Tailored Medical Management of the Complex Postoperative Crohn's Disease Patient

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Abstract

Keywords

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Despite advancements in medical therapy, many patients with Crohn's disease continue to require surgery for intestinal resection and/or management of perianal disease at some point in their disease course. Unfortunately, in this complex group of patients, postoperative disease recurrence rates are high. Medical prophylaxis can be used to prevent Crohn's disease recurrence or manage residual disease after surgery, but the ideal timing to start medications after surgery varies based on patient risk factors and patient preference for medication use. Currently, the largest medical treatment effects are seen with thiopurines and antitumor necrosis factor antibodies, but there are continually expanding options as new medical therapies are developed. A proposed algorithm stratified based on patient risk factors is provided.

The past two decades have seen the advent of newer and more tailored medical therapies including biologic agents for the management of the inflammatory bowel diseases, Crohn's disease, and ulcerative colitis. However, despite these advances, many patients with Crohn's disease continue to require surgery. Rates of abdominal surgery for Crohn's disease can be as high as 80% when including studies from tertiary care centers, while population-based studies demonstrate lower rates of approximately 16% at 1 year, 33% at 5 years, and 47% at 10 years.^{1–3} Similar rates are seen in studies evaluating only pediatric onset Crohn's disease.⁴ Furthermore, both referral center and population-based studies suggest that there has been minimal to no decrease in the rate of Crohn's disease surgery since the introduction of biologic agents.³ Unfortunately, such surgery is usually not curative as Crohn's disease typically recurs at some point in the postoperative course with anywhere from 35 to 70% of patients requiring repeat surgery within 10 years.^{1,5}

The etiology of postoperative Crohn's recurrence remains incompletely understood but appears to be multifactorial with contributions from bacterial flora, environmental factors, immune response, and genetic variants.⁶ From a surgical standpoint, recurrence rates are higher for patients undergoing anastomotic procedures than those for patients

requiring ileostomies. However, the type of anastomosis created after resection in Crohn's disease does not impact on the risk of recurrence.^{7,8} An important study evaluated 139 patients who underwent an ileocolic resection for Crohn's and were randomized to side-to-side or end-to-end anastomosis.⁷ No differences were found in endoscopic or clinical recurrence rates at 1 year following surgery.⁷

Given these significant problems of high rates of surgery and frequent postoperative recurrence in Crohn's disease, maximizing postoperative medical management is essential. In this review, we will discuss approaches to identifying high-risk patients, optimal medical management of Crohn's disease following surgery with a particular focus on types of medications and when to use them after surgery. Review of recently published key medical prophylaxis clinical trials and guidelines will be discussed.

Defining Postoperative Recurrence in Crohn's Disease

Before discussing risk stratification and medical management of postoperative Crohn's disease, it is important to understand which endpoints are being assessed when discussing frequency of postoperative recurrence. Typically,

recurrence is first detected on endoscopic studies and can be noted as early as 3 months postoperatively—this is referred to as *endoscopic recurrence*. As will be discussed further later, there is a progression of endoscopic lesions, from scattered aphthous ulcers to severe ulcerations and strictures, which is predictive of subsequent clinical course. Recurrence of symptoms (*clinical recurrence*) and the need for further surgical resection (*surgical recurrence*) typically follow later in the postoperative course. It is important to recognize that assessment of symptoms in the postoperative course can be challenging as factors such as altered anatomy, bile acid-induced diarrhea, and small intestinal bacterial overgrowth can lead to symptoms that mimic those of active Crohn's.

With that understanding of definitions and endpoints, a review of postoperative Crohn's disease studies demonstrates that endoscopic recurrence rates can be as high as 70 to 90% at 1 year following surgery, clinical recurrence rates can be as high as 20 to 30% at 1 year, and the need for repeat surgery occurs in anywhere from 35 to 70% of patients at 10 years.^{1,5}

