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“Patients with Crohn's disease commonly experience clinical recurrence, which can lead to disease complications and a need for further surgery. Risk factors for postoperative recurrence have been identified, although few are modifiable, and more data are needed in this area.”

Despite advances in medical therapy, up to 75% of patients with Crohn's disease will undergo at least one intestinal resection during their disease course [1–3]. Common surgical indications include failure of medical management, Crohn's disease complications (strictures, fistulas and abscesses) and, rarely, malignancy. Postoperative Crohn's disease recurrence is common, with endoscopically evident disease occurring in 70–90% of patients within 12 months of surgery [4,5]. Endoscopic recurrence most commonly occurs in the neoterminal ileum, proximal to the ileocolic anastomosis. Approximately 50% of patients will have a Crohn's disease clinical recurrence within 5 years of surgery [4,6,7]. Typically, by the time symptoms manifest, the disease has progressed to include the development of a complication, often requiring additional surgery. Up to 70% of patients require an additional surgical resection within 10 years of their initial surgery [8,9]. Although preventing postoperative Crohn's disease and modifying potential risk factors for postoperative recurrence have been the focus of numerous research studies, it remains a difficult problem.

Defining recurrence

Since clinical recurrence lags behind endoscopic recurrence, the detection of active inflammation and disease complications is challenging. The earliest signs of postoperative recurrence are the presence of aphthous ulcerations in the neoterminal ileum. A detailed scoring system, developed by Rutgeerts *et al.*, helps predict

future clinical recurrence based on endoscopic findings [10]. Patients with endoscopic scores of i0 (no ulcers or evidence of Crohn's disease) or i1 (≤ 5 aphthous ulcers in the neoterminal ileum) 1-year postoperatively are at low risk for progression to clinical or surgical recurrence. Patients who have evidence of more advanced endoscopic disease, that is i2 (>5 aphthous ulcers in the neoterminal ileum), i3 (deep ulcers with more extensive inflammation) or i4 (severe inflammation, nodularity and stenosis), experience a 3-year clinical recurrence rate of 15, 40 and 90%, respectively [11]. Independent of the postoperative treatment strategy, we recommend an ileocolonoscopy be performed in all Crohn's disease patients 6–12 months following a surgical resection. The presence of endoscopic recurrence should prompt initiation of medical therapy, or escalation of therapy to a more potent regimen. Currently, ileocolonoscopy is the best modality for assessment of early postoperative recurrence and, until noninvasive measures are validated, this remains our diagnostic tool of choice.

Risk factors for recurrence

Several risk factors have been identified that help predict which Crohn's disease patients are most likely to experience a postoperative recurrence. Factors associated with the highest risk for postoperative recurrence include smoking, penetrating or perforating disease, and prior Crohn's disease surgery [12–16]. Other risk factors that have been associated with postoperative recurrence include early age at initial surgery,

short duration of disease prior to initial surgery, both ileal and colonic disease distribution, and the use of corticosteroids prior to surgery. Whether the type of surgical anastomosis, that is side-to-side or end-to-end, is associated with postoperative recurrence is controversial [17–19].

“Factors associated with the highest risk for postoperative recurrence include smoking, penetrating or perforating disease, and prior Crohn’s disease surgery.”

Is there anything that can be done to stop the vicious cycle of postoperative Crohn’s disease recurrence and re-operation? The only modifiable risk factor for postoperative recurrence is smoking, thus, tobacco cessation must be emphasized. A recent meta-analysis showed a 2.5-fold higher risk of re-operation within 10 years among smokers compared with nonsmokers [20]. The detrimental effect of smoking on postoperative disease course is even more severe in female patients, and is dose dependent [12,13].

Medications for preventing postoperative Crohn’s disease

The timing of and whether to institute medical therapy postoperatively is a difficult issue, and the approach needs to be personalized for each individual patient. One approach is to begin medical therapy shortly after surgery, while the patient is in surgical remission, and attempt to prevent recurrence. Alternatively, medications may be withheld until the patient presents with endoscopic or clinical recurrence. This symptom-based approach mirrors the approach used to treat patients with newly diagnosed Crohn’s disease, and may delay effective therapy until the patient experiences a complication requiring surgery.

Multiple medications have been evaluated for the prevention of postoperative Crohn’s disease recurrence. The available data suggest that probiotics, corticosteroids (systemic and rapidly metabolized steroids) and 5-aminosalicylates are probably of little benefit in preventing postoperative recurrence [21]. Antibiotics have been shown to be of some benefit in preventing both postoperative clinical and endoscopic recurrence of Crohn’s disease. Studies of both metronidazole and ornidazole have shown a reduction in postoperative clinical and endoscopic recurrence, respectively [22,23]. Unfortunately, it is difficult for patients to tolerate antibiotics such as metronidazole over the long term, owing to side effects. In addition, the benefit is lost when these medications are discontinued.

