

Prevention and Treatment Options for Postoperative Crohn's Disease: A Clinical Dilemma

Kofi Clarke, MD, and Miguel Regueiro, MD

Dr. Regueiro serves as Associate Professor of Medicine in the Division of Gastroenterology, Hepatology, and Nutrition at the University of Pittsburgh School of Medicine, where he is Co-Director of the Inflammatory Bowel Disease Center and Director of the Gastroenterology, Hepatology, and Nutrition Fellowship Program. Dr. Clarke is a fellow in the Division of Gastroenterology, Hepatology, and Nutrition at the University of Pittsburgh School of Medicine.

Address correspondence to:
Dr. Miguel Regueiro
University of Pittsburgh Medical Center
200 Lothrop Street
PUH-C Wing Mezzanine Level
Pittsburgh, PA 15213;
Tel: 412-648-2344;
Fax: 412-383-8913;
E-mail: mdr7@pitt.edu

Abstract: The majority of patients with Crohn's disease require surgery for disease-related complications. Postoperative Crohn's disease recurrence is common after intestinal resection. The optimal management strategy for postoperative recurrence of Crohn's disease is controversial. In the absence of universally adopted guidelines, clinicians and patients must discuss and weigh the risks and benefits of postoperative pharmacotherapy. Those patients at low risk of disease recurrence may not require treatment. On the other hand, patients with more aggressive disease and high risk of recurrence may be best treated early in the postoperative period with an immunomodulator or antitumor necrosis factor agents. Ideally, postoperative treatment decisions would be made using predictable, reliable, and reproducible clinical prediction criteria that would guide treatment. This article reviews the data on postoperative Crohn's disease, including predictors of early recurrence, available options for postoperative monitoring, timing of initiation, and choice of postoperative therapy for prevention and management.

Despite the widespread acceptance and use of immunomodulator therapy, approximately 75% of Crohn's disease patients require intestinal surgery for complications resulting from strictures, penetrating disease, and abscesses.¹⁻³ Postoperative recurrence of Crohn's disease is common. Surgical resection is not curative, and postoperative histologic recurrence in macroscopically normal intestine has been reported as early as 1 week.⁴ Endoscopic evidence of disease recurrence is present in 70–90% of patients within 1 year of intestinal resection.^{5,6} Symptomatic clinical recurrence is seen in one third of patients at 3 years and in 60% of patients at 10 years.¹

Predictors of Early Recurrence

Although early symptomatic recurrence after surgery for Crohn's disease remains unpredictable,⁷ several studies have evaluated possible

Keywords

Crohn's disease, postoperative recurrence, 5-aminosalicylates, immunomodulators, infliximab

predictors of early disease recurrence.^{8,9} These predictors may provide some guidance for patient stratification and selection for early treatment and follow-up colonoscopy. The type of anastomosis, surgical complications requiring early reoperation, and early age of disease onset indicate aggressive disease and warrant earlier use of postoperative pharmacotherapy.^{7,9} Patients with Crohn's disease who smoke have a 2.5-fold increased risk of surgical recurrence and a 2-fold increased risk of clinical recurrence compared to nonsmokers.¹⁰ Patients with a family history of Crohn's disease are twice as likely to have a second ileocolic resection, but certain genotypes (eg, CARD15 mutations) have not been associated with a higher risk of disease recurrence.¹¹ A small Japanese study reported a reduction in the risk of postoperative disease recurrence at 1 year in patients who received postoperative enteral elemental nutrition.¹² Other risk factors associated with early postoperative disease recurrence include the nature of disease activity (ie, penetrating/fistulizing disease, short disease duration before surgery, and ileocolonic disease).¹³⁻²⁰

Postoperative Monitoring

Radiologic tests, clinical symptoms, serologic markers, and endoscopy (both capsule endoscopy and colonoscopy) have been evaluated as a means for early detection of postoperative disease recurrence. With the exception of endoscopic evaluations and small intestine contrast ultrasonography (SICUS), the other parameters have not been consistently good markers for detection of early disease recurrence.