Identifying Patients at High Risk of Postoperative Crohn's Disease Recurrence

Complicating the decision making of how to manage patients after surgery is the fact that identification of risk factors in studies often has yielded conflicting results. Within those limitations, current smoking, perforating disease phenotype at index surgery, pathologic findings of granulomas or myenteric plexitis, presence of perianal disease, and the creation of an anastomosis appear to be most predictive for an increased risk of disease recurrence.^{6,9-13} Among these, establishment of intestinal continuity and smoking are the best replicated risk factors.⁶ Highlighting the important role of intestinal continuity in postoperative recurrence, Rutgeerts et al showed that five patients with Crohn's disease who had undergone intestinal resection with ileocolic anastomosis and proximal diverting ileostomy had no endoscopic evidence of recurrence in the neoterminal ileum 6 months after surgery. However, after bowel continuity was restored, essentially all patients had rapid endoscopic recurrence in the neoterminal ileum.¹⁴ Smoking, which is the only modifiable risk factor, has been shown to be associated with a 2-fold increase in clinical relapse after surgery among smokers compared with nonsmokers and a 2.5-fold increase in the risk of further surgery by 10 years.¹² Importantly, smoking cessation has been correlated with a decreased risk of postoperative recurrence, emphasizing the importance of addressing this modifiable risk factor.^{15,16}

The Role of Endoscopy in Guiding Postoperative Crohn's Disease Management

Endoscopic recurrence typically precedes clinical symptoms following surgery for Crohn's disease with evidence of endoscopic disease in the neoterminal ileum in as many as 70 to 90% of patients 1 year following ileocolonic resection and anastomosis.¹⁷⁻¹⁹ Given this rapid and high rate of recurrence,

endoscopic evaluation for Crohn's disease in the postoperative setting has been shown to be helpful for both diagnostic and risk stratification purposes. In a study evaluating the pattern of endoscopic recurrence in 114 patients who had serial colonoscopies after undergoing ileocolonic resection, 77% of patients developed endoscopic recurrence within 1 year of surgery with disease typically confined to the neoterminal ileum and anastomosis.¹⁸ The most common endoscopic finding was aphthous ulcers, found in 76% of those with endoscopic recurrence, while more advanced lesions of nodules and large ulcers were found in 24% of patients.¹⁸ Furthermore, over a 3-year time period, there was a progression of endoscopic lesions with nodules and larger linear or serpiginous ulcers developing more frequently and in patients examined more than 3 years after surgery; 46% developed a rigid, ulcerated stenosis of the anastomosis and/or the neoterminal ileum.¹⁸ These findings demonstrate the typical pattern of endoscopic recurrence after ileocolonic resection for Crohn's disease and highlight the progression from mild to severe endoscopic disease.

A subsequent study by Rutgeerts et al followed up 122 Crohn's patients who had undergone a first or second ileocolic resection and who received no initial postoperative medical therapy.²⁰ All patients had a colonoscopy to the neoterminal ileum within 1 year after surgery and findings were scored based on an endoscopic scoring system that the investigators developed and that is still in use today, the Rutgeerts endoscopic score. The components of this score are shown in ►Table 1.²⁰ The endoscopic score at the first follow-up colonoscopy examination was shown to be the most strongly associated risk factor for subsequent symptomatic recurrence.²⁰ Specifically those with no (i0) or only mild recurrence (i1) within 1 year of surgery did very well on subsequent follow-up with a low risk of symptomatic recurrence over the next 5 years. However, those with more advanced endoscopic lesions including diffuse aphthous ileitis/inflammation (i3) or large ulcers, nodules, and/or narrowing (i4) had very high rates of symptomatic recurrence on follow-up. In fact, all patients with an i4 endoscopic score developed symptomatic recurrence within 4 years of surgery.²⁰ In addition, the severity of endoscopic recurrence within 1 year of surgery also predicted the evolution of progression of endoscopic scores at repeat colonoscopy 3 years postoperatively.²⁰

Table 1 Rutgeerts endoscopic scoring system

Classification	Endoscopic description
i0	No lesions
i1	Less than 5 aphthous ulcers
i2	More than 5 aphthous ulcers with intervening normal mucosa or Skip areas of larger lesions or Lesions confined to the ileocolic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, nodules, and/or narrowing

Therefore, endoscopic examination of the ileocolic anastomosis and neoterminal ileum plays an important role for both diagnosis and risk stratification with the severity and extent of endoscopic recurrence being strongly associated with clinical recurrence risk. Based on such evidence, endoscopic monitoring for disease recurrence has been adopted as one potential strategy after surgery for Crohn's disease. Recommendations regarding the use of endoscopy to guide decision making in the postoperative setting have been incorporated into societal guidelines as follows:

