Chapter 11
Post-operative Prophylaxis in Patients with Crohn's Disease

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Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory condition, characterized by abscesses, fistulization and stricturing that can affect any part of the gastrointestinal tract, but most commonly affects the terminal ileum and proximal colon. Up to 80 % of CD patients will require at least one abdominal surgery in their lifetime [1]. Unfortunately, surgery is not curative and recurrence is the norm, rather than the exception. Endoscopic recurrence occurs in upwards of 70–90 % of patients within 1 year of surgery [2, 3]. Clinical recurrence is seen in approximately one third of patients within 3 years of surgery [4]. Additionally, up to 50 % of patients will require a repeat surgery within 5 years, while up to 70 % will require a repeat operation within 20 years of their original procedure [4–7]. While prevention of post-operative recurrence is a significant challenge in clinical practice, it is essential for not only the maintenance of the patient's health status and quality of life, but also for the prevention of disease relapse and future surgeries [8]. Having a multidisciplinary approach involving collaboration between surgeons and gastroenterologists is critical for optimizing post-operative care; however patients often delay their follow-up with their gastroenterologist, leaving the surgeon as the sole manager of the patient's post-operative treatment. Communicating a well-organized and clear

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plan shortly after resection is especially important because patients who are at high risk of recurrence may be less likely to accept treatment as they enjoy their surgically-induced "remission [9]."

In this chapter, we describe the clinically relevant risk factors for post-operative recurrence as well as the medical options available for prevention. Finally, we provide a practical guide on how to approach the post-operative Crohn's patient based on an individualized, evidence-based plan.

We conducted a Pubmed search from 2005 to 2016 using a combination of the search terms "Crohn's disease", "postoperative", "prophylaxis", "recurrence", "relapse", "prevention", "risk factors", "anastomosis type", and "treatment". Selected embedded references that were published prior to 2005 and considered seminal papers by the authors were also included.

PICO table

Patients	Intervention	Comparator	Outcome
Patients with Crohn's disease following surgical resection	Medical prophylaxis	Endoscopic surveillance	Disease recurrence, need for reoperative surgery

Recurrence in Post-operative Crohn's

The recurrence rates of CD after surgery are very high, especially in those not receiving medical prophylaxis. Endoscopic findings that indicate recurrence of disease include aphthous erosions, deep linear ulcers, mucosal inflammation, fistulae and strictures [10]. Typically, the prevailing phenotype of a patient's disease are thought to be consistent before and after resection, meaning that patients who initially had penetrating disease as an indication for their surgery will often experience penetrating disease when they recur [11].

The most common site of recurrence is at the surgical anastomosis, especially the proximal side [2]. Luminal contents, specifically intestinal flora, appear to play an important role in the pathogenesis of recurrence. While a sustained remission is common among patients with a diverting ileostomy even without medical therapy, those patients who undergo re-anastomosis often have disease recurrence shortly following the procedure [12–14].

Risk Factors for Relapse

Identifying possible risk factors for recurrence in Crohn's patients is essential for optimizing care for the postoperative patient. Risk stratifying patients based on these factors allows tailoring of therapy to help avoid both over- and under-treatment of patients.

Patient Factors

Smoking cigarettes has been the most consistently identified patient-related risk factor for disease recurrence. Compared to non-smokers, smokers have increased rates of endoscopic recurrence and clinical relapse, shorter time to clinical relapse and increased risk of requiring additional surgical intervention [15–19]. There also appears to be a dose effect, with heavier smokers having an increased risk of recurrence compared to milder smokers [20, 21]. Additionally, studies have shown that patients who quit smoking have significantly reduced surgical re-intervention rates, which are comparable to that of non-smokers [18, 22, 23].

There is interest in whether certain genetic variants or profiles of the gut microbiome are potential risk factors for post-operative recurrence, as both are known to be important in the pathogenesis of IBD. Whereas mutations in NOD2 have been identified as a marker for the need for resection in CD cohorts, it has not been shown to have a consistent association with post-operative relapse. However, a recent study identified an association between CAD8 homozygosity and an increased risk of surgical recurrence [24, 25]. Another recent study suggested that microbiota profiles at the time of surgery may have some prognostic value in identifying those patients at risk for developing earlier disease recurrence [26]. Both of these areas of inquiry require further research to help clarify their roles in the pathogenesis of disease recurrence.

