Learning Objectives

• To identify the risk factors associated with postoperative Crohn’s disease recurrence.
• To understand the medication options for prevention and treatment of postoperative Crohn’s disease recurrence.
• To outline appropriate surveillance strategies to identify recurrent Crohn’s disease after surgical resection.

Approximately two-thirds of Crohn’s disease patients will require surgery in their lifetime. While surgery removes the diseased intestine, it is not curative and recurrence is common. The endoscopic recurrence rate of Crohn’s disease one year after intestinal resection is 70–90%. Recurrence of Crohn’s disease can be defined by clinical symptoms or by endoscopic, radiological, or histopathological means. Most patients who have recurrence by these definitions will not have symptoms, i.e., clinical recurrence of Crohn’s disease. A prospective, cohort study by Rutgeerts et al. evaluated 89 patients who underwent ileocolonic resection in order to assess predictors of recurrent disease. This study found the strongest predictor of recurrent Crohn’s disease to be the severity of endoscopic lesions found on colonoscopy one year after surgery.

Risk Factors for Post-operative Recurrence

Several risk factors have been identified for post-operative Crohn’s disease recurrence. (Table 1) The three factors that portend the greatest risk for postoperative recurrence are: 1) active tobacco smoking after surgery, especially in women and heavy smokers; 2) patients with penetrating disease, i.e. fistulas, abscesses, intestinal perforation; and 3) those with two or more surgeries.

Post-operative Crohn’s Disease Surveillance

Scheduled post operative assessment for recurrence allows for early detection and intervention. The Crohn’s disease activity index (CDAI) is a clinical research score that is used to define clinical activity and response to medical therapy. Although the most widely applied activity score in research studies and publications, the CDAI may not accurately predict postoperative Crohn’s disease recurrence. Ileocolonoscopy six months to one year after intestinal resection is important for the evaluation of endoscopic recurrence, regardless of clinical symptoms.

Medications for Postoperative Prevention

There are a number of studies which have evaluated the efficacy of medications for preventing Crohn’s disease recurrence after intestinal resective surgery. Studies of 5-aminosalicylates for the prevention of post-operative recurrence have failed to provide convincing evidence for benefit in the majority of patients. The nitroimidazole antibiotics (metronidazole and ornidazole) offer hope that these medications may be effective in preventing postoperative Crohn’s disease. The limitation is that the benefit is maintained only if the antibiotic is continued and most patients do not tolerate high doses of nitroimidazole antibiotics for very long.

Both azathioprine and 6-mercaptopurine (6-MP) are effective medications for maintenance of medically induced Crohn’s disease remission and have been considered aggressive treatment for postoperative prevention. Four studies have evaluated these agents for the prevention of postoperative Crohn’s disease. In a recent meta-analysis, the four azathioprine/6 mercaptopurine studies were evaluated and compared. Azathioprine/6MP was 8% more effective than the control at preventing clinical recurrence and the number needed to treat was 13 (NNT=13). Severe endoscopic recurrence, i.e. ileal score of 3 or 4, was not prevented by azathioprine/6MP and no more effective than the control. There are five anti-TNF postoperative prevention studies, three with infliximab and two with adalimumab. (summarized in Table 3)

Proposed Guidelines for the Management of Postoperative Crohn’s Disease

There are no formal guidelines for the prevention of postoperative Crohn’s disease. The decision on postoperative medications should be based on the patient’s risk for postoperative recurrence. The following recommendations are the author’s suggestions. (Figure 1) Patients at low-risk for postoperative recurrence are those who have had longstanding Crohn’s disease (>10 years), and whose indication for surgery is a short (<10cm), fibro-stenotic stricture. Given the slow progression of disease in a limited segment of bowel, these patients are less likely to have aggressive postoperative recurrence, and are not routinely placed on post-operative medications. An ileocolonoscopy should be performed 6-12 months postoperatively and if there is no endoscopic recurrence, i.e.: i0 or i1, no medication is started and a colonoscopy is repeated 1-3 years later. If there is evidence of early endoscopic recurrence (Rutgeert’s score i2), an immunomodulator or anti-TNF agent is started.
Table 1: Risk Factors for Postoperative Crohn’s Disease Recurrence

**Strongest Risk Factors**
- Smoking
- Penetrating disease
- History of prior resection

**Strong Risk Factors**
- Progression to surgery despite immunomodulators and biologics
- Short duration of disease prior to surgery
- Colon and small bowel involvement
- Young age at disease onset
- Perianal fistula

**Inconclusive Risk Factors**
- Family history of IBD
- Type of anastomosis
- Gender
- Corticosteroids prior to surgery
- Length of diseased intestine

Table 2: Clinical and Endoscopic One Year Recurrence Rates from Randomized Treatment Trials

<table>
<thead>
<tr>
<th>Medication class</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>Nitridimazole</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>0–10%</td>
</tr>
</tbody>
</table>