Azathioprine and 6-mercaptopurine are efficacious in maintaining remission in patients with moderate-to-severe Crohn’s disease. These immunomodulator medications have historically been considered aggressive postoperative therapy, however, 1-year endoscopic remission rates are approximately 50% [24,25]. Immunomodulators have been shown to be more effective than mesalamine in preventing postoperative recurrence, although a significant number of patients discontinue immunomodulator therapy owing to medication-related side effects. D’Haens *et al.* compared 3 months of postoperative metronidazole therapy added to either azathioprine or placebo given to prevent postoperative

recurrence [26]. Patients receiving metronidazole and azathioprine combination therapy showed significantly lower 1-year recurrence rates (43.7 vs 69%). A recent meta-analysis by Peyrin-Biroulet *et al.* found immunomodulator medications to be more effective than either placebo or mesalamine in preventing 1-year clinical recurrence and severe endoscopic recurrence, although the numbers needed to treat were 13 and 7, respectively [27].

The role of tumor necrosis factor antibody (anti-TNF) medications in the management of postoperative Crohn’s disease has recently been explored. Regueiro *et al.* performed a randomized, double-blind, placebo-controlled trial evaluating infliximab for the prevention of postoperative Crohn’s disease recurrence [28]. A total of 24 subjects received either infliximab or placebo starting 4 weeks after a ‘curative’ ileocolonic resection. Although 1-year endoscopic recurrence was the primary outcome, the authors also evaluated clinical recurrence, a histological activity score and serological inflammatory markers. Only one out of 11 infliximab subjects (9.1%) compared with 11 out of 13 placebo subjects (84.6%) had evidence of endoscopic recurrence at the study end point. Significant differences in favor of infliximab therapy were also seen for the major secondary end points examined. These results were even more impressive considering that the infliximab group had a significantly greater number of smokers and significantly fewer users of concomitant immunomodulator therapy. Data from a 2-year follow-up have recently been presented, suggesting that the improved outcomes can be maintained in subjects who continue infliximab therapy [29]. These findings have been corroborated by Sorrentino *et al.* in an open-label study [30]. The major limitation to the current postoperative anti-TNF studies is the small sample size, and a larger, multinational trial is scheduled to start enrolling patients later this year.

Discussion on the management of postoperative Crohn’s disease

There are no formal guidelines for the prevention of postoperative Crohn’s disease. We suggest the decision on treatment be based on the patient’s risk for postoperative recurrence. We consider patients at low risk for recurrence as those who have had longstanding Crohn’s disease (>10 years), and whose indication for surgery is a short (<10 cm), 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 thus we do not routinely place these patients on postoperative medications. An ileocolonoscopy should be performed 6–12 months postoperatively and if there is no endoscopic recurrence (i.e., i0 or i1) we do not start medication, and repeat a colonoscopy 1–3 years later. If there is evidence of early endoscopic recurrence (Rutgeerts’ score $i \geq 2$), we recommend an immunomodulator or anti-TNF agent.

We consider patients at moderate risk for postoperative recurrence as those naive to immunomodulators, with a relatively short duration of disease (<10 years) prior to surgery, who undergo resection for a long segment (>10 cm) of small bowel inflammation. We start these patients on an immunomodulator within 2 weeks of surgery. Given the compelling data on the combination of metronidazole with azathioprine for preventing postoperative

Crohn's disease, we favor adding a nitroimidazole antibiotic if possible. Unfortunately, most patients do not tolerate high-dose metronidazole for an extended period of time, limiting this option.

“The only data to date on postoperative anti-TNF therapy is with infliximab, and whether all anti-TNFs are equally efficacious at preventing recurrence has not yet been established.”

Patients at high risk for recurrence are those with penetrating disease (e.g., 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, we initiate an anti-TNF agent within 2–4 weeks of surgery. An ileocolonoscopy is then performed 1-year postoperatively. In those with an ileal score of i0 or i1, we continue the anti-TNF agent. If there is significant endoscopic recurrence (i.e., a score greater than i2), we check anti-TNF antibodies and serum trough levels and escalate anti-TNF dosing when appropriate and/or add an immunomodulator.

Despite recent advances in the prevention of postoperative recurrence of Crohn's disease, several questions remain unanswered. Whether to initiate postoperative treatment shortly after surgery as a prophylactic measure versus delaying treatment for 3–6 months until ileocolonoscopy findings are available is not clear. The only data to date on postoperative anti-TNF therapy is with infliximab, and whether all anti-TNFs are equally efficacious at preventing recurrence has not yet been established. Finally, we currently perform an ileocolonoscopy within 1 year of surgery to determine

recurrence and guide management. Other less invasive modalities for detecting postoperative recurrence may emerge and accurately define disease activity. Tests such as small bowel ultrasound, computed tomography and magnetic resonance enterography, as well as stool studies for fecal lactoferrin and calprotectin have shown promising initial results at detecting postoperative recurrence, and may one day be routinely used for postoperative screening [31–34].

Conclusion

Patients with Crohn's disease commonly experience clinical recurrence, which can lead to disease complications and a need for further surgery. Risk factors for postoperative recurrence have been identified, although few are modifiable, and more data are needed in this area. Antibiotics, immunomodulator medications and anti-TNF agents have been shown to be efficacious in preventing postoperative recurrence of Crohn's disease, although the potential risks and benefits of therapy need to be balanced in individual patients. Postoperative risk stratification helps guide the decision on initiating medical therapy. Endoscopic evaluation within 6–12 months of surgery is currently the most accurate modality for detecting preclinical recurrence, and should be used to guide therapeutic decisions.

Financial & competing interests disclosure

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