Gender, age, age at diagnosis, and prior family history are not consistent risk factors in the literature [27–30].

Crohn's Disease Behavior

Perforating-type disease, perianal disease and previous surgery for CD have been shown to be associated with increased risk of disease recurrence [11, 31–33]. An association between the presence of granulomas in the resected specimen and recurrence has also been consistently demonstrated [13, 28, 30, 34]. The evidence for duration of disease prior to surgery as a risk factor for recurrence is inconsistent [35, 36].

Surgical Factors

Certain perioperative events, such as sepsis, blood transfusions and post-operative complications have not been associated with CD recurrence. While clearing margins of macroscopic disease is imperative, there appears to be no relationship between microscopic CD found at the resection margin and disease recurrence [37]. As laparoscopic surgery has become more popular, there has been interest in whether the technique reduces post-operative disease recurrence. Whereas

laparoscopic technique can offer advantages in the surgical management of CD, including reduced duration of hospital stay, reduced cost and lower morbidity, studies have shown no significant difference in endoscopic or surgical recurrence rates when compared to open procedures [38, 39].

Type of anastomosis has been considered an important potential risk factor for CD recurrence. Due to the subsequent wide lumen created with side-to-side anastomosis, which in theory would prevent early stenosis, subsequent fecal stasis and secondary ischemia, it has been postulated that this technique offers some outcome benefits. Unfortunately, observational studies have not supported this [40]. In a multicenter randomized controlled trial by Mcleod et al., anastomotic type did not affect the recurrence rate of CD after ileocolonic resection [41]. Despite this, other studies have suggested that side-to-side anastomosis may reduce post-operative complications and surgical recurrence [42–44]. Of note, the Kono-S anastomosis, which is a novel antimesenteric functional end-to-end handsewn anastomosis, is a technique with improved endoscopic and surgical recurrence rates; however, long-term outcomes and comparative studies need to be performed in order to confirm its superiority [45].

Myenteric plexitis found during surgery has been consistently shown to be associated with higher rates of endoscopic and surgical recurrence [46–48]. Visceral fat area has also been associated with post-operative recurrence and is believed to have clinical implications with respect to optimizing prophylaxis [49]. Additionally, the European Crohn's and Colitis Organization determined that disease of more than 100 cm should be considered a risk factor for increased incidence of post-operative recurrence [50].

Assessment of Recurrence

Endoscopically identified disease recurrence occurs early and therefore is the preferred measure of relapse in post-operative patients. This is because it precedes clinical symptoms, which do not correlate well with endoscopic findings [51, 52].

The most commonly used endoscopic scoring system to evaluate disease recurrence after resection in CD is the Rutgeerts' score [2]. This is a reliable scoring system that assesses the presence and severity of recurrence in the distal neoterminal [53] (Fig. 11.1). The Rutgeerts' scoring system has become widely used because it has been shown to correlate with subsequent clinical relapse: while less than 5 % of those with scores of i0 and i1 will develop clinical recurrence within 3 years, 14, 40 and 90 % of patients with i2, i3 and i4 scores will develop clinical relapse, respectively [2, 13, 54]. When using this system, it is important to recognize that ulcers are not necessarily due to disease recurrence, and that it is common to have suture-related trauma or marginal ulceration/ischemia at the anastomosis site. Such ulcers should not be included when grading within the scoring system.

