INTRODUCTION

Crohn’s disease is a chronic inflammatory condition that affects the GI tract anywhere between the mouth and the anal verge. Approximately 780,000 people in the United States carry the diagnosis of Crohn’s disease and the incidence and prevalence have been on the rise. The majority of patients with Crohn’s disease will require an intestinal resection, most commonly an ileocceal resection. The indication for surgery is usually for medically refractory disease or complications such as strictures, abscess, fistulae, or rarely malignancy. In a recent systematic review, it was reported that the 1 year cumulative risk of surgery for Crohn’s disease patients is estimated to be 16.3%, 33.3% at 5 years, and as high as 46.6% at 10 years.

Natural Course of Postoperative Crohn’s Disease and Recurrence Rates

After a curative ileocecal resection, the prevention of Crohn’s disease recurrence remains a challenge. Recurrence in these patients usually occurs at the ileocolonic anastomosis and in the neo-terminal ileum. Studies have shown that histologic recurrence may occur as early as 1 week after surgery. Endoscopic recurrence of Crohn’s disease tends to follow with recurrence rates as high as 70-90% at 1 year after surgery in patients who do not receive postoperative Crohn’s disease medications. Crohn’s disease recurrence after resection is often silent and this accounts for the lag between endoscopic and clinical recurrence, with the latter occurring later. Clinical recurrence rates, as
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Table 1. Rutgeerts Endoscopic Recurrence Scoring System

<table>
<thead>
<tr>
<th>Endoscopic Score</th>
<th>Definition</th>
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<tbody>
<tr>
<td>i0</td>
<td>No lesions</td>
</tr>
<tr>
<td>i1</td>
<td>≤5 aphthous lesions</td>
</tr>
<tr>
<td>i2</td>
<td>&gt;5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis</td>
</tr>
<tr>
<td>i3</td>
<td>Diffuse aphthous ileitis with diffusely inflamed mucosa</td>
</tr>
<tr>
<td>i4</td>
<td>Diffuse inflammation with already larger ulcers, nodules, and/or narrowing</td>
</tr>
</tbody>
</table>

i0 and i1 imply endoscopic remission while i2-i4 imply recurrent endoscopic disease

defined by the Crohn’s disease Activity Index (CDAI), were shown to occur in 20-40% of patients at 1 year from surgery, and 35-50% by 5 years postoperatively.6,9,11,14 It is not an uncommon scenario for patients to require yet another surgical resection once clinical symptoms ensue in the postoperative setting (i.e. clinical recurrence). A quarter (25%) of patients will require a second intestinal resection by 5 years after their initial surgery, and up to 35% of patients by 10 years.15 The indication for subsequent intestinal resection tends to be similar to the indication of the initial operation.16-19

Surveillance of Postoperative Crohn’s Disease

The most sensitive modality for detection of postoperative Crohn’s disease is via an ileocolonoscopy which allows for the evaluation of the neo-terminal ileum mucosa. Due to the high rates of early endoscopic recurrence, it has been recommended that ileocolonoscopy is performed 6-12 months postoperatively.13,17,20-22 This would allow for early detection and aggressive treatment of recurrent disease, if present.

Endoscopic Scoring of Postoperative Crohn’s Disease

The most widely used endoscopic scoring system was developed by Rutgeerts et al.11 Although it is not validated, this score is widely used and predicts a patient’s risk for future clinical and surgical recurrence. Based on the endoscopic appearance of the neo-terminal ileum, patients are categorized into one of 5 groups: i0, i1, i2, i3, or i4 (Table 1). Patients with a score of i0 (normal appearing neo-terminal ileum) and i1 (<5 small aphthous ulcers in the neo-terminal ileum) have a low likelihood of progression to clinical or surgical recurrence in the next 5 years and are considered to be in endoscopic remission. Specifically, 85% remain in clinical remission over a 2-year time period and are considered very low risk for requiring a second operation.11,23,24 Patients with scores of i2, i3, and i4 are at a high risk to require a second Crohn’s disease intestinal operation within the following 5 years and are designated as having endoscopic recurrence.11,23,24

Risk Factors for Postoperative Crohn’s Disease Recurrence

There are several risk factors that have been shown to contribute to the postoperative recurrence of Crohn’s disease. These factors are classified as (1) patient-related factors, (2) disease-related factors, and (3) surgery-related factors.25

The only modifiable risk factor is tobacco smoking.26-30 Not only does smoking tobacco increase endoscopic and clinical recurrence rates, surgical rates were seen to increase by 2.5 fold.31 Recurrence rates were higher in females and those who were smoking greater than 15 cigarettes per day.28,32

Fistulizing or penetrating Crohn’s disease and the need for prior Crohn’s disease related intestinal resection have also been shown to be strong risk factors for postoperative recurrence.33 Data on peri-operative steroid use as a risk factor for Crohn’s disease recurrence has been inconclusive. Recently, however, a multi-centre observational study by de Barcelos et al. showed that perioperative steroid use was the only significant risk factor for early postoperative endoscopic recurrence.34 A number of other disease-related risk factors have been studied as potential risk factors and these include young age at diagnosis of Crohns’ disease, young age at initial intestinal resection, and short duration of disease prior to the need for surgery.16,17,19,25,27,28,30,35-40

Surgical risk factors pertaining to the intestinal resection itself have been extensively studied, but all have been inconclusive in identifying strong factors for postoperative recurrence of Crohn’s disease.
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DISPATCHES FROM THE GUILD CONFERENCE, SERIES #5

Table 2. One Year Clinical and Endoscopic Recurrence Rates Reported in Randomized Controlled Studies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical Recurrence</th>
<th>Endoscopic Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25% – 77%</td>
<td>53% - 79%</td>
</tr>
<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>Nitroidimazole</td>
<td>7% - 8%</td>
<td>52% - 54%</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>34% – 50%</td>
<td>42 – 44%</td>
</tr>
</tbody>
</table>

5-ASA: 5-aminosalicylic acid; AZA: azathioprine; 6MP: 6-mercaptopurine

Table 3. Postoperative Endoscopic Recurrence (≥i2) Rates Reported in Anti-TNF Studies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anti-TNF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorrentino (MTX/IFX vs 5-ASA 2yr)</td>
<td>0%</td>
<td>100% (5-ASA)</td>
</tr>
<tr>
<td>Regueiro (IFX vs PBO RCT 1 yr)</td>
<td>9%</td>
<td>85% (PBO)</td>
</tr>
<tr>
<td>Yoshida (IFX vs PBO RCT 1 yr)</td>
<td>21%</td>
<td>81% (5-ASA)</td>
</tr>
<tr>
<td>Armuzzi (IFX vs AZA RCT 1 yr)</td>
<td>9%</td>
<td>40% (AZA)</td>
</tr>
<tr>
<td>Fernandez-Blanco (ADA)</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Papamichael (ADA 6m)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Savarino (ADA 3yr)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Aguas (ADA 1 yr)</td>
<td>21%</td>
<td>N/A</td>
</tr>
<tr>
<td>Savarino (ADA vs AZA vs 5-ASA 2 yrs)</td>
<td>6%</td>
<td>65% (AZA), 83% (5-ASA)</td>
</tr>
</tbody>
</table>

anti-TNF: anti-tumor necrosis factor; MTX: methotrexate; IFX: infliximab; 5-ASA: 5-aminosalicylic acid; PBO: placebo; RCT: randomized controlled trial; AZA: azathioprine; ADA: adalimumab

Variables that were explored include: length of resected bowel, width of surgical margins, type of anastomosis, perioperative complications, and presence of granulomas in the surgical specimen.4,24,25,28,36,39,41-44

Medications Studied for the Management of Postoperative Crohn’s Disease

There have been many studies on the early use of different medication classes for the prevention of postoperative Crohn’s disease after resective surgery. Table 2 displays the 1 year clinical and endoscopic recurrence rates that have been reported in various randomized controlled studies of patients after an ileocecal resection and the use of immunomodulators,45-47 nitroidimazole,48,49 budesonide,50,51 5-aminosalicylic acid52-55 and placebo. The lowest endoscopic recurrence rates were seen with immunomodulators (azathioprine and 6 mercaptopurine) at 42-44%. Postoperative recurrence rates were further decreased with the widespread use of anti-tumor necrosis factors (anti-TNF) medications. Table 3 summarizes the postoperative endoscopic rates reported with these medications.56-64

Most recently, data from the PREVENT trial65 showed that the clinical recurrence rates in patients on infliximab was less than the rates on placebo at week

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76 or less, however this difference was not statistically significant (12.9% vs 20%; p=0.097). Endoscopic recurrence rates, however, were significantly lower in patients receiving infliximab compared to placebo (22.4% vs 51.3%; p<0.001).

In the POCER trial, endoscopic recurrence rates at 18 months after surgery compared those who underwent an ileocolonoscopy at 6 months after an ileocecal resection (active care arm) and who subsequently received medication escalation if needed (endoscopic ileal score ≥12), to those patients who did not get a 6 month ileocolonoscopy (standard care arm). All patients received metronidazole 400 mg by mouth twice daily for the first 3 months postoperatively. Additionally patients who were classified as high risk (smokers, penetrating disease, and/or prior intestinal resection) received azathioprine. Those who were intolerant of azathioprine were given adalimumab instead. At 18 month follow up, endoscopic recurrence rates were significantly lower amongst patients in the active care arm compared to those in the standard arm (60/122=49% vs 35/52=57%; p=0.03). It was also noted that within the high-risk active arm patients, those who received adalimumab had lower 6 month endoscopic recurrence rates when compared to those who received azathioprine (6/28=21% vs 33/73=45%).

Management of Postoperative Crohn’s Disease – Technical Review and Guidelines

Recently, the American Gastroenterological Association (AGA) published a technical review on the management of postoperative Crohn’s disease. This review addressed clinical questions pertaining to the different management strategies for postoperative Crohn’s disease patients and their role in reducing recurrence. For instance, this review addressed if routine early pharmacologic prophylaxis was superior to endoscopy-guided treatment in reducing long-term recurrence in postoperative Crohn’s disease patients. Another question related to the comparative effectiveness of the different medications used amongst Crohn’s disease patients who are receiving early postoperative pharmacological prophylaxis. Similarly, comparative effectiveness of the different medications used to decrease endoscopic recurrence in patients who already developed postoperative asymptomatic endoscopic recurrence. Additionally, this review compared whether routine endoscopic monitoring at 6-12 months postoperatively is superior to no endoscopic monitoring.

The authors provide two approaches to patients with postoperative Crohn’s disease (Figures 1, 2). Based on individuals’ risk factors, patients are stratified in to groups to aid physicians in their further management. Some physicians prefer to practice the ‘watchful waiting’ approach, while other physicians are more proactive and initiate medications postoperatively for
prophylaxis and secondary prevention of recurrent Crohn’s disease. Despite the published algorithms, deciding the best option for patients often remains a dilemma.

It is the authors’ personal practice to initiate postoperative Crohn’s disease prophylaxis to prevent recurrence. Almost all patients receive a medication postoperatively, whether using an immunomodulator or combination therapy with a biologic agent and an immunomodulator. Depending on a patient’s risk factors, he/she is categorized in to a low-risk, moderate-risk, or high-risk group (Figure 1). All patients regardless of their group will receive an ileocolonoscopy for surveillance of endoscopic recurrence, 6-12 months postoperatively. The authors stratify patients into risk categories when approaching postoperative management. Low risk patients include those who are undergoing their first intestinal resection for a short stricture and those who have had long standing disease (>10 years). Patients in the low risk group are not administered medications, however, if there is evidence of recurrent Crohn’s disease (ileal score of ≥i2), treatment with an immunomodulator and/or anti-TNF is initiated. Otherwise, they would remain off of any medications, but should continue to have surveillance colonoscopies every 1-3 years. Patients who are in the moderate risk group are those who are undergoing their first intestinal resection for a long stricture (>10 cm) or for inflammatory Crohn’s disease and who have had disease for shorter than 10 years. Patients in this moderate risk group start thiopurines in the postoperative setting +/- metronidazole. While the authors still believe there is a role for immunomodulators in patients not previously receiving this type of medication, there has been a recent trend to only use thiopurines in combination with biologics rather than monotherapy. Nonetheless, we still use immunomodulators for this moderate risk group naïve to treatment, but escalate to an anti-TNF if there is evidence of subsequent recurrence. Patients in the high-risk group include those with penetrating disease, more than 2 intestinal resection surgeries, and who are smokers. In these high-risk patients, we recommend a combination of an immunomodulator with anti-TNF. Whether therapeutic drug monitoring of biologic therapy would allow for monotherapy anti-TNF (without an immunomodulator) for postoperative management needs further study.

Table 4. Summary of the Recently Published AGA Clinical Guidelines for the Management of Postoperative Crohn’s Disease

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
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<tbody>
<tr>
<td>In patients with surgically induced remission of CD, the AGA suggests early pharmacological prophylaxis over endoscopy-guided pharmacological treatment</td>
<td>Conditional</td>
<td>Very Low</td>
</tr>
<tr>
<td>In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>In patients with surgically induced remission of CD, the AGA suggests against using mesalamine (or other 5-aminosalicylates), budesonide, or probiotics</td>
<td>Conditional</td>
<td>Low, Very Low</td>
</tr>
<tr>
<td>In patients with surgically induced remission of CD receiving pharmacological prophylaxis, the AGA suggests postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>In patients with surgically induced remission of CD not receiving pharmacological prophylaxis, the AGA recommends postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>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</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

AGA: American Gastroenterological Association; CD: Crohn’s Disease
Crohn’s disease management is unknown. Another approach to the management of postoperative Crohn’s disease is to stratify patients by risk of recurrence but utilize endoscopic recurrence to guide therapy (Figure 2). In this approach, patients are separated into a high-risk group and a low risk group for recurrence where only patients in the high-risk group would receive Crohn’s disease medications. The medication of choice is a thiopurine agent, but in cases of thiopurine intolerance, anti-TNF medications are used instead. Again, similar to the algorithm in Figure 1, all patients would undergo an ileocolonoscopy at 6 months postoperatively, and depending on evidence of endoscopic recurrence, medication escalation is made. Of note, the authors of POCER have also reported the potential for fecal calprotectin as a surrogate marker for Crohn’s disease recurrence and may be a noninvasive method to measure recurrence.

CONCLUSION

The majority of patients with Crohn’s disease will require an intestinal resection at some point in their lifetime. Postoperative management of these patients remains a challenge. It is important to identify high-risk patients who exhibit risk factors for recurrence and to aggressively treat these patients to prevent or ameliorate recurrence of their Crohn’s disease. All patients regardless of their risk should have an ileocolonoscopy 6-12 months postoperatively to initiate or adjust medications in cases of endoscopic recurrence (ideal score ≥i2). The authors provide the algorithm that they utilize in their practice when approaching postoperative Crohn’s disease patients (Figure 1).

References


