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Managing Postoperative Crohn's Disease Made Easy

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Postoperative recurrent Crohn's disease is common and often clinically silent at onset, requiring objective assessments for diagnosis and surveillance. Patients with a history of multiple bowel resections, penetrating disease, or who smoke cigarettes after surgery are at highest risk for disease recurrence. Antibiotics, aminosalicylates, and immunomodulators have been shown to modestly reduce the risk of clinical and endoscopic disease recurrence. In contrast, monoclonal antibodies, specifically anti-tumor necrosis factor (TNF) medications, are effective at suppressing disease recurrence and may have the potential to alter the natural course of disease after surgery. In this manuscript, the management of postoperative Crohn's disease is summarized, and a simplified approach to prevention, monitoring, and treatment is provided.

Risk and Diagnosis of Postoperative Crohn's Disease

Despite significant medical therapeutic advances, as many as 20-30% Crohn's disease (CD) patients require bowel surgery.[1,2] The most common indication for surgery in adult CD patients is stricturing or penetrating complications (e.g. fistula, intraabdominal abscess). Unfortunately, CD is rarely curable by surgery, and postoperative recurrence (POR) of CD is inevitable for the majority of patients. In the prebiologic era, natural history studies found that 70–90% of CD patients developed endoscopic evidence of POR within 1 year of their surgery, and that 30–60% of postoperative CD patients became symptomatic from recurrent disease within 3–5 years of their surgery.[3-5] Consequently, up to 50% of these patients in the prebiologic era required repeat surgery within 5 years of their first surgery.

Postoperative CD recurrence is often clinically silent. Rutgeerts et al. found that only 20% and 34% of patients were symptomatic 1 and 3 years after surgery, despite endoscopic disease in 73% and 85% of these patients, respectively.[4] Other studies demonstrated poor agreement between endoscopic scores and clinical Crohn's Disease Activity Index (CDAI) scores (kappa coefficient 0.12).[6] Thus, relying on symptoms significantly underestimates mucosal disease activity.

The degree of endoscopic disease activity, as judged by the Rutgeerts score, correlates with subsequent progression to symptomatic recurrence.[4] Since symptom assessment is an unreliable and

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delayed measure of POR, ileocolonoscopy utilizing the Rutgeerts scoring system is the current gold standard for POR assessment. The Rutgeerts scoring system defines severity of disease on a 0 (normal) to 4 (severe) scale based on the extent of aphthous ulcerations in the neoterminal ileum.[4] The more severe the endoscopic recurrence, e.g. i3 or i4, the more likely the development of clinical symptoms (i.e. clinical recurrence), and requirement for future surgery (i.e. surgical recurrence). Although the Rutgeerts scoring system has not been validated to define remission or recurrence, many studies have proposed that endoscopic remission corresponds with a Rutgeerts score of 0 or 1, while endoscopic recurrence corresponds to scores of 2-4.

Though ileocolonoscopy is sensitive at detecting POR, the invasive nature of the test is associated with patient discomfort, high cost, and procedural risk. Thus, noninvasive assessments are of particular interest. Fecal calprotectin (fCal) levels, produced by gut leukocytes and epithelial cells at sites of mucosal injury including Crohn's disease, correlate with Rutgeerts scores (r = 0.65, $P < 0.0001$).[7] Based on available data, fCal cutoffs between 100-150 ug/g have been proposed, identifying endoscopic recurrence with 70-89% sensitivity, 58-69% specificity, and a negative predictive values > 90%.[8,9] Additionally, serial fCal levels may predict early endoscopic and clinical recurrence and demonstrates treatment response.[10-13] Thus, fCal may have a role in proactive monitoring and assessing therapeutic response in postoperative CD.

Risk Factors for Postoperative Recurrence

Factors associated with POR include clinical, disease, surgical, histologic, microbiotic, and molecular characteristics. Active smoking after surgery doubles the risk of endoscopic, clinical, and surgical recurrence[14] and smoking cessation can reduce recurrence rates. Younger age at disease onset and rapid progression (<10 years) to surgical resection may increase recurrence risk.[15-17] A history of prior surgical resections for Crohn's may impart the strongest risk for future POR.[15,19] Penetrating disease behavior (fistula, abscess) at the time of surgery is associated with increased clinical and surgical recurrence.[19]

Emerging data suggests that the surgical approach and anastomosis technique may influence POR. Data suggests that extended mesenteric excision, akin to an oncologic resection, may reduce recurrence; however, this is awaiting prospective validation.[20] A recently described novel anastomosis technique, termed the Kono-S anastomosis, has been associated with significant reduction in endoscpopic and surgical recurrence compared to conventional anastomosis, suggesting a potential role for surgical technique selection in CD.[21,22] Furthermore, histologic findings including presence of granulomas, myenteric and submucosal plexitis,[23,24] and positive surgical margins may identify individuals at increased risk for POR.