American Gastroenterological Association

- "In patients with surgically induced remission of CD not receiving pharmacological prophylaxis, the American Gastroenterological Association (AGA) recommends postoperative endoscopic monitoring 6 to 12 months after surgical resection over no monitoring." (Strong recommendation, moderate quality of evidence.)²¹
- "In patients with surgically induced remission of CD with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing anti-TNF and/or thiopurine therapy over continued monitoring alone." (Conditional recommendation, moderate quality of evidence.)²¹

European Crohn's and Colitis Organization

- "Ileocolonoscopy is the gold standard in the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course [EL2]. Ileocolonoscopy is recommended within the first year after surgery where treatment decisions may be affected [EL2]."¹³

Supporting such recommendations are the results of a randomized postoperative Crohn's endoscopic recurrence (POCER) trial, in which 184 consecutive patients undergoing surgical resection with an endoscopically accessible anastomosis received medical therapy and were monitored for disease recurrence via one of two approaches in randomized fashion.²² More specifically, all patients received postoperative treatment with metronidazole for 3 months and, in addition, those who met predefined criteria for high risk of recurrence also received treatment with azathioprine or 6-mercaptopurine; patients who had intolerance to thiopurines were instead treated with adalimumab. All patients were then randomized in a 2:1 ratio to either undergo a colonoscopy at 6 months following surgery with adjustment of therapy based on endoscopic findings (active care) or to no colonoscopy at 6 months (standard care). In the active care group, endoscopic evidence of recurrence at 6 months dictated changes in medical therapy as follows: those at low risk stepped up to therapy with a thiopurine, those on a thiopurine stepped up to addition of adalimumab, and those on adalimumab had dose escalation of the adalimumab. The primary endpoint of the study was endoscopic recurrence (Rutgeerts score of i2, i3, or i4) at 18 months after surgery. Intention-to-treat analysis of patients who received at least one dose of study drug demonstrated a lower rate of endoscopic recurrence at 18 months in the active care group (49%)

compared with the standard care group (67%); $p = 0.03$.²² Furthermore, 22% of patients in the active care group had endoscopic remission (Rutgeerts score of i0) at 18 months compared with only 7% in the standard care group; $p = 0.03$.²² Demonstrating the important role of colonoscopy in guiding therapeutic decisions, 39% of patients in the active care group had a step up in treatment based on the results of the colonoscopy done at 6 months. Of these patients, 38% had achieved endoscopic remission at repeat colonoscopy at 18 months. However, it is also important to note that among patients with endoscopic remission at 6 months, 41% developed endoscopic recurrence 1 year later, emphasizing the importance of continued monitoring.²² In reviewing these results, one can conclude that the POCER study provides prospective, randomized evidence that endoscopy can guide postoperative Crohn's disease medical management decisions to lower the risk of recurrence.

Medical Management of Postoperative Crohn's Disease

The POCER study highlights some of the important issues related to medical therapy in the postoperative Crohn's disease patient. Decisions regarding if and when to start medical therapy after surgery have to incorporate multiple factors including patient preferences, assessment of risk factors for recurrence, and choosing which of the different medical treatment options to pursue. Among patients with risk factors, prophylaxis of any disease recurrence is the main goal and therapy must be started quickly after surgery. In contrast, for patients felt to be at low risk for recurrence, postoperative colonoscopy can be used to guide decision making for medical therapy as noted earlier. With this approach, the goal is no longer true prophylaxis but rather detecting endoscopic recurrence early and preventing further progression and development of clinical or surgical recurrence.

Once a decision is made to start therapy, understanding the evidence behind different treatment options is helpful in guiding therapeutic choices. Several agents including nitroimidazole antibiotics (metronidazole, ornidazole), mesalamine, azathioprine or 6-mercaptopurine, and antitumor necrosis factor (TNF) antibodies have shown at least some degree of benefit in prophylaxis of disease recurrence, but the most promising results come with use of azathioprine/mercaptopurine and anti-TNF antibodies (► **Table 2**).²³