Among patients who have undergone intestinal resection for Crohn's disease, clinical symptoms, as defined by the Crohn's Disease Activity Index, have correlated poorly with endoscopic recurrence.²¹ Similarly, there is no good clinical correlation between disease activity and fecal levels of lactoferrin and calprotectin after resection of diseased bowel. Crohn's disease patients maintain high levels of both markers even in the absence of symptoms.²²

SICUS is a noninvasive technique that may be useful for assessing disease recurrence after surgery. In a study investigating the accuracy of SICUS compared to ileocolonoscopy for the assessment of Crohn's disease recurrence after ileocolonic resection, 72 Crohn's disease patients were followed postoperatively. SICUS had a sensitivity of 92.5% for detecting recurrence but a low specificity of 20% and an accuracy of 87.5%. The finding of bowel wall thickening detected by SICUS correlated well with endoscopic disease recurrence ($P=.0001$; $r=0.67$).²³ Although SICUS has the advantage of being noninvasive, its low specificity is a limitation, and ileocolonoscopy remains the modality of choice for detecting mucosal Crohn's disease recurrence.

Table 1. Endoscopic Recurrence Score

Endoscopic score	Definition
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Remission=endoscopic score of i0 or i1; recurrence=endoscopic score of i2–i4.

Wireless capsule endoscopy (WCE) is another non-invasive alternative to ileocolonoscopy. Biancone and associates²⁴ compared SICUS and WCE to colonoscopy for detecting Crohn's disease recurrence 1 year after surgery. In the study, 22 Crohn's disease patients underwent SICUS and colonoscopy, followed by WCE. Seventeen patients were studied by all three modalities. SICUS detected lesions in all 17 patients, with 1 false positive; colonoscopy detected lesions in 16 patients, and WCE detected lesions in 16 of the 17 patients, with 1 true negative. A recent study by Gralnek and colleagues proposed a WCE scoring index that more accurately defines Crohn's disease recurrence and includes three parameters: villous edema, ulcers, and stenosis.²⁵ Overall, WCE is safe, but there is a risk of capsule retention that necessitates surgical extraction in 10–13% of patients.

Endoscopic recurrence correlates with the subsequent development of clinical recurrence as well as the need for reoperation.⁶ Rutgeerts and coworkers⁶ developed an endoscopic recurrence score (Table 1 and Figure 1) that correlates with the likelihood of future clinical and surgical recurrence. One-year endoscopic scores of i0 or i1 correlate with a low risk of endoscopic progression and with clinical recurrence rates of less than 10% over 10 years. Endoscopic scores of i2 correlate with clinical recurrence rates of 20% over 5 years, whereas scores of i3 and i4 correlate with clinical recurrence rates of 50–100% and a high likelihood of requiring reoperation. Overall, among patients who have undergone surgical resection for Crohn's disease, as many as 70% require repeat surgery within 20 years. This scoring system provides a uniform guide to clinicians for discussions with

