Nearly one million people in the United States suffer from Crohn’s disease (CD), with studies showing increase in the rate of prevalence of CD from 214 per 100,000 people in 2004-2005, to 236 per 100,000 people in 2008-2009.1,2 Crohn’s disease (CD) is a chronic immune mediated inflammatory disorder of the gastrointestinal system that can involve anywhere from the mouth to the anus. Over one-half of patients with CD will have an intestinal complication of strictures, fistulas and abscesses3 and nearly 70% require surgical resections by 15 years.4 Surgery can induce remission but is not curative, as most patients undergoing an ileo-cecal resection will develop endoscopic recurrence one year after surgery.5 More importantly, these patients do not manifest symptoms (i.e. they are clinically “silent”) until another complication presents and surgery is required. Primary care physicians will often see these patients and it is important to understand the natural course and management of postoperative Crohn’s disease.

Natural History of Post-Operative Crohn’s Disease (Figure 1)

The risk of post-operative endoscopic recurrence (POR) in CD is 90% by one year.6 Clinical symptoms are not apparent in the early stages and only 35-50% of patients will develop clinical manifestations such as diarrhea, abdominal pain, nausea or vomiting by five years.5,7 Postoperative Crohn’s disease is clinically silent, but histological disease activity in an endoscopically normal neo-terminal ileum may occur as early as one week after surgery.8,5,7,9 To define endoscopic postoperative recurrence, the Rutgeerts score remains the standard to define disease severity5 (Table 1 and Figure 2). The endoscopic score often does not correlate with symptoms10 and patients with more severe endoscopic recurrence (i3 or i4) will require another surgery by 10 years.11x

Definition of Recurrence
Postoperative Crohn’s disease recurrence may be defined in several ways.

- **Histologic Recurrence (HR)**
  Histologic recurrence is defined as the presence of histological activity on mucosal biopsies obtained during ileocolonoscopy.12 As mentioned previously, these changes can be seen within one week of the
Medical Management of Post-Operative Crohn’s Disease

**Figure 1. Natural History of Post-Operative Crohn’s Disease**

<table>
<thead>
<tr>
<th>1-3 weeks</th>
<th>1 year</th>
<th>3-5 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic Disease</td>
<td>Endoscopic Recurrence (70-90%)</td>
<td>Clinical recurrence (30-60%)</td>
<td>Surgery (50%)</td>
</tr>
</tbody>
</table>

**Clinical Recurrence (CR)**
Clinical symptoms are an imperfect measure of Crohn’s disease recurrence. In the early postoperative phase patients may have symptoms related to the surgical resection (e.g. bile salt diarrhea, altered motility or malabsorption). Additionally, clinical symptoms may be lacking despite endoscopic recurrence (i.e. clinically silent) and could provide a false sense of remission despite active Crohn’s disease. Although clinical recurrence was used in earlier postoperative Crohn’s disease studies, future research will utilize endoscopic recurrence as a primary objective measure of Crohn’s disease.

**Other Markers of Recurrence**
Owing to the invasive nature of endoscopic assessment for recurrence, other modalities for objective assessment are being studied:

1. **Fecal calprotectin**: Levels of <100μg/g have shown good negative predictive value and can be used to determine patients in remission. Conversely, patients with levels > 150 μg/g would be those to target for an ileocolonoscopy to assess recurrence.

2. **Small bowel ultrasound**: Bowel wall thickness of >3mm maybe a non-invasive marker to predict early POR, with patients with >6mm bowel thickness having a 40% risk of surgical recurrence. This may be a valuable, non-invasive measure of recurrent Crohn’s disease; however, this takes technical expertise and may be limited to certain centers.

3. **Computed tomography (CT) enterography and magnetic resonance (MR) enterography**: These have shown variable correlation with endoscopic and clinical activity scores, and are not ready for practice yet.

The role of histologic activity in a patient with an endoscopically normal ileum is not clear. The author’s practice is to consider patients in an i0 endoscopic remission (ER) for at least three years with absent histologic activity of disease as deep remission and discuss the risks and benefits of de-escalation of treatment/stopping therapy with annual endoscopic surveillance. If the patient has histologic activity of disease, we would risk stratify patients, and those at high risk for recurrence (e.g. greater than two resections, penetrating disease, current smokers) will be advised against de-escalation or stopping therapy.

