Future Directions of Postoperative Crohn's Disease

Significant advances have been made in the management of postoperative CD including the understanding of the natural history and pathogenesis, risk factor assessment, and strategies to prevent POR. Despite these, several questions remain unanswered and future work is required. Personalization of risk for patients utilizing clinical, environmental, microbiome, histologic, genetic, and "-omics" data may provide unique pathways for management strategies. Further assessment of non-invasive monitoring via intestinal ultrasound and biomarkers requires established data to integrate these methods into clinical practice. Data on newer biologics and small molecules in the prevention and treatment of postoperative CD are needed as well. Innovative methods of managing POR and incorporation of artificial intelligence may help standardize the care of these patients. Postoperative CD remains a significant challenge and efforts to optimize care are ongoing. ■

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