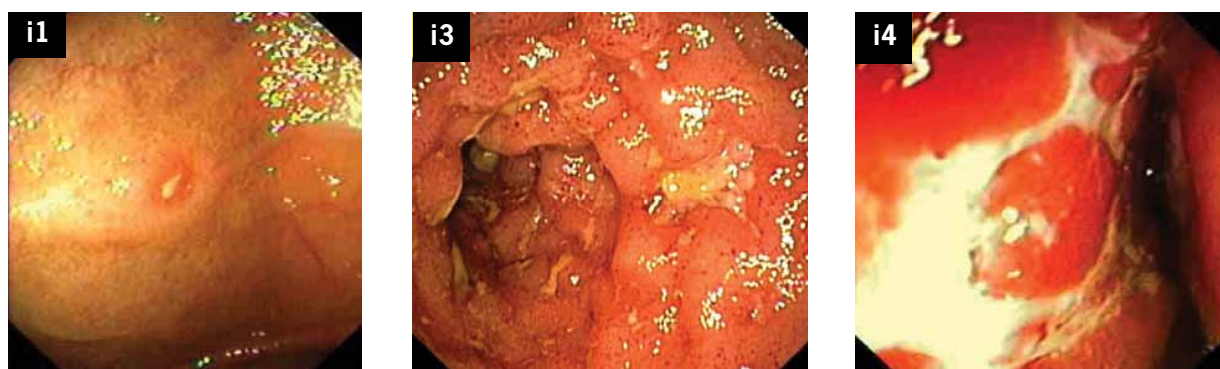


Figure 1. Rutgeerts endoscopic scoring system: neoterminal ileum (endoscopic views of Table 1).

patients on treatment choices, including treatment risks versus benefits.

Therapeutic Options/Medications

There are data from randomized controlled trials and experiential studies on the treatment of postoperative Crohn's disease with different medications and supplements. The design of the trials, endpoints, and follow-up duration are varied. Several trials on different agents are reviewed.

The Placebo Effect

In a recent systematic review and meta-analysis of 12 randomized, placebo-controlled trials, the pooled placebo rate of maintaining clinical remission postoperatively was 56% (95% confidence interval [CI], 47–64%; range, 34–89%) during a median follow-up of 52 weeks (range, 12–156 weeks). The pooled placebo endoscopic recurrence rate was 58% (95% CI, 51–65%; range, 36–80%) during the same follow-up period. However, there was significant heterogeneity among the trials, and prior steroid therapy was the only factor consistently found to be associated with remission.²⁶ In a second meta-analysis of 14 trials with over 1,400 patients, Cao and colleagues concluded that medical treatment has a sufficiently beneficial effect on decreasing the risk of clinical postoperative recurrence in patients with Crohn's disease. In the per-protocol analysis, medical treatment was associated with a significantly lower incidence of clinical recurrence (0.84, 0.72–0.97; $P=.020$), but there were no significant differences in endoscopic recurrence (0.94, 0.85–1.05; $P=.268$) or severe endoscopic recurrence (0.76, 0.55–1.04; $P=.084$) between the two groups of patients.²⁷

The wide variation in the placebo effect is not fully explained. It may be due to heterogeneity in the trials or due to the trial design.

Probiotics and Prebiotics

The possible role of gut bacteria in the immune pathogenesis of Crohn's disease has led some investigators to evaluate the efficacy of prebiotics and probiotics in prevention of postoperative recurrence in Crohn's disease. In a trial by the GETAID group that evaluated *Lactobacillus johnsonii LA1* versus placebo, Marteau and colleagues failed to show any benefit over placebo in postoperative endoscopic recurrence at 6 months using Rutgeerts' scale.²⁸ In a separate trial by Van Gossum, treatment with *L. johnsonii LA1* for 12 weeks in patients with Crohn's disease after ileocecal resection did not decrease endoscopic recurrence. The mean endoscopic score was not significantly different from placebo at 3 months (LA1 vs placebo: 1.50 ± 1.32 vs 1.22 ± 1.37 ; treatment effect: $P=.48$; smoke effect: $P=.72$).²⁹ In a study with Synbiotic 2000, a cocktail of 4 prebiotics and 4 probiotics, there was no effect on the postoperative recurrence of Crohn's disease.³⁰ Prantera and coworkers confirmed these results and did not find any difference in endoscopic recurrence rates between patients on *Lactobacillus GG* versus placebo ($P=.297$).³¹

To date, probiotics and prebiotics do not show any advantage over placebo in preventing postoperative endoscopic recurrence.

Aminosalicylates

There is a wealth of data evaluating sulfasalazine and mesalamine in the postoperative setting. The results are summarized in Table 2. The first two trials with sulfasalazine had very small patient populations (66 and 48) and did not show any benefit in the reduction of postoperative recurrence of Crohn's disease.^{32,33} The third trial with sulfasalazine by Ewe and associates had a larger number of patients but did not demonstrate significant statistical reduction over placebo.³⁴

The results from placebo-controlled trials on mesalamine are mixed.³⁵⁻³⁷ A total of 7 trials are listed in Table 2.