**Endoscopic Recurrence (ER)**
Endoscopic evaluation is currently the gold standard for determining postoperative recurrence and guidance of medical management. The Rutgeert’s scoring system is most widely used to grade endoscopic disease activity. The score is assessed by evaluating the 10 cm of the ileum proximal to the anastomosis (neoterminal ileum). Endoscopic recurrence is the strongest predictor of clinical recurrence (i.e. symptoms associated with Crohn’s disease) and ultimate progression to a future surgery (Table 1 and Figure 2). Patients with normal mucosa (i0) or less than five aphthous ulcers (i1) have <10% risk of clinical recurrence (CR) at 5-10 years, whereas those with severe disease (i3, i4) have been shown to have >90% risk of CR at 5-10 years. Owing to the good inter-observer agreement for the Rutgeert’s scoring system, it has become the most standardized method of endoscopic assessment of disease post-operatively. Even though this scoring system has not been validated by studies to define recurrence or remission, most studies have continued to use the Rutgeert’s score to determine remission/recurrence, with scores of i0 or i1 defining remission and i2, i3 and i4 defining disease recurrence.
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Figure 2. Endoscopic Photos of Postoperative Crohn’s disease Recurrence in the Ileum

**Risk Factors for Recurrence (Table 2)**

There are multiple risk factors that can translate to a higher rate of POR. Those patients who are at higher risk of recurrence should initiate postoperative prevention medication(s). A summary of pertinent risk factors are:

- **Patient Related Factors**
  - **High Risk**
    1. Smoking, especially women and those smoking >15 cigarettes/day
    2. Younger age at time of surgery (<30 years)
    3. Shorter disease duration prior to surgery
  - **Equivocal to No Effect**
    1. Gender
    2. Family history of inflammatory bowel disease (IBD)

- **Disease Related Factors**
  - **High Risk**
    1. Multiple prior surgeries (greater than two)
    2. Disease location, ileal/ileocolonic or extensive disease
    3. Penetrating disease
    4. Perianal disease
  - **Histopathology Related Factors**
    - **High Risk**
      1. Presence of granulomas (except crypt rupture granulomas)
      2. Myenteric plexitis
  - **Surgery Related Factors**
    - **High Risk**
      1. Length of bowel resected
    - **Equivocal to No Effect**
      1. Type of anastomosis (side to side versus end to end)

**General Principles of Management (Figure 3)**

The aim of management is to alter the natural history of the disease by preventing post-operative (continued on page 30)
reurrence and repeat surgery. This requires appropriate triage of high-risk patient, vigilant endoscopic surveillance for assessment of recurrence, choosing appropriate pharmacotherapy and escalating therapy as needed. Those at highest risk for recurrence are any patient who has had two or more resections, especially when two surgeries have occurred within 10 years of each other.

• **When to Start Treatment?**

There are two general principles of management:

1. Early post-operative prophylactic anti TNF within 2-4 weeks of surgery for high risk patients followed by a 6-12 month ileocolonoscopy\(^ {45–47}\)

2. No postoperative therapy for low risk patients but ileocolonoscopy at six months with initiation of treatment for recurrence

• **Medications for Prevention of Recurrence**

There are multiple treatment options that can be targeted for prevention of POR, however the data currently is strongest for biologics, namely infliximab. Table 3 shows the comparative effectiveness of various treatment modalities as prophylaxis to prevent POR.