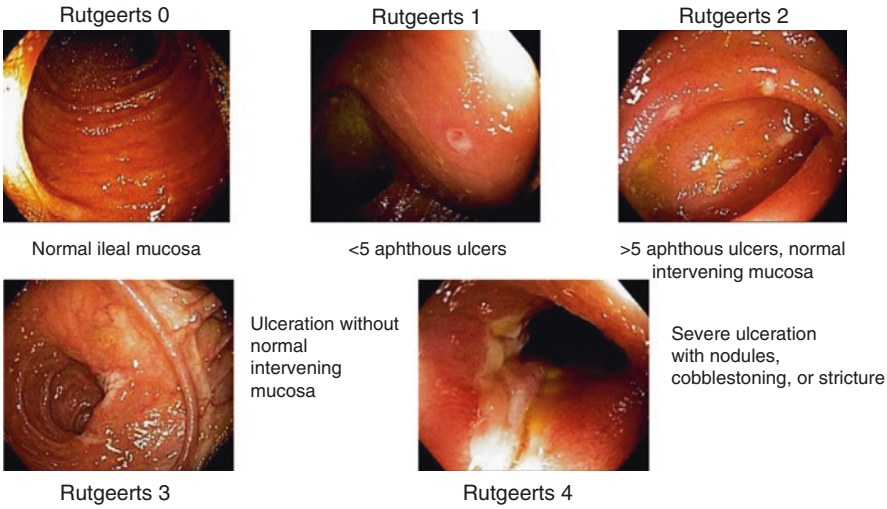

Fig. 11.1 The Neo-TI: the Rutgeert's Score

In terms of timing of evaluation for post-operative recurrence in asymptomatic patients, many guidelines suggest performing a colonoscopy within a year after surgery. More recent evidence has shown that a substantial proportion of endoscopic recurrence occurs within 6 months, many of which were severe with Rutgeerts' score ≥ i3. These findings highlight the importance of earlier evaluation for post-operative recurrence [55].

Non-invasive Methods of Assessing Post-operative Recurrence

While endoscopy is the gold standard for monitoring post-operative recurrence, there is a lot of interest in findings surrogate markers that would avoid the risks, expense and inconvenience inherent in an invasive procedure. Clinical scoring systems, such as the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw index poorly correlate with endoscopic findings [56–58]. Additionally, commonly used biochemical markers of inflammation, such as ESR and CRP, also have not been shown correlate with endoscopic recurrence in post-operative patients [58, 59].

The evidence behind fecal calprotectin (FC) has been very promising for fulfilling the role of a non-invasive method for assessing post-operative recurrence. FC levels correlate well with endoscopic recurrence as measured by the Rutgeerts' score, and patients who have received treatment for their recurrence with subsequent endoscopic improvement have also seen improvement in their FC [58, 60–62]. In a study by Yamamoto and Kotze, a cutoff value of 170 μg/g for FC

Table 11.1 Effectiveness of various methods to assess post-operative endoscopic recurrence

Evaluation method	Efficacy	Quality of evidence
Endoscopy	+++	High
FC	+++	High
SICUS	++	Moderate
WCE	++	Low
ESR/CRP	–	High
Clinical disease scores	–	High

had a sensitivity of 0.83 and a specificity of 0.93 to predict clinical recurrence [62]. In another study, Wright et al. found FC to correlate with endoscopic recurrence and endoscopic severity scores. The authors determined that a cutoff for FC of 100 μg/g had a sensitivity of 0.89 and a negative predictive value of 91 % for disease recurrence. The study concluded that utilizing FC to monitor post-operative patients may allow for 47 % of patients to avoid colonoscopy [58]. Based on these findings, FC may play a valuable role in the post-operative management algorithm, possibly allowing for endoscopy to be reserved for only those patients with abnormal values.

Other non-invasive methods of monitoring postoperative patients have shown promise. In a study by Calabrese et al, small intestinal contrast ultrasonography (SICUS) was shown to have a sensitivity of 92.5 %, specificity 20 % and accuracy of 87.5 % when compared to endoscopy [52]. Additionally, bowel wall thickness was found to correspond with endoscopic severity, although SICUS findings have not been shown to correlate with clinical recurrence [52, 63, 64, [65]. While it's use may be limited by its low specificity, SICUS may have a role in assessing the neoterminal ileum in patients with stenotic lesions not allowing passage of the endoscope [66].

Wireless capsule endoscopy (WCE) also has good sensitivity and specificity in assessing post-operative recurrence. In prospective studies, WCE identified lesions in upwards of 76 % of study subjects that could not be visualized by endoscopy (ibid) [67, 68]. While initial findings are encouraging, further research on WCE role in the post-operative patient needs to be performed (Table 11.1).