Microbiome, serologic, genetic and other "-omics" signatures have been described in individuals who progress to POR, but data remains inconclusive for routine clinical care at the current time.

Risk stratification has been adopted in recent gastroenterological societal guidelines.[25] Patients at high risk for recurrence include those who are younger, actively smoking, multiple prior surgical resections, penetrating disease behavior, with or without perianal disease (Table 1). Patients deemed low risk include older (> 50 years), nonsmokers, first surgery for short segment (< 10 to 20 cm) of fibrostenotic disease, and disease duration for greater than 10 years. Such risk stratification can help identify patients warranting more aggressive treatment and monitoring after surgery.

Table 1. Risk categories and contributing factors with postoperative recurrence according to American Gastroenterological Association.[25]

Risk Category	Risk Factors
High Risk	Age < 30 Penetrating disease behavior, with or without perianal disease 2 prior resections Active smoking
Low Risk	Age > 50 Inflammatory or fibrostenotic disease First resection Short segment disease (<10 to 20 cm) Disease duration > 10 years

Nonbiologic Treatment Options for Preventing Postoperative Crohn's Disease

Medical therapies including antibiotics, aminosalicylates, and immunomodulators have been shown to moderately reduce the risk of clinical and endoscopic disease recurrence.[26] (Table 2) Mesalamine is safe, but only modestly effective in preventing endoscopic POR compared to placebo with a number needed to treat (NNT) of about 8.[27] Thiopurines including azathioprine or 6-mercaptopurine are superior to mesalamine, and reduce endoscopic recurrence with NNT of 4; however, limited benefit in preventing severe recurrence (i3, i4), and side effects and long-term risks of thiopurines have led to a reduction in clinical use in the U.S.[27]

Metronidazole (20 mg/kg) may significantly reduce the incidence of severe (i3-4) endoscopic recurrent disease compared to placebo-treated patients at 3 months after surgery (3 of 23; 13% vs. 12 of 28; 43%; $P = 0.02$), and clinical recurrence at 1 year (1 of 23; 4% vs. 7 of 28; 25%; $P = 0.044$).[28] The limitation of metronidazole is that patients often do not tolerate high doses, can develop neuropathies with prolonged exposure, and long-term prevention of recurrence is lost when the antibiotic is stopped. Lower dose metronidazole (250 mg TID) may confer similar risk reduction compared to placebo.[29]

Probiotics, Vitamin D supplementation, and curcumin have been evaluated with no significant effect in reducing POR in prospective trials.

Biologics for Prevention of Postoperative Crohn's Disease

Growing evidence demonstrates that anti-TNF therapy is the most effective treatment to prevent POR and may have the potential to change the natural course of Crohn's disease after surgery. In the seminal PREVENT trial, Regueiro et al. demonstrated that infliximab can be used in a prophylactic manner in individuals at high risk for recurrence. Postoperative infliximab significantly reduced endoscopic recurrence at week 76 compared to placebo (22.4% vs. 51.3%, $P < 0.001$), although not clinical recurrence (12.9% vs 20.0%, P=0.097).[30] This protective effect appears to extend to other anti-TNFs as ADA has also been found to prevent POR in several studies.[31-33] Data is emerging on the effectiveness and comparative efficacy of newer biologics compared to anti-TNFs; however, these agents remain under investigation despite routine clinical utilization.

Table 2. Efficacy of various therapies and knowledge gaps for the prevention and treatment of postoperative recurrence.

Therapy/ Intervention	POR Prevention	Treatment of POR
Curcumin	-	?
Enteral Nutrition	+	?
Probiotics	-	?
Nitroimidazole/ Antibiotics	+	-
Mesalamine	-	-
Budesonide	-	?*
Thiopurines	+	+
Anti-TNF	+++	+++
Vedolizumab	++?	?
Ustekinumab	++?	?