The study conducted by Lochs and coworkers, which evaluated 318 patients, showed a trend toward a reduction in clinical relapse (24.5% vs 31.4%; $P=.1$).³⁸ Endoscopic relapse rates, a secondary endpoint, were reported for 97 of the participating patients, with a slight decrease in endoscopic recurrence in the mesalamine group at 6 weeks (30% vs 27%, placebo) and 18 months (50% vs 66%). The study by McLeod and associates showed a significant decrease in clinical recurrence at 72 months (31% mesalamine vs 41% placebo; $P=.031$), and modest reductions in a combined endpoint of endoscopic or radiologic evidence of recurrence.²¹ Two studies by Caprilli and colleagues showed favorable results for the use of mesalamine as postoperative prophylaxis. The first study³⁹ reported that mesalamine treatment reduced cumulative endoscopic recurrence rates at 24 months, with patients in the active treatment arm experiencing relapse rates of 52% compared to 85% in placebo patients. The second study,⁴⁰ which compared two dosage regimens of mesalamine, showed a greater reduction in endoscopic recurrence among those treated with 4.0 g daily of mesalamine compared to those receiving 2.4 g daily (46% vs 62%; $P=.04$).

Overall, aminosalicylates appear to have a modest benefit in preventing postoperative recurrence of Crohn's disease.

Antibiotics

Two studies have examined the utility of nitroimidazole antibiotics in the prevention of postoperative Crohn's disease recurrence. The first trial⁴¹ evaluated 60 patients and reported a 13% reduction in endoscopic recurrence rates comparing metronidazole to placebo ($P=.02$). Metronidazole also reduced the clinical recurrence rates at 1 year (4% vs 25%), but the benefit was not sustained at 2 and 3 years. The second trial randomized patients to either 1 g daily of ornidazole or placebo starting within 1 week of surgery and continued for 1 year. Clinical recurrence rates at 1 year were significantly reduced in the treatment arm, 7.9% compared to placebo (37.5%; $P=.0046$). Endoscopic recurrence at 12 months was also significantly reduced compared to placebo (79% vs 53.6%; $P=.037$). There were more side effects in the treatment group, leading to a higher drop-out rate ($P=.041$).⁴²

Although nitroimidazole antibiotics reduce both clinical and endoscopic recurrence, these agents are poorly tolerated and the maintenance benefit is only sustained if the medications are continued long term.

Budesonide

Two double-blind randomized trials with budesonide did not show any benefit in the prevention of postoperative recurrence of Crohn's disease. In the first study, budesonide did not show a significant reduction in endo-

scopic recurrence at 3 and 12 months. In the second study, there was no statistically significant difference in both clinical and endoscopic recurrence rates at 1 year between the treatment and placebo groups.^{43,44}

Immunomodulators

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective medications for the maintenance of medically induced Crohn's disease remission, but the results are disparate for postoperative prevention. In an open-label, randomized study comparing AZA (2 mg/kg/d) to mesalamine (3 g/d), there was no difference in clinical relapse risk at 24 months between the two groups.⁴⁵ A study by Hanauer and coworkers compared 6-MP (50 mg), mesalamine (3 g), and placebo in a randomized, double-blind, double-dummy fashion. Clinical recurrence rates at 24 months were 50%, 58%, and 77% for 6-MP, mesalamine, and placebo, respectively. However, only 69% of the patient population finished the study and was evaluated for the clinical recurrence endpoint.⁴⁶ Endoscopic recurrence rates were 43%, 63%, and 64%, and radiographic recurrence rates were 33%, 46%, and 49%, respectively. D'Haens and associates⁴⁷ also showed that a combination of metronidazole for 3 months with AZA for 12 months is superior to metronidazole alone in reducing postoperative endoscopic recurrence of Crohn's disease in patients at 12 months (55% vs 78%; $P=.035$).