Symptoms After Surgery Are Not Necessarily due to Recurrence

It is important to know that common post-operative symptoms, such as diarrhea and pain, may not necessarily be due to CD recurrence. Therefore, prior to initiating treatment for suspected disease recurrence, objective markers of disease should be pursued. Ideally this can be done with endoscopy, although FC may be an acceptable alternative. As clinical symptoms poorly correlate with endoscopic activity, treatment should be based on endoscopic findings or appropriate surrogate markers and not solely on clinical symptoms, in order to prevent both over- and under-treating the patient.

Medical Prophylaxis Options

Following surgical resection, CD patients are often cleared of all of their disease, thus marking an ideal time to prevent further disease from occurring. As discussed above, most patients will unfortunately experience recurrence if not on medical therapy. Many studies have focused on the efficacy of medical therapies in preventing progressive disease, disability and further surgical interventions in the post-operative setting.

Minimal Benefit: Probiotics/5-ASA/Corticosteroids

Given the role that the gut flora plays in the recurrence of disease and evidence of the effectiveness of antibiotics in preventing disease, there has been growing interest in the use of probiotics to alter the microbiota and prevent recurrence. However, multiple studies have failed to show any benefit in the use of probiotics in the post-operative setting [69, 70]. 5-ASA medications are appealing for post-operative treatment, due to their favorable safety profile, ease of administration and low cost, however the results have been inconsistent and their effect on clinical and endoscopic recurrence is minimal at best [71–73]. Furthermore, neither systemic nor local corticosteroids have been shown in the literature to be effective at reducing post-operative recurrence [74, 75].

Moderate Benefit: Antibiotics/Immunomodulators

Due to evidence suggestive of the role of bacteria in disease recurrence, many studies have evaluated the effectiveness of antibiotics in preventing relapse. Whereas ciprofloxacin has not been shown to prevent relapse, nitroimidazole antibiotics (metronidazole and ordinazole) decrease the risk of clinical and endoscopic recurrence [76–78]. Rutgeerts' et al. demonstrated that only 3 months of treatment with metronidazole led to a decrease in recurrence that extended to 12-months following surgery compared to those taking placebo [79]. Studies have shown a further reduction in recurrence rates when metronidazole is used in combination with azathioprine compared to either medication used alone [80]. Additionally, antibiotics have been shown to be cost-effective for preventing post-operative recurrence, even in low-risk patient, although widespread use may be limited by high rates of intolerance [81].

Immunomodulators (IMM) appear to have a modest effect on preventing post-operative recurrence. Thiopurines (azathioprine and 6-MP) have been found to be more efficacious than placebo at reducing clinical relapse and severe endoscopic recurrence at 1 year [77, 82]. They have also been shown to reduce the risk of endoscopic recurrence compared to mesalamine [77]. Long term data has suggested that

thiopurine treatment for over 36 months decreased the need for additional surgical intervention when compared to use of less than 36 months or no treatment at all [83]. In a comparative cost-effectiveness analysis, Azathioprine and 6MP had the most favorable incremental cost effectiveness ratio [84]. Because of the strong evidence of its effectiveness, the AGA has recommended that thiopurines should be used in those with "high risk" for recurrence or in whom postoperative recurrence would be deleterious [85].

High Benefit: Biological Therapy

Biologics have been growing in popularity over the past 10 years and have been found to be the most effective at reducing post-operative recurrence risk. An early small study by Regueiro et al. demonstrated that endoscopic recurrence was reduced from 84.6 % in the placebo arm to 9.1 % in the infliximab treated group at 1 year [86]. In the larger PREVENT study, Regueiro et al. again showed that infliximab decreases endoscopic recurrence compared to placebo, however the reduction of clinical recurrence, which was the primary endpoint, did not reach statistical significance. Of note, adverse event rates, including infections, were similar between the groups [87].

Adalimumab has also been studied and is considered to be equally efficacious at reducing recurrence [88]. Savarino et al. reported that the adalimumab was highly effective at prevention of endoscopic and clinical recurrence at 2 years. Endoscopic recurrence of CD was seen in only 6.3 % of patients receiving adalimumab compared to 64.7 % and 83.3 % of patients who received azathioprine and mesalamine monotherapy, respectively [8]. In the recent Postoperative Crohn's Endoscopic Recurrence (POCER) study, 79 % of high-risk patients who received adalimumab remained in endoscopic remission compared to 55 % of patient receiving a thiopurine [89].