*Authors' opinion: Budesonide may be used for short term induction therapy, but similar to luminal ileal CD, is not likely effective for long-term therapy

Treating Postoperative Crohn's Disease: Waiting for Endoscopic Recurrence

There remain unanswered questions with postoperative Crohn's. Natural history studies have demonstrated that most but not all patients will develop recurrent disease. Thus, initiating prophylactic biologic therapy in all postoperative Crohn's disease patients would certainly mean overtreating a subset with consequent risks and costs. Additionally, whether prophylactic biologic therapy is more effective than waiting to treat recurrent disease is unknown. Anti-TNF therapy may be effective at treating early recurrent disease in certain patients, but response is often not complete or universal and efficacy of other biologics in this situation is largely unknown.

It does appear that early detection and treatment of POR improves outcomes. The timing of the first colonoscopy after surgery to detect endoscopic

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recurrence and prevent progression was assessed in the pivotal POCER study.[34] The authors demonstrated that colonoscopy at 6 months after surgery with treatment escalation for identified recurrence improved endoscopic rates at 18 months compared to routine care without a 6 month colonoscopy (49% vs. 67%, $P = 0.03$). This data suggests that early colonoscopy at 6 months with adjustment in therapy based on findings improves subsequent recurrence rates and may alter the course of postoperative Crohn's disease.

Strategies for Postoperative Crohn's Disease Management

Key questions that remain in the practical management of postoperative Crohn's disease are: (1) which patients should receive immediate postoperative therapy as prophylaxis against POR, and (2) in which patients would it be reasonable to wait to treat endoscopic recurrence? The current prevailing strategy for postoperative Crohn's disease management is to stratify postoperative treatment based on risk, and treats only those patients at high risk for recurrence with prophylactic medical therapy (Figure 1). High risk factors include age less than 30, multiple prior Crohn's-related surgeries, penetrating disease behavior (e.g., intraabdominal fistula or abscess), and active smoking. The authors also consider those with residual disease (gross or positive margins) after surgery to be at high risk for POR. High-risk individuals should be considered for prophylactic biologic therapy postoperatively.

For individuals at high risk, or with surgical or histopathologic factors for recurrence, e.g. myenteric plexitis, trasmural lesions, granulomas all requiring validation studies, one can consider incorporating early biomarker monitoring with fecal calprotectin at 3 months postop. If calprotectin elevated > 150 ug/ml, earlier colonoscopy (prior to month 6) to evaluate for recurrence is reasonable though prospective studies have not validated this approach to reduce subsequent recurrence