Although the data are sparse, 6-MP/AZA may prevent postoperative Crohn's disease recurrence in select patients.

Biologics

Data on the use of biologic agents for the prevention of postoperative Crohn's disease recurrence are limited. The most striking results were reported by Regueiro and associates of a randomized controlled trial evaluating 24 patients assigned to receive infliximab (Remicade, Centcor) 5 mg/kg or placebo 4 weeks after surgery,⁴⁸ with treatment continuing every 8 weeks for 1 year. Endoscopic recurrence was reported in 9.1% of active treatment patients and 84.6% of placebo patients at 1 year ($P=.0006$). More severe grades of endoscopic recurrence were found in the placebo group: 23.1% of endoscopic grade 3 recurrence and 30.8% of grade 4 recurrence. Five of the placebo patients experienced clinical relapse compared to none in the infliximab group. Although the numbers are small, the patients who received placebo for 1 year and had evidence of endoscopic recurrence (i2–i4) had an attenuated response to infliximab (ie, their endoscopic scores improved, but over half still had scores of at least i2).⁴⁹

In a small prospective pilot study, Sorrentino and coworkers compared a combination of infliximab 5 mg/kg and methotrexate 10 mg/week orally to mesalamine

Table 2. Postoperative Crohn's Disease Studies of 5-Aminosalicylate (5-ASA) Treatment

Study author	Study design	Number	Drug	Outcomes
Wenckert A, et al. ³²	Double-blind, multicenter trial; block randomization	N=66	Salazosulphapyridine (SASP) 3 g/d	At 18 months, 4/33 SASP patients relapsed vs 9/33 placebo patients (NS).
Summers RW, et al. ³³	Multicenter, randomized, double-blind; postoperative patients were a planned subgroup	N=48 (post-operative subgroup)	Sulfasalazine 0.5 g/15 kg; or azathioprine (1 mg/kg); or prednisone (0.25 mg/kg); or placebo	None of the study drugs were superior to placebo.
Ewe K, et al. ³⁴	Multicenter, randomized, double-blind; 3-year follow-up	N=232	Sulfasalazine (SZ) 3 g/d	At 1 year, recurrence in the SZ group was 18/111 (16%) compared to 34/121 (28%) in the placebo group ($P<.01$). Recurrence was also lower in the second year of follow-up: 9 in the SZ group vs 12 in the placebo group ($P<.01$).
Sutherland LR, et al. ³⁵	Randomized, placebo-controlled, double-blind, parallel design	N=293	Mesalamine 750 mg QID	At 48 weeks, 25.3% of the mesalamine patients relapsed vs 36.7% of the placebo patients ($P=.056$).
Florent C, et al. ³⁶	Multicenter double-blind controlled trial comparing 5-ASA to placebo, starting within 15 days after surgery	N=126	Mesalamine 1 g TID vs placebo	The endoscopic relapse rate was 50% in the 5-ASA group and 63% in the placebo group ($P=.16$).
Brignola C, et al. ³⁷	Double-blind, multicenter clinical trial; 5-ASA or placebo within 1 month after surgery. After 12 months, rate and severity of recurrence assessed.	N=87	Controlled-release mesalamine 3 g/d vs placebo	The rate of severe recurrence was 24% in the mesalamine group and 56% in the placebo group ($P<.004$).
Lochs H, et al. ³⁸	Prospective, randomized, double-blind, multicenter study; 5-ASA vs placebo. Treatment was started within 10 days after resective surgery and continued for 18 months.	N=318	Mesalamine 4 g	Cumulative relapse rates after 18 months were 24.5% in the mesalamine group and 31.4% in the placebo group.
McLeod RS, et al. ²¹	Randomized, controlled trial	N=163	Mesalamine 3 g/d	The symptomatic recurrence rate in the treatment group was 31% compared to 41% in the control group ($P=.031$). Endoscopic and radiologic rates significantly decreased, and relative risks were 0.654 in an effectiveness analysis and 0.635 in the efficacy analysis.
Caprilli R, et al. ³⁹	Multicenter, randomized, controlled trial; oral mesalamine vs no treatment	N=110	Mesalamine 2.4 g/d	At 24 months, cumulative endoscopic recurrence rates were 52% and 85% and symptomatic recurrence rates were 18% and 41% in the mesalamine and placebo groups, respectively ($P=.006$).
Caprilli R, et al. ⁴⁰	Double-blind, randomized, multicenter, prospective, controlled clinical trial; comparing two regimens of 5-ASA starting 2 weeks after surgery.	N=206	Mesalamine 2.4 g/d vs 4 g/d	Endoscopic recurrence of more than 0 was significantly higher in the 2.4 g/d group than in the 4.0 g/d group (62% vs 46%; $P<.04$).