6-Mercaptopurine and azathioprine are purine analogs that effect immune modulation by inhibition of de novo purine ribonucleotides and by blunting the proliferation of rapidly dividing cells such as lymphocytes. They are not FDA approved for the treatment of Crohn's disease but have been widely used for many years. There have been several, mostly small, studies comparing azathioprine or 6-mercaptopurine to either placebo or other agents in the prevention of postoperative Crohn's disease recurrence. A Cochrane review of these studies showed that thiopurines had lower clinical relapse rates compared with placebo (relative risk = 0.74, 95% confidence interval [CI]: 0.58–0.94), but with low-quality evidence.²⁴ There was an uncertain effect when thiopurines were compared with

Table 2 Comparison of large, randomized trial for medical prophylaxis of postoperative Crohn's disease recurrence

	N	Endoscopic recurrence rates ^a			Clinical recurrence rates		
		Placebo	Treatment	p-Value	Placebo	Treatment	p-Value
TOPPIC ^{25,b}	240	49%	43%	0.38	23%	13%	0.07
PREVENT ^{31,c}	297	51%	22%	<0.001	20%	13%	0.097

^aEndoscopic recurrence defined as a Rutgeerts endoscopic score of i2 or greater

^bRecurrence within 3 years postoperatively.

^cRecurrence at 1 year postoperatively.

mesalamine agents.²⁴ More recently, a large placebo-controlled trial called TOPPIC evaluated 240 patients who were randomized to 6-mercaptopurine at a dose of 1 mg/kg per day versus placebo after surgery and who were then followed up for 3 years.²⁵ The primary endpoint was clinical recurrence (as assessed using the Crohn's disease activity index) that required medical treatment or surgical intervention. Results showed a small but not significant effect of treatment with 13% of patients in the 6-mercaptopurine group versus 23% patients in the placebo group developing clinical recurrence requiring medical or surgical intervention ($p = 0.07$).²⁵ Of note, drug dose was not adjusted based on measured drug levels and it was found that 60% of patients treated with 6-mercaptopurine had subtherapeutic levels at week 49. Interestingly, however, subgroup analysis revealed that 6-mercaptopurine was effective in reducing clinical recurrence in smokers compared with nonsmokers ($P_{\text{interaction}} = 0.018$). There was no difference of endoscopic recurrence when defined as a Rutgeerts score of i2 or greater, but if the cutoff was changed to a Rutgeerts score of i1 or greater, a treatment benefit was noted with recurrence rates of 64% in the 6-mercaptopurine group versus 82% in the placebo group at week 49 ($p = 0.01$). Finally, the authors performed an updated meta-analysis of this study combined with two other randomized, placebo-controlled trials and found that there was a treatment benefit for thiopurines compared with placebo (relative risk = 0.57, 95% CI: 0.38–0.85).²⁵

Anti-TNF antibodies are biologic agents that have had great impact on the medical management of Crohn's disease and ulcerative colitis. In the postoperative setting, initial small studies suggested a significant effect of infliximab and adalimumab in the prevention of postoperative Crohn's recurrence and in reducing progression of disease once endoscopic recurrence was noted.^{26–30} For example, a small placebo-controlled trial randomized 24 patients with Crohn's disease to receive infliximab or placebo starting within 4 weeks of surgery and showed that endoscopic recurrence was much significantly lower in the infliximab group (9 vs. 85% in the placebo group; $p = 0.0006$).²⁶ Subsequently, a large randomized clinical trial, the PREVENT study, enrolled 297 Crohn's disease patients who had undergone ileocolic resection with ileocolonic anastomosis and met criteria for increased risk of recurrence.³¹ Subjects were randomized to treatment with infliximab or placebo every 8 weeks. The primary endpoint of the study, clinical recurrence at or before week 76, was not met with recurrence rates of 13% for the infliximab group and 20% for the placebo group

($p = 0.097$). However, endoscopic recurrence classified as Rutgeerts score of i2 or greater was significantly different with rates of 22% for the infliximab group and 51% for the placebo group ($p < 0.001$).³¹ An even more impressive difference was noted when analyzing more severe endoscopic recurrence grades of i3 or i4 with only 19% of infliximab-treated patients having that degree of recurrence compared with 81% of placebo-treated patients.