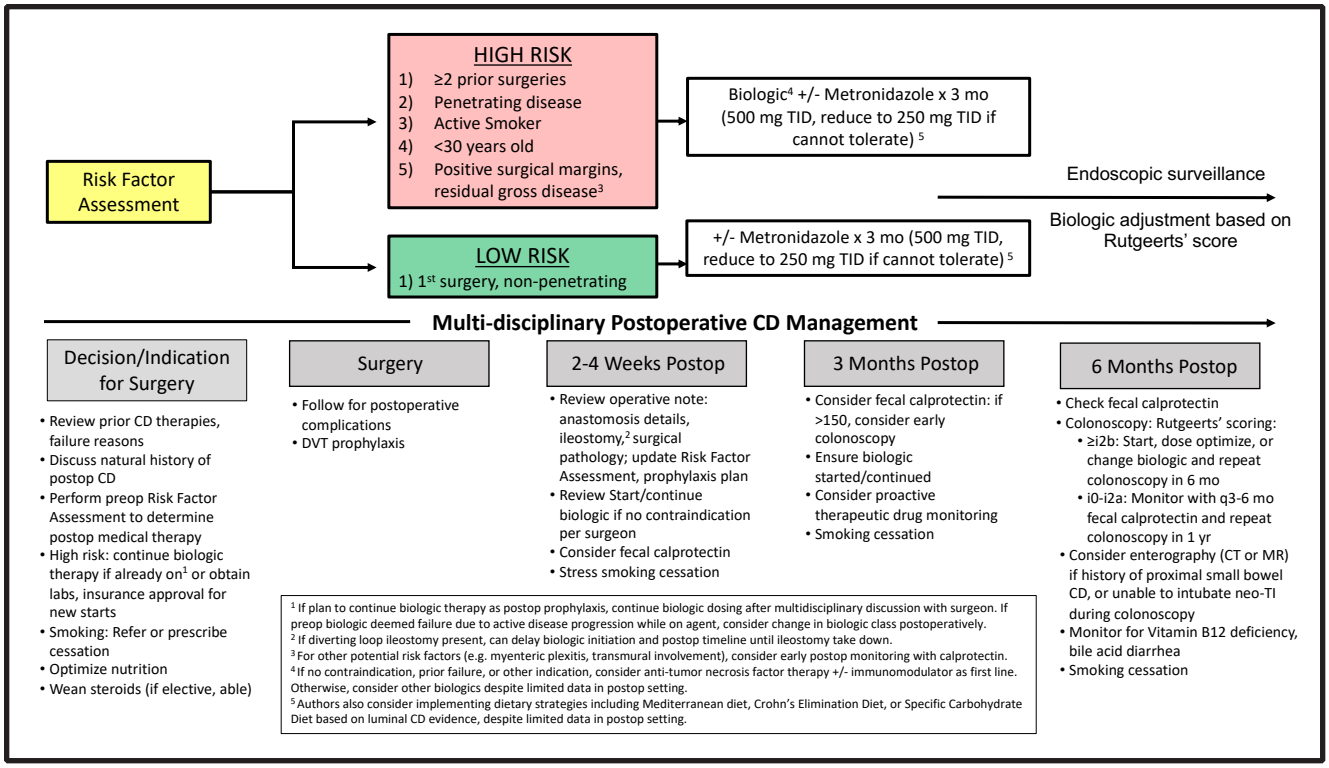

Figure 1. Proposed algorithm for the management of postoperative Crohn's disease. Low risk of postop recurrence defined by long-standing Crohn's disease, first surgery, and short stricture. High risk defined by multiple prior resections, penetrating disease, active cigarette smoking, young age or with confirmed microscopic or gross disease left in situ.

compared to waiting until 6 months.

In high-risk patients who are receiving preoperative biologic therapy and plan to utilize biologic therapy postoperatively, it is important to distinguish preoperative therapeutic failure (e.g., active disease progression despite adequate drug exposure) from "failure" due to preexisting damage (e.g. fibrostenotic stricture) or complication (e.g., penetrating disease). With verified therapeutic failure, the biologic mechanism of action should be changed postoperatively. If anti-TNFs were used preoperatively, one could consider non-anti-TNF agents despite the relative paucity of postop data for either vedolizumab or ustekinumab. It is the authors' opinion that with a preexisting stricture or complication, the preoperative biologic exposure does not necessarily represent a true therapeutic failure, but was rather instituted too late in the disease course to reverse the existing tissue damage. Consequently, the agent or therapeutic class may be continued postoperatively for prophylaxis, particularly for anti-TNFs (+/- immunomodulator) due to the wealth of evidence for their efficacy in POR. Despite historical concerns about risk of perioperative complications with biologics, more recent large prospective studies controlling for confounding factors (e.g. malnutrition, steroids) have not seen a detrimental effect of perioperative biologic exposure.[35] Thus, in this situation, the authors also frequently continue the biologic dosing throughout the perioperative period after discussing with the surgical team.

Low-risk patients are identified by those without prior surgical history, nonsmokers, and lacking other high risk factors. Individuals identified as low risk for POR would refrain from prophylactic biologic therapy and instead consider metronidazole therapy (20 mg/kg or approximately 500 mg TID) for at least 3 months (Figure 1). If unable to tolerate this dose due to side effects, dosing can be decreased to 250 mg TID. The benefit of postoperative metronidazole appears to be limited to the duration of time the patient is actively taking the medication. As such, POR is likely delayed by postoperative metronidazole rather than prevented. Until the microbiome-altering agent without side effects is identified, and can be sustained long-term, the use of metronidazole beyond 3 months will be limited.