While the focus of this chapter is on post-operative prophylaxis, it is important to know that for patients who experience endoscopic recurrence, biologics have been shown to be superior at reducing endoscopic scores and clinical relapse compared to immunomodulators or 5-ASA [61, 86, 90].

There is currently no data in the post-operative setting or certolizumab pegol, natalizumab or vedolizumab.

Table 11.2 The effectiveness for preventing endoscopic recurrence with associated level of evidence of potential therapies for post-operative prophylaxis

Therapy	Effectiveness	Level of evidence
Probiotics	–	High
Corticosteroids	–	Moderate
Mesalamine	+	Moderate
Nitroimidazole antibiotics	++	High
Ciprofloxacin	–	Moderate
Immunomodulators	++	Moderate
Anti-TNF	+++	High

Authors' Approach to Post-operative Crohn's Patients

While the costs of over-treatment cannot be ignored, under-treatment may place the patient at risk for disease recurrence, as most post-operative patients without prophylaxis will experience recurrence within a year. Despite evidence of its far superior effectiveness in preventing relapse, initiating biological therapies as prophylaxis even for high risk patients may be prohibitively expensive and exposes more patients unnecessarily to potential side-effects [81, 84]. Responsible choice of therapeutic approach therefore must be individualized for each patient. Studies have demonstrated the benefit of early evaluation of recurrence within 6 months of surgery. The recent prospective, randomized POCER study demonstrated that tailoring prophylaxis to risk category coupled with early disease assessment and subsequent treatment "step-up" if recurrence occurred significantly reduced disease relapse and led to increased macroscopic normality compared to those who did not receive the early evaluation [89].

Given the strength of the evidence, we have adopted an approach that all patients who can tolerate metronidazole receive 3 months of treatment at a dose of 350 mg TID following surgery. Low-risk patients are those with long-standing disease (>10 years), who are undergoing their first surgical intervention for a short (<10 cm) fibrostenotic lesion. It is believed that disease recurrence progresses more slowly in these patients and therefore chronic prophylactic therapy is not required at the outset. For high-risk patients, those who smoke, have penetrating or perianal disease, history of multiple prior resections and those with evidence of granulomas or myenteric plexitis in the resected sections, initial combination therapy with an anti-TNF and an IMM should be considered. All smokers should be counseled on its contribution to disease recurrence and be offered assistance with quitting or access to a smoking cessation program. For moderate risk patients, those who do not fit into the other categories mentioned, we recommend treating with IMM monotherapy in the post-operative period.

While early monitoring of disease recurrence has been shown to be beneficial, there is no standard approach on how to do so. In our practice, we measure fecal calprotectin in patients 3 months post-surgery, as levels of FC are known to stay elevated for the first 2 months. Given its high NPV, for patients with FC values <100 mg/kg, we continue them on their current therapy and either repeat FC or perform colonoscopy at 6 months. While some evidence suggests that patients with FC > 100 should have a colonoscopy at 6 months, we risk stratify these patients depending on their level of calprotectin. In the study by Sorrentino et al., patients who had no post-operative recurrence had FC levels <200 mg/kg. Therefore, for patients with FC between 100 and 200, we continue their current medical therapy and perform a colonoscopy at 6 months [8]. For patients with FC levels >200 mg/kg, we optimize or escalate their medical therapy at that time and then perform a colonoscopy at 6 months.

At colonoscopy, patients with i0 or i1 Rutgeerts' score are continued on their current medical therapy, while for patients with i2 or higher, therapy is initiated,

optimized or escalated. This may be accomplished by starting IMM or anti-TNF therapy and optimizing their dosing using therapeutic drug monitoring. A careful assessment of the history, examination and need for therapeutic drug monitoring should be considered when deciding which option to implement.

Once a patient has had their medical therapy optimized and their disease status is stable, it is necessary to assess them every 6–12 months with a measure of disease recurrence, either with FC or colonoscopy. If objective evidence of recurrence occurs, we recommend further optimization of therapy using the algorithm discussed above.

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