A technical review of all medical postoperative treatment options (but not including the recently published TOPPIC trial) concluded that thiopurines and anti-TNF agents reduced both endoscopic and clinical recurrence rates. For thiopurines, the relative effect odds ratios 0.35 (95% CI, 0.14–0.85) for endoscopic recurrence and 0.40 (95% CI, 0.17–0.95) for clinical recurrence, while for anti-TNF agents, the corresponding odds ratios were 0.51 (95% CI, 0.28–0.94) and 0.24 (95% CI, 0.15–0.39).²³ Further building on these conclusions, a meta-analysis that compared the relative efficacy of all pharmacologic interventions concluded that anti-TNF monotherapy was the most effective pharmacologic intervention.³²

Although studies of postoperative Crohn's disease management have not always shown an effect for medical therapy or have not met their primary endpoints, there is enough evidence to support the use of thiopurines and anti-TNF agents. Guidelines from the AGA and European Crohn's and Colitis Organization (ECCO) support this as follows.

American Gastroenterological Association

- “In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents (conditional recommendation, moderate quality of evidence).”²¹

European Crohn's and Colitis Organization

- “Prophylactic treatment is recommended after ileocolonic intestinal resection in patients with at least one risk factor for recurrence [EL2]. To prevent postoperative recurrence, the drugs of choice are thiopurines [EL2] or anti-TNFs [EL2].”¹³

Conclusion

For patients with Crohn's disease who undergo intestinal resection, disease will recur in the majority at some point in their disease course and thus prevention of such recurrence is an important goal. However, decision making in the postoperative setting is affected by several factors including

findings that some patients are at low risk of recurrence or may not develop clinical recurrence for many years after surgery. Smoking is the only modifiable risk factor and smoking cessation has been correlated with a decreased risk of postoperative recurrence. Initiation of postoperative medical therapy especially thiopurines and anti-TNF antibodies holds promise in reducing the risk of recurrence. Endoscopic evaluation of the anastomosis and neoterminal ileum 6 to 12 months after surgery using the Rutgeerts scoring system (►Table 1) can play a key role in guiding decision making. Specifically, endoscopic findings can inform decisions as to when to start therapy if medications are not started immediately after surgery and also regarding the need to optimize or change therapy. Supporting the use of endoscopic findings are results from the POCER study, a randomized clinical trial which provides evidence that endoscopy can guide postoperative Crohn's disease management to lower the risk of recurrence.

Of the many medical therapies that have been studied for prophylaxis of postoperative Crohn's disease recurrence, thiopurines and anti-TNF agents appear to hold the most promise. Although results from small studies appear promising, the two largest controlled trials of 6-mercaptopurine (TOPPIC) and infliximab (PREVENT) did not meet the primary endpoint of reducing clinical recurrence (►Table 2). However, evaluation of secondary endpoints and subgroup analyses suggest a benefit for these therapies. Based on such results, both AGA and ECCO guidelines recommend thiopurines or anti-TNF agents as the agents of choice when postoperative therapy is initiated.

Given some remaining uncertainties as to which patients to treat and which medications should be used, there have been various approaches recommended as to when and how to start therapy after surgery. Treating all patients postoperatively does not make sense from a cost-effectiveness standpoint and because patients at low risk of recurrence may have many years of an endoscopic and symptom free state. In addition, some patients prefer not to take medication after surgery when they are feeling well and given concerns regarding possible side effects of medications. Based on all these factors, a reasonable approach when considering postoperative management is to counsel all patients who smoke about the importance of cessation and to stratify each patient as being at low or high risk for disease recurrence. Those at low risk include nonsmokers, patients undergoing their first intestinal resection for Crohn's, and absence of high risk factors. Such patients do not need to start medical therapy postoperatively and can be followed up closely clinically and with a colonoscopy 12 months after surgery. If significant endoscopic recurrence is found at that time, medical therapy should then be initiated. Those at high risk include current smokers, patients with penetrating disease at index surgery, finding of granulomas or myenteric plexitis on pathology, and the presence of perianal disease. In addition, factors such as the need for extensive small bowel resection and prior intestinal resection should be considered in patients at higher risk. Such patients should start

therapy with an anti-TNF agent with or without a concomitant immunomodulator shortly (ideally within 4 weeks) after surgery and should then undergo a colonoscopy 6 to 12 months after initiation of therapy with adjustment of therapy if significant endoscopic recurrence is found. In patients who have previously failed anti-TNF agents, treatment with a thiopurine or with a different biologic class agent can be considered.

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