All patients would then undergo a colonoscopy at 6 months from surgery. Concurrent calprotectin assessment (measured prior to colonoscopy preparation) is helpful if future biomarker monitoring is desired to align calprotectin levels to endoscopy findings. If the colonoscopy reveals active Crohn's disease (≥ i2), untreated patients would be started on biologic therapy, and those receiving prophylactic biologic therapy would undergo therapeutic drug monitoring, dose optimization, or change in biologic agent. If POR is identified and therapy is altered, disease activity monitoring with repeat colonoscopy should occur in 6 months to verify mucosal improvement. Those without endoscopic recurrence could be monitored with serial calprotectin every 3-6 months and ongoing colonoscopy surveillance in 1 year with subsequent intervals determined by findings. In individuals with prior proximal CD or incomplete colonoscopies, cross sectional imaging with enterography (CT or MR) offer a relatively sensitive and accurate detection of POR. Avoidance of radiation exposure with MR enterography should be considered in individuals with history of multiple abdominal CT scans, plans for serial imaging, or young age.

Symptoms that mimic active Crohn's disease can occur following an ileocecal resection and it is important for providers to understand possible etiologies and diagnostic plan. Postsurgical abdominal pain or discomfort is common in the days to weeks following the event, but typically steadily dissipates with time. Non-Crohn's potential etiologies to be considered include postoperative complications (anastomotic leak, abscess, hematoma), impaired gastrointestinal motility (e.g. ileus, opioid-induced constipation or gastroparesis), adhesive disease, cholelithiasis, cholecystitis, nephrolithiasis, or urinary tract infections. History, physical exam, and targeted laboratory evaluations and radiographic studies when indicated can help tease apart these etiologies.

Increased frequency and loose consistency of bowel movements can be normal gastrointestinal consequences of a resection surgery and intestinal adaption can occur in the months following. Fiber supplementation can often improve this clinical situation. Other postoperative diarrheal states should also be considered including Clostridium

difficile infection, bile acid diarrhea secondary to ileal resection, and small intestinal bacterial overgrowth. Stool testing for C. difficile, glucose or lactulose breath testing, and a trial of bile acid sequestrant (e.g, cholestyramine, colestipol) can be informative. Finally, in individuals with an extensive resection or with multiple prior resections, physiologic short gut syndrome can be identified by malabsorptive diarrhea with elevated fecal fat content, often accompanied by dehydration, weight loss, electrolyte disturbances and renal injury in the acute state.

Postoperative health maintenance should include periodic assessments of nutritional status including Vitamin B12 and Vitamin D, immunization considerations for those on biologic therapy, monitoring weight and dietary intake, smoking cessation when applicable, and ensuring execution of the postoperative Crohn's disease management and monitoring plan.

CONCLUSIONS

Despite medical and management advances, a significant portion of CD patients requires resective surgery. Postoperative recurrence of CD is common, often silent, and requires appropriate therapeutic and monitoring strategies to prevent disease progression. Preoperative risk stratification can help identify patients who may benefit most from prophylactic medical therapy postoperatively. To date, anti-TNFs remain the most effective therapy for prevention of Crohn's disease in high-risk patients. Ongoing surveillance with colonoscopy starting at 6 months postoperatively with or without biomarker monitoring allows for early recurrence identification and treatment. There remain many key knowledge gaps in risk factors, biomarkers, and management algorithms for postoperative Crohn's disease. ■

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Answers to this month's crossword puzzle:

1 N	I	2 T	R	3 O	G	4 L	Y	5 C	E	6 R	I	7 N	■	8 D
E	■	H	■	L	■	B	■	U	■	A	■	O	■	I
9 A	10 B	R	A	D	11 E	■	12 P	E	P	T	I	D	E	S
13 R	I	O	■	■	V	■	■	■	■	E	■	E	■	C
S	■	14 M	O	15 L	E	16 C	U	17 L	A	R	■	18 S	C	H
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19 C	H	O	L	A	N	G	I	T	I	20 S	■	21 F	O	R
■	■	S	■	R	■	E	■	E	■	C	■	■	■	G
22 C	L	E	A	N	■	23 N	O	R	■	24 A	25 B	26 A	T	E
R	■	D	■	■	■	T	■	A	■	27 B	A	R	■	■
28 A	M	■	29 O	30 D	D	■	31 F	L	U	■	32 C	M	■	33 L
M	■	34 C	■	R	■	■	A	■	■	■	I	■	35 P	A
36 P	R	U	37 R	I	T	38 U	S	■	39 W	I	L	S	O	N
S	■	40 R	E	P	■	N	■	■	H	■	L	■	■	C
■	41 B	E	D	■	42 M	I	C	R	O	B	I	O	M	E