NS=not significant.

Table 3. Clinical and Endoscopic Recurrence Rates from Randomized Treatment Trials

Medication class	Clinical recurrence rate	Endoscopic recurrence rate
Placebo	25–77%	53–79%
5-ASA	24–58%	63–66%
Budesonide	19–32%	52–57%
Nitroimidazole	7–8%	52–54%
AZA/6-MP	34–50%	42–44%
Infliximab	0%	9%

5-ASA=5-aminosalicylate; 6-MP=6-mercaptopurine; AZA=azathioprine.

800 mg TID two weeks after surgery.⁵⁰ At two years of follow-up, none of the infliximab/methotrexate group had endoscopic or clinical recurrence, whereas only 25% of the mesalamine group was disease-free.

It remains to be seen whether antitumor necrosis factor (TNF) therapy given as postoperative prophylaxis before mucosal recurrence is more effective than when given in response to endoscopic recurrence.

Recommendations

Table 3 summarizes data on postoperative clinical and endoscopic recurrence with various treatments. It is

the authors’ opinion that nitroimidazole antibiotics, 6-MP/AZA, and anti-TNF agents are most effective for the prevention of postoperative Crohn’s disease. Determining the appropriate agent for prevention and management of postoperative Crohn’s disease relies on stratifying the risk of recurrence.

Postoperative Evaluation and Risk Stratification

During the perioperative period, we propose that patients be stratified into low-, moderate-, and high-risk groups for recurrence. Without formal postoperative maintenance guidelines, we provide our recommendations on the treatment of these patients. Figure 2 summarizes our proposed approach, which is discussed below.

Low-Risk Patients Patients with no history of smoking, a short stricture less than 10 cm in size, more than 10 years of lead time to first surgery, and an uncomplicated peri- and postoperative course are at a low risk for recurrence, making watchful waiting a reasonable treatment option. We believe that this group should undergo disease reassessment at 6–12 months, with colonoscopy as the first management choice and WCE/SICUS as an alternative. If there is significant endoscopic recurrence (i2– i4), we believe that this changes the patient’s disease course to an aggressive one and thus recommend an anti-TNF agent. Patients with evidence of mild endoscopic recurrence (eg, an i1) should receive an immunomodulator with or without a 3-month course of metronidazole. Having no endoscopic recurrence (i0) within 1 year likely signifies a low likelihood of recurrence; thus, it would be reason-

