

Management and Prevention of Postoperative Crohn's Disease

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G&H What risk factors predict recurrence of Crohn's disease following surgical resection?

MR A number of risk factors may predict recurrence of Crohn's disease (CD) following resection. The patients who are most likely to experience a postoperative recurrence are those with penetrating or perforating CD who present with an intestinal fistula, abscess, or free perforation. Other patients at high risk for recurrence include those who have had multiple surgeries and those who smoked before surgery and continue to smoke after surgery.

G&H What can clinicians do to prevent postoperative recurrence of CD?

MR Cigarette smoking is the only modifiable risk factor for postoperative recurrence that has been identified to date. For patients who are cigarette smokers prior to surgery, the absolute best strategy for preventing postoperative recurrence is to completely stop smoking. As for medical treatment options that could help to prevent postoperative recurrence, appropriate management depends on the patient's risk of recurrence. Recent data suggest that initiating anti-tumor necrosis factor (anti-TNF) therapy after CD surgery may prevent recurrence in high-risk patients.

G&H Which medications can help to prevent postoperative recurrence?

MR The medicines that have been considered for preventing postoperative recurrence include 5-aminosalicylic acid (5-ASA); antibiotics, typically ornidazole in Europe

or metronidazole in the United States; immunomodulators, including 6-mercaptopurine (6-MP) and azathioprine; and anti-TNF agents. Based on currently available data, 5-ASA is safe but probably has limited benefit for long-term prevention of endoscopic and clinical recurrence; however, this drug is still commonly used after surgery, especially in Europe. Antibiotics may be very good at preventing recurrence, but they also have limitations; high doses of antibiotics cannot be easily continued long term, and recurrence is common once they are stopped. Immunomodulators, specifically 6-MP and azathioprine, are probably the most commonly used agents for prevention of recurrence after surgery, although data on their benefit are somewhat mixed. Finally, emerging data suggest that anti-TNF agents, specifically infliximab (Remicade, Centocor), may be useful for preventing postoperative recurrence, at least in certain high-risk patients—those with penetrating disease, multiple surgeries, and smokers.

G&H How should CD patients be managed if their risk of postoperative recurrence is