1. **5-ASAs**

These have shown to have little effect on POR and we do not recommend 5-ASA use as a postoperative prevention strategy.\(^ {48}\)

2. **Antibiotics**

A major Cochrane meta-analysis has shown a significant reduction in CR and three month ER when nitroimidazoles were compared to placebo.\(^ {48}\)

3. **Immunomodulators**

Thiopurines, 6-mercaptopurine (6-MP) and azathioprine do not significantly decrease endoscopic recurrence, although studies have shown potential benefit in clinical recurrence.\(^ {49–51}\)

Thiopurines are rarely used as monotherapy and most often used as combination therapy as an adjunct to anti-tumor necrosis alpha agents (anti-TNF).\(^ {52}\)

4. **Budesonide**

This has not been shown to be of any benefit in the post-operative setting and we do not recommend budesonide.\(^ {53}\)

5. **Probiotics**

At least two major randomized control trials (RCTs) which have compared probiotics (Lactobacillus GG and VSL#3) to placebo and have not shown any benefit in prevention of POR in CD patients.\(^ {54,55}\)

6. **Biologics**

These are the most effective pharmacological agents for the prevention of POR in CD. The best studied among biologics have been anti-tumor necrosis alpha (anti-TNF) agents.

**Infliximab**

Infliximab (IFX) has been the most studied medication for use in the post-operative setting.

---

**Table 1. Postoperative Ileal Endoscopic Recurrence score or Rutgeert’s Score**

<table>
<thead>
<tr>
<th>Endoscopic Score*</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>i0</td>
<td>no lesions</td>
</tr>
<tr>
<td>i1</td>
<td>&lt; 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>

*Remission: endoscopic score of i0 or i1; recurrence: endoscopic score of i2, i3, or i4
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A placebo controlled RCT comparing infliximab to placebo, showed reduced 1-year rates of ER (9.2% vs. 84.6%, p=0.0006), CR (0.0% vs. 38.5%) and HR (27.3% vs. 84.6%, p=0.01) when IFX was started within four weeks of surgery compared to placebo. These were followed up by the landmark prospective, multicenter, randomized, double blind, placebo-controlled trial called the PREVENT trial. The study included patients with increased risk of POR defined as: at least one or more prior resection within 10 years, resection for penetrating CD complication (abscess, fistula), history of perianal fistulizing CD, or active smoking. The primary end point was clinical recurrence at 76 weeks. Prophylactic IFX was associated with numerically lower but not statistically significant rates of CR (12.9% vs 20%, p=0.097) and composite CR and ER rates (4.1 vs 9.3%) when compared to placebo. In a secondary analysis there were significantly lower rates of ER alone (22.4% vs 51.3%) or composite ER or new penetrating complication compared to placebo (30.6% vs. 60.0%, p<0.001). Therefore, despite the lack of achieving the primary clinical recurrence endpoint, the lower endoscopic recurrence rates in PREVENT suggest a biological benefit of infliximab as postoperative prevention.

Adalimumab
Adalimumab (ADA) has also been studied in the post-operative setting. Complete clinical, radiographic and endoscopic remission in patients treated with ADA post ileocecectomy was noted. Patients on prophylactic ADA have very low rates of ER at six months (1/8, 12.5%) and 24 months (2/8, 25%) when started 14 days postoperatively.

Table 2. Factors Associated with Risk of Post-Operative Recurrence in Crohn’s Disease (Adapted from Click et al. 2017)

<table>
<thead>
<tr>
<th>Patient</th>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Smoking</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Age at Onset</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Disease Duration Prior to Surgery</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Visceral Adiposity</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating/Perforating</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Prior CD Surgery (&gt;2)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Small bowel involvement</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Perianal Disease</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histopathology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Myenteric Plexitis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Granulomas Present</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomosis Type</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Open versus laparoscopic</td>
<td>~</td>
<td></td>
</tr>
<tr>
<td>Length of resected segment</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

+ Weak
++ Moderate
+++ Strong
~ Equivocal or unknown

Table 3. One Year Clinical and Endoscopic Crohn’s Disease Recurrence Rates Reported in Randomized Controlled Trials (Adapted from Requeiro et al., 2009)

<table>
<thead>
<tr>
<th>Drug</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-Aminosalicylates</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>Azathioprine/6-Mercaptopurine</td>
<td>34% - 50%</td>
<td>42% - 44%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0%-13%</td>
<td>9%-22%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>13%</td>
<td>6%</td>
</tr>
</tbody>
</table>
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Figure 3. Algorithm for Management of Postoperative Crohn’s Disease