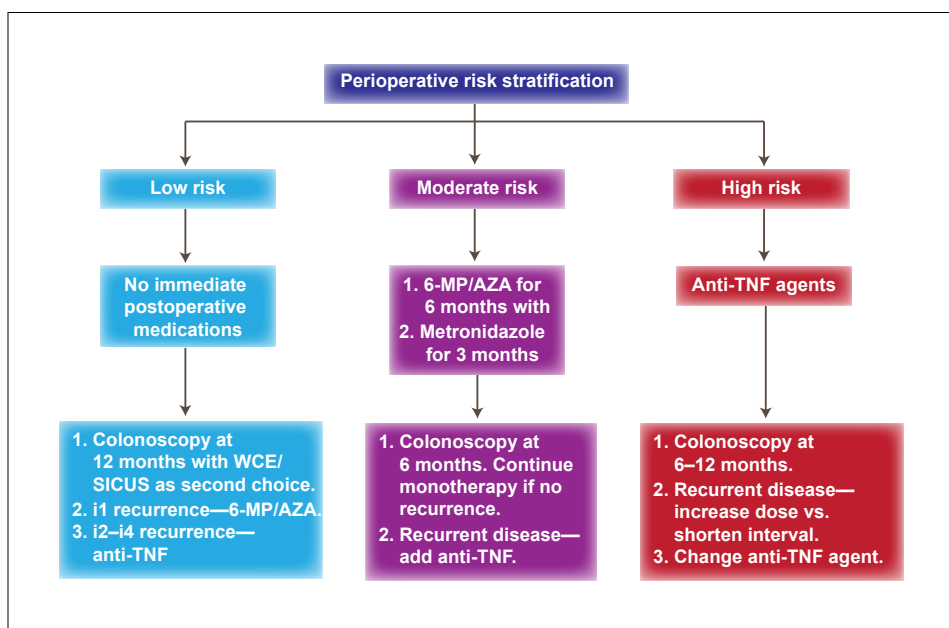


Figure 2. Algorithm for postoperative follow-up.

Surveillance colonoscopy:
 Low-risk patients
 1–3 year intervals
 Moderate-risk patients
 1–3 year intervals
 High-risk patients
 1–2 year intervals
 6-MP=6-mercaptopurine;
 AZA=azathioprine;
 SICUS=small intestine contrast ultrasonography;
 TNF=tumor necrosis factor; WCE=wireless capsule endoscopy.

able for these patients not to take any medications but to repeat a colonoscopy within 3 years.

Moderate-Risk Patients In patients with a long fibrostenotic stricture or inflammatory stenosis (ie, >10 cm and short) and time to index surgery of less than 10 years, we recommend 3 months of metronidazole in combination with postoperative immunomodulator treatment (6-MP, AZA). We also suggest performing a postoperative colonoscopy within 6–12 months of surgery. The immunomodulators should be continued if there is no endoscopic recurrence and anti-TNF agents added if there is evidence of endoscopic recurrence. We follow these patients with colonoscopy every 1–3 years and adjust treatment accordingly.

High-Risk Patients In patients with more than 2 surgeries, penetrating/perforating disease, complicated peri- and postoperative course, and a history of habitual smoking, we recommend initiation with infliximab within 4 weeks of surgery and every effort should be made for smoking cessation. We also recommend a colonoscopy at 6–12 months. In patients with endoscopic recurrence, we recommend dose intensification (ie, dosage increase or shortening of infusion intervals). Another option would be changing to another anti-TNF agent. For patients without endoscopic recurrence, we recommend continuing the anti-TNF treatment. The optimal duration of postoperative anti-TNF treatment beyond 1 year is not currently known. The optimal interval for surveillance colonoscopy is not clear, but we recommend no more than 1–2 years.

Summary

Crohn's disease recurrence after surgery is the norm rather than the exception. Prevention of postoperative recurrence is important, but the optimal medical strategy has yet to be defined. Cigarette smoking cessation is a critical part of any postoperative prevention plan. Patients with a high risk of postoperative recurrence (eg, multiple resections or penetrating disease) should be considered for medical therapy shortly after surgery. The most convincing data to date on prevention of postoperative disease recurrence in high-risk patients are from the recent infliximab study. Nitroimidazole antibiotics and immunomodulators may provide benefit for those patients with low-to-moderate risk of postoperative recurrence, and going without therapy may be reasonable for those with very low risk of recurrence. Independent of the postoperative treatment, we recommend colonoscopy monitoring for Crohn's disease recurrence within the first year. Depending upon endoscopic recurrence or remission 1 year after surgery, treatment may be tailored.

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