A Review of Postoperative Crohn’s Disease

While surgical resection remains a mainstay of the treatment of Crohn’s disease (CD), postoperative recurrence of disease is common. The ideal management of patients after surgery is unclear and varies widely in clinical practice. Both patients and clinicians must weigh the risks and benefits of treatment in reaching a decision. Those at low risk of postoperative recurrence may not need any therapy while those at moderate risk of disease recurrence may be treated with immunomodulator therapy. Patients with the highest risk for recurrence should ideally be treated with biologic therapy. Regardless of risk, all patients should undergo ileocolonoscopic surveillance at 6–12 months after surgery. This review will outline the current evidence for various medical therapies in the prevention of postsurgical recurrence and outline a management algorithm of these patients based on risk stratification.

INTRODUCTION
Crohn’s disease is characterized by chronic inflammation often exacerbated by acute relapses. Surgery still plays a critical role in the management of this patient population, and postoperative care is challenging. Current therapy in Crohn’s disease is moving beyond the goal of induction and maintenance of remission. In addition to these standard outcome measures, successful management can also be quantified by assessing the incidence of complications and measuring the patient’s quality of life. This paper discusses (i) standard methods to identify recurrent Crohn’s disease, (ii) risk factors for recurrence, (iii) and review of postoperative medical management.

BACKGROUND
Despite medical treatment advancements with immunomodulators and biologic therapy, the failure of
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(continued from page 20)

Figure 1A. Grade i\textsubscript{0}: No lesions in the distal ileum.

Figure 1B. Grade i\textsubscript{1}: \(\leq 5\) apthous lesions.

Figure 1C. Grade i\textsubscript{2}: >5 apthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to ileocolonic anastomosis.

Figure 1D. Grade i\textsubscript{3}: Diffuse apthous ileitis with diffusely inflamed mucosa.

Figure 1E. Grade i\textsubscript{4}: Diffuse inflammation with already larger ulcers, nodules and/or narrowing.

Medical management is an indication for surgery to treat related complications (i.e., stricture and fistulae formation). Seventy-five percent of patients will require surgical intervention at least once during their lifetime (1). However, unlike ulcerative colitis, surgery is not typically curative.

Resection of the diseased bowel is not curative and most recurrences occur at the resection site or proximal to the surgical anastomosis (2). After ileocolonic resection and anastomosis, endoscopic recurrence of disease arises in the neoterminal ileum in 30% of patients after 3 months (3), and has been reported as early as 1 week after surgery (4). At one year, 70-90% of patients will have endoscopic evidence of recurrent
disease (5). Clinical recurrence rates have been reported to be as high as 20–30% at 1 year with a 10% increase in each of the subsequent years. The need for repeat surgery occurs in 15–45% of patients at 3 years, 26–65% at 10 years and 33–82% at 15 years (6).

DISEASE RECURRENCE

After surgical resection, the use of ileocolonoscopy has been the primary surveillance tool used to assess for recurrence of Crohn’s disease. However, given the invasive nature of ileocolonoscopy, alternative techniques have been evaluated to assess postoperative recurrence. Transabdominal ultrasonography (TUS) has been proposed for detecting small bowel lesions in patients with suspected or known CD, showing a sensitivity of 67%–84% and 81%–95%, respectively (7). In experienced hands, small intestine contrast ultrasonography (SICUS) has been shown to detect intestinal lesions in patients with suspected small bowel diseases with a high (>95%) sensitivity and specificity, when compared with small bowel follow-through and enema (8). SICUS has shown a significant correlation with the findings during endoscopy (7).

The Rutgeerts scoring system is the most widely applied, studied, and clinically established scoring system to predict endoscopic progression and clinical recurrence (Figure 1) (9). 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 (9).

The Crohn’s Disease Activity Index (CDAI) (10) has been used in medical trials with scores of <150 being indicative of remission (Table 1). However, there have been conflicting reports in regards to the utility of the CDAI as a measure of clinical recurrence. The CDAI has also been shown to have poor agreement with the prediction of endoscopic recurrence 1 year after surgery. In a study by Regueiro et al, patients who were found to have endoscopic remission (i0, i1) and endoscopic recurrence (i2, i3, i4) had an identical mean CDAI score of (134). The sensitivity of CDAI (using a threshold of >200) for predicting 1-year postoperative recurrence was only 33%, with a corresponding false-

<table>
<thead>
<tr>
<th>Clinical or laboratory variable</th>
<th>Weighting factor</th>
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<tbody>
<tr>
<td>Percentage deviation from standard weight.</td>
<td>× 1</td>
</tr>
<tr>
<td>Number of liquid or soft stools each day for seven days.</td>
<td>× 2</td>
</tr>
<tr>
<td>Abdominal pain (graded from 0–3 on severity) each day for seven days.</td>
<td>× 5</td>
</tr>
<tr>
<td>Absolute deviation of Hematocrit from 47% in men and 42% in women.</td>
<td>× 6</td>
</tr>
<tr>
<td>General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days.</td>
<td>× 7</td>
</tr>
<tr>
<td>Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite).</td>
<td>× 10</td>
</tr>
<tr>
<td>Presence of complications.*</td>
<td>× 20</td>
</tr>
<tr>
<td>Taking Lomtitil or opiates for diarrhea.</td>
<td>× 30</td>
</tr>
</tbody>
</table>

*One point each is added for each set of complications:
- The presence of joint pains (arthralgia) or frank arthritis
- Inflammation of the iris or uveitis
- Presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- Anal fissures, fistulae or abscesses
- Other fistulae
- Fever (>100°F) during the previous week.

Table 1.
The Crohn’s Disease Activity Index (11)
negative rate of 67%. This means approximately two-thirds of patients with objective endoscopic recurrence had a CDAI <200 (most <150) and thus did not meet criteria for clinical recurrence (5).

Another study reported a CDAI of ≥148 predicted recurrence with a sensitivity of 70%, and specificity of 81%. This study suggested that the CDAI is likely not suitable for use as a primary outcome measure and a combination of symptom assessment plus endoscopic evidence of recurrence should remain the gold standard definition for assessing outcomes (11).

RISK FACTORS

There are multiple risks factors that predispose patients to disease recurrence. Factors such as the presence of granulomas, perforating disease phenotype, ileal or ileocecal resection with ileocolic anastomosis and smoking have all been identified. In a multivariate analysis, surgery for a perforating indication was an independent predictor of early recurrence (14). In addition, recurrences requiring additional surgery occurred twice as fast in the perforating type as in the nonperforating type (12,13). However, the presence of an ileocolic anastomosis and smoking are the only well-replicated predictors of postoperative recurrence, making prevention a challenging problem (6,14,15).

The pathogenesis of CD involves complex interactions between microbial, environmental, immunological, and genetic variables. Understanding these interactions provides the basis for understanding factors, which influence disease recurrence. A dysregulation of the mucosal immune system leading to an excessive immunologic response to normal microflora has been well established. The composition of the intestinal microflora is complex. The evidence which links bacterial flora and intestinal inflammation includes an observation of a relatively high concentrations of bacteria (>10–12 organisms/g) in the normal distal ileum and colon (4). In part, this may explain the predominance of CD in these segments of the gastrointestinal tract (4). An imbalance favoring more pathogenic organisms (Clostridia spp., Bacteroides vulgatus and Escherichia) has been observed in mucosal biopsies during active inflammation. In an important study, Rutgeerts et al, demonstrated that five patients with CD who had undergone resection with a diverting loop ileostomy proximal to an ileocolic anastomosis had no endoscopic evidence of recurrence in the neoterminal ileum 6 months after surgery (16). However, after bowel continuity was restored, essentially all patients displayed rapid endoscopic recurrence in the neoterminal ileum. These findings suggest that the diversion of bowel contents protects the neoterminal ileum from recurrent inflammation and that bacterial flora and/or other components of the fecal stream play a key role in disease initiation (17).

The best defined and most important environmental factor in CD is smoking. Smoking is strongly associated with a higher relapse rate, a more aggressive disease course, and increased risk of postoperative recurrence (18). A meta-analysis by Reese et al. demonstrated a twofold increase in clinical relapse after surgery in smokers compared with non-smokers, as well as a 2.5-fold increase in the risk of further surgery by 10 years (19). Several explanations have been postulated to delineate the exact mechanism that smoking has on disease activity. These explanations describe a direct immunosuppressive effect of smoking influencing cellular and humoral immunity (20). Another plausible explanation is that vascular changes caused by components of tobacco smoke (such as oxidizing chemicals) may have prothrombotic effects which in turn could exacerbate ischemia of the bowel wall (21). Other environmental factors, which may have an effect on disease activity, include medications. For example, oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs) have been studied and found to be associated with disease relapse (22).

There have been several studies examining the association between genetic variants and surgical recurrence in Crohn’s patients. The NOD2/CARD15 gene variants have been the most studied. The gene encodes a protein that functions as an intracellular sensor of muramyl-dipeptide, a bacterial cell wall component (23). Three common mutations within this gene lead to a compromised host immune response to enteric bacteria. A study by Büning et al reported a higher risk of postoperative relapse and reoperation, with 12 of 29 patients (41.4%) with NOD2/CARD15 mutations requiring a second operation compared with only 2 of
12 patients (16.7%) without NOD2/CARD15 mutations (24). A later study by Alvarez-Lobos et al showed that patients with NOD2/CARD15 variants underwent surgery more frequently (OR 3.63; 95% CI 1.42 to 9.27) and required surgery at an earlier time (25).

**TREATMENT**

Numerous studies have emerged over the last twenty years attempting to elucidate ideal prophylaxis and treatment of postoperative recurrent Crohn’s Disease. The major agents that have been studied are the 5-Aminosalicylate agents, probiotics, antibiotics, immunomodulators, and biologic therapies. These studies have yielded mixed results and as such, a universally accepted management algorithm has not yet emerged. Here we will outline the available medical therapies, the major conclusions to date about efficacy and safety of each, and present a management algorithm based on the reviewed data.

The results of studies using 5-aminosalicylates for post-operative Crohn’s disease have been varied. This has been partly due to studies using different endpoints, particularly clinical versus endoscopic recurrence, the latter being a more robust measurement of disease remission. A Cochrane group meta-analysis found that twelve patients needed to be treated with mesalamine to prevent one clinical recurrence and eight patients be treated to prevent one endoscopic recurrence (26). A more recent meta-analysis with additional studies found that, while sulfasalazine offered no benefit over placebo, mesalamine was more effective than placebo or no therapy with a number needed to treat (NNT) of ten patients (27). Of the 11 randomized controlled trials included, most of them used clinical endpoints rather than endoscopic or radiologic endpoints.

A previously published meta-analysis also showed mesalamine decreased clinical but not endoscopic postoperative Crohn’s disease recurrence (28). A multicenter, double-blind, double-placebo randomized controlled trial comparing efficacy of mesalamine and azathioprine in postoperative Crohn’s patients with moderate or severe endoscopic recurrence showed no difference at 1 year in rates of clinical relapse (29). Despite the most recent meta-analysis showing some possible effect greater than placebo or no therapy, the 5-ASA products are of questionable utility as the demonstrated effect is quite small and was mainly shown to decrease clinical but not endoscopic recurrence. Therefore, mesalamine remains an option for use in patients with a contraindication to immunosuppression though is not the therapy of choice in postoperative Crohn’s disease.

Although antibiotics such as metronidazole and ornidazole have been shown to be effective in reducing severity of endoscopic recurrence, these are not useful for long term administration due to toxicities (e.g. gastrointestinal symptoms, neuropathy) (30,31).

Five studies of probiotic use to prevent postoperative Crohn’s disease recurrence were evaluated in the aforementioned Cochrane review. In this review, no difference was found between placebo and probiotics in clinical or endoscopic recurrence (29).

The immunomodulators consist of 6-Mercaptopurine (6-MP) and azathioprine (AZA). These agents inhibit DNA synthesis, and are particularly effective at impeding cells that are rapidly proliferating. Several studies have compared these agents to 5-aminosalicylate products and placebo with evidence that immunomodulators are more effective in preventing postoperative Crohn’s disease recurrence, though the difference in effect appears limited.

In 2008 D’Haens et al. compared metronidazole plus AZA versus metronidazole alone in postoperative Crohn’s disease patients at high risk for recurrence (32). The control group received placebo for 12 months whereas the other group received additional AZA for 12 months. At 12 months the patients treated with AZA had significantly less endoscopic recurrence compared to the placebo group. There was no significant difference in adverse effects between the two groups.

Domenech et al. examined the effect of azathioprine on a group of 56 postoperative Crohn’s disease patients who had undergone curative resection (33). Of these, the cumulative probability of endoscopic recurrence was 44%, 69% and 82% at 1, 3 and 5 years respectively. The paper concluded that AZA was effective in delaying but not preventing endoscopic recurrence of postoperative Crohn’s disease.

Recently a double blind, double dummy randomized control trial studied the effects of azathioprine...
versus mesalamine in patients less than two years post-operative from curative resection with endoscopic recurrence. None of the 78 patients in the study had clinical recurrence at the time of entry. At 12 months, none of the AZA patients had clinical recurrence compared to four of the mesalamine patients, a statistically significant finding. Furthermore, while only one third of the mesalamine patients had a one-point drop in Rutgeert’s score, two thirds exhibited such a drop in the azathioprine group. Side effects led to cessation in 22% of the AZA patients and none of the mesalamine patients (30).

Knowledge of the efficacy of anti-TNF agents in mucosal healing led to the study of infliximab for both prophylaxis and treatment of recurrence of Crohn’s disease after surgical resection. The first study to demonstrate the potential of infliximab was performed by Sorentino et al. (34). Twenty-three patients who had undergone surgical resection for Crohn’s disease were studied and 16 received mesalamine and seven received infliximab and methotrexate. At 2 years after surgery, patients in the mesalamine group had a 75% endoscopic recurrence rate and the infliximab-methotrexate group experienced a 0% recurrence rate.

The only randomized controlled trial of infliximab therapy to date for postoperative recurrence compared infliximab and placebo. The 24 patients in this study were permitted to remain on stable preoperative doses of immunomodulators and 5-aminosalicylate products but not steroids or antibiotics. Infliximab was initiated within 4 weeks of surgery in the treatment group. Endoscopic recurrence at 1 year was significantly lower in the infliximab group at 9.1% compared to 84.6% in the placebo group (p = .0006) (35). Histologic recurrence rate at 1 year was similarly significantly lower in the infliximab group at 27.3% versus 84.6% in the placebo group. Adverse events were similar in frequency between the two groups.

Infliximab has also been studied in the treatment of patients with established disease recurrence after surgery. Yamamoto et al. divided a group of 26 patients who were clinically asymptomatic with endoscopic recurrence at 6 months after resection. The groups were treated with either mesalamine, azathioprine, or infliximab. At 6 months endoscopic disease was improved in 75% of the infliximab group patients, 38% of those on azathioprine and 0% in the mesalamine group (p = .006) (36).

Results of efficacy of prophylaxis of the above-mentioned classes of medications are summarized in this table (Table 2) (37).

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Clinical Recurrence (%)</th>
<th>Endoscopic Recurrence (%)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>25–77</td>
<td>63–79</td>
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<tr>
<td>5-ASA</td>
<td>24–58</td>
<td>63–66</td>
</tr>
<tr>
<td>Budesonide</td>
<td>19–32</td>
<td>52–57</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>7–8</td>
<td>52–54</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>34–50</td>
<td>42–44</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Data from Regueiro M. Management and prevention of postoperative Crohn’s disease. Inflamm Bowel Dis 2009;15:1583–90. This material is reproduced with permission of John Wiley & Sons, Inc.

The management of postoperative Crohn’s disease remains controversial. The data suggest that prevention of recurrence yields better long-term outcomes than treatment in response to relapse. However, not all patients will suffer a relapse after curative resection. Thus identifying patients at greatest risk for recurrence and those most likely to benefit from prophylactic treatment is of the utmost importance.

Immediately after surgery, patients may be stratified by the risk of disease recurrence. High risk patients are those with penetrating disease or history of more than two surgeries. At low to moderate risk are those with Crohn’s disease for less than ten years, or inflammatory disease, or a long stricture. Very low risk patients are those with longstanding Crohn’s disease who have undergone only one surgery or have only a short stricture. Those at very low risk should be surveyed regularly with colonoscopy but do not require prophylactic treatment. Patients at low to moderate risk may initially be treated with an immunomodulator and if they remain in endoscopic remission, may be simply followed endoscopically. High risk patients
may be treated with a biologic agent after surgery and if they remain in endoscopic remission, may be taken off therapy and followed with regular surveillance colonoscopies. The recommendations are outlined below (Figure 2) (38). Additionally, the risks of side effects of medications must also be weighed prior to their use.

One year after surgery with a colonoscopy, regardless of treatment. Therapy and further surveillance should be based on colonoscopic findings. Furthermore, all patients who are smokers should be actively counseled in tobacco cessation.

**CONCLUSION**

Many questions remain about the postoperative management of Crohn’s disease, including how long to continue medications, if effective treatment of recurrent disease can be achieved, and if all biologics can effectively prevent and/or treat disease recurrence. The management of the postoperative Crohn’s patient is complex and partially explained by intricate environmental, microbial and genetic interactions, with smoking being the most established and modifiable risk factor. Despite the complexity, over the last two decades significant strides have been made in our understanding and approach to this disease process. While a more reliable clinical assessment tool to accurately predict endoscopic findings is needed to decrease invasive testing, ileocolonoscopy still remains the gold standard for surveillance. Furthermore, a variety of medical therapies has been developed, with biologics showing the most promise.

To provide the most effective management for this complex issue, the identification of high risk patients for disease recurrence is the first step. This high risk patient group will likely benefit the most from medical management. The goal of therapy as well as the likelihood of recurrent disease must be clearly communicated with the patient. When treating the patient, the risk of toxic medication exposure must be weighed.
against the benefits of significant morbidity reduction. The interpretation of a significant morbidity reduction will vary between patients, thus a clear understanding of the patient expectations by the Gastroenterologist is needed to guide appropriate future management.

References