* Monotherapy anti-TNF may be a reasonable option with therapeutic drug monitoring but data are lacking to support this approach in postoperative Crohn’s disease; Post-op: post-operative; Anti-TNF: Anti tumor necrosis factor alpha; ↑ Increase; Δ Change

resection. Another RCT, comparing ADA to AZA and mesalamine showed significantly lower ER (6.3% ADA vs 64.7% AZA vs 83.3% Mesalamine) and CR (12.5% ADA vs. 64.7% AZA vs 50% Mesalamine) in patient receiving ADA compared to the other two treatment arms. Although there are no large randomized controlled trials, the totality of data from uncontrolled studies suggests that ADA is superior to both immunomodulators and 5-ASA at preventing postoperative Crohn’s disease recurrence.

Other Biologics
There are limited data on vedolizumab for the prevention of postoperative Crohn’s disease. In a small open label, uncontrolled study, anti-TNF therapy had a lower rate of post-operative recurrence compared to Vedolizumab. To date, there are no postoperative prevention data with ustekinumab, however safety data suggest no complications with pre-operative use or post-operative initiation.

(continued on page 34)
Safety of Anti-TNF and Health Maintainence
There are several studies evaluating the safety of anti-TNF agents in perioperative Crohn’s disease surgery. The majority of data have shown that anti-TNFs did not increase postoperative infections or wound healing. As such, the authors recommend initiation of anti-TNFs as soon after surgery as possible for maximal benefit as a prevention of recurrence strategy. Typically, we wait for the surgeon to “clear” the patient, typically 2-4 weeks after surgery, to initiate postoperative anti-TNF.

Comparison of Different Medications for Prevention of POR
Prospective, comparative effective studies are lacking in the postoperative setting. In the absence of these trials, Singh et al. conducted a Bayesian network meta-analysis comparing the efficacy of various pharmacological agents in the post-operative setting for CD. The meta-analysis included 21 trials with seven treatment strategies, comprising 2006 patients. The results of the meta-analysis concluded that anti-TNF agents were the most effective therapy for prevention of POR with large effect sizes compared to all other treatment modalities (CR: RR 0.02-0.20; ER: RR 0.005-0.04). More recently the AGA technical review and guidelines supported the recommendation to initiate postoperative anti-TNF within 2-4 weeks after surgery.

Endoscopic Surveillance
Ileo-colonoscopy is the “gold standard” for evaluating mucosal CD. The routine use of endoscopic surveillance in the post-operative setting was informed by a landmark multicenter, prospective, double blind, randomized controlled trial across 17 centers in Australia and New Zealand (POCER trial). The primary endpoint of the study was endoscopic recurrence at 18 months. Patients were randomized into two endoscopy surveillance arms, active vs standard care, and stratified by risk of POR. The active care arm patients had an ileo-colonoscopy at six months with escalation of medical therapy if there was endoscopic recurrence (≥ i2), whereas the standard care arm did not have a six month interval ileocolonoscopy. Patients were stratified to postoperative treatment based on risk factors. All patients, independent of risk strata, received three months of metronidazole. There was a lower ER rate at 18 months in the patients randomized to the active care arm compared to the standard care arm (49% vs. 67%, p=0.03). The results from the POCER studies informed the AGA guidelines in recommending an ileo-colonoscopy at six months in postoperative Crohn’s disease patients.

SUMMARY AND PRACTICAL RECOMMENDATIONS
Based on available data, we recommend risk stratifying patients as low risk (hypothetical risk at 18 months: CR- 20% and ER-30%) versus high risk (hypothetical risk at 18 months: CR- 50% and ER-80%). Low risk patients may not require immediate postoperative therapy but should have an ileocolonoscopy at six months with or without a fecal calprotectin at three months. High risk patients are those who should initiate postoperative anti-TNF within 2-4 weeks after surgery.

If there is active Crohn’s disease on the postoperative colonoscopy (≥ i2) therapy should be initiated for those not previously administered medication, and optimized or escalated for those receiving medication (Figure 3). To date, anti-TNFs, specifically infliximab, have been the most extensively studied for the prevention of post-operative Crohn’s disease. Data on the use of vedolizumab and ustekinumab are lacking, however for those who have previously failed anti-TNFs would be a reasonable alternative for high risk patients.

References


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