Table 3: Endoscopic Recurrence Rates in the Anti-TNF Postoperative Prevention Studies

<table>
<thead>
<tr>
<th>Study (author/medication/duration)</th>
<th>Anti-TNF</th>
<th>Placebo/5ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorrentino et al.10 Infliximab/2 years</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Regueiro et al.11 Infliximab/1 year</td>
<td>9%</td>
<td>85%</td>
</tr>
<tr>
<td>Yoshida et al.13 Infliximab/1 year</td>
<td>21%</td>
<td>81%</td>
</tr>
<tr>
<td>Fernandez-Blanco et al.12 Adalimumab/1 year</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Papamichael et al.14 Adalimumab/6 mos.</td>
<td>0%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Figure 1: Algorithm for Postoperative Management of Crohn’s Disease

- **Perioperative risk stratification**
- **Low risk**
  - No immediate postoperative medications
  - Surveillance colonoscopy for recurrent disease:
    - Low risk patients – 1-3 year intervals
    - Moderate risk – 1-2 year intervals
    - High risk – 6-12 month intervals
- **Moderate risk**
  - 1. 6MP/AZA for 6 months
  - 2. Metronidazole for 3 months
  - Surveillance colonoscopy for recurrent disease:
    - Low risk patients – 1-3 year intervals
    - Moderate risk – 1-2 year intervals
    - High risk – 6-12 month intervals
- **High risk**
  - 1. Colonoscopy at 6-12 months.
  - 2. Recurrent disease – increase dose vs shorten interval
  - 3. Change anti-TNF agent

6MP – 6 mercaptopurine
SICUS – small intestine contrast ultrasonography
WCE – wireless capsule endoscopy

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Patients at moderate risk for postoperative recurrence are those naïve to immunomodulators, with a relatively short duration of disease (<10 years) prior to their first surgery, who undergo resection for a long segment (>10cm) of small bowel inflammation. These patients are started on an immunomodulator within two weeks of surgery. Given the compelling data on the combination of metronidazole with azathioprine for preventing postoperative Crohn’s disease, a nitroimidazole antibiotic is added if possible. Unfortunately, it is my experience that most patients do not tolerate high dose metronidazole for an extended period of time, thereby limiting this option. An ileocolonoscopy is performed 6-12 months post-operatively and if there is evidence of endoscopic recurrence an anti-TNF agent is added. If the initial post-operative ileocolonoscopy shows no endoscopic recurrence, the immunomodulator is continued and a colonoscopy is repeated 1-3 years later.

Patients at a high risk for recurrence are those with penetrating disease, i.e., abscess, perforation or internal fistula, smokers, patients with a prior surgery for Crohn’s disease, and those who progressed to surgery despite treatment with an immunomodulator. For these patients, an anti-TNF agent is started within 2-4 weeks of surgery. An ileocolonoscopy is then performed one year post-operatively. In those with an ileal score of 0 or 1, the anti-TNF agent is continued. If there is significant endoscopic recurrence, ≥2, the options for treatment include anti-TNF dose intensification, change in the biologic agent, and/or the addition of an immunomodulator when appropriate.

**Top Down Therapy for Postoperative Crohn’s Disease?**

In recent years, there has been significant controversy about the appropriate treatment paradigm for CD. Specifically, the relative merits of treatment titration, i.e. “bottom up” therapy, have been touted as a means by which to limit patient exposure to potentially unnecessary, toxic therapies. Conversely, “top-down” therapy proposes that aggressive early intervention may in fact modify disease course and provide outcomes superior to the bottom-up approach. Efforts to compare these approaches can be extremely challenging. Patients enrolled in such studies are, by definition “newly diagnosed.” However, it is impossible to accurately know the extent or duration of pre-existing silent CD, and the extent of related tissue scarring and remodeling. Postoperative CD may provide a unique setting in which to evaluate these approaches by starting with macroscopically normal bowel at a defined point in time. It is possible that studies conducted among such patients could eventually provide missing outcome data about the impact of treatment on the natural course of disease. Finally, there may be patients for whom primary treatment intervention is a surgical resection followed by aggressive medical therapy. It is conceivable that this approach could redefine the natural course of Crohn’s disease and sustain deep remission and prevention of recurrence in a manner not previously realized.

**Key Points**

- Nearly two-thirds of Crohn’s disease patients will require surgery in their lifetime: postoperative recurrence is common and clinically silent until a complication develops.
- Risk factors associated with a high likelihood for postoperative recurrence include cigarette smoking, penetrating disease, or more than one surgery in the patient’s lifetime.
- Patients at low risk for recurrence probably do not need postoperative treatment.
- Patients at moderate risk for recurrence should receive azathioprine/6-mercaptopurine with or without metronidazole after surgery.
- Patients at high risk for recurrence should be considered for an anti-TNF after surgery.
- In all patients an ileocolonoscopy should be performed 6-12 months after surgery and periodically thereafter to assess disease recurrence.

**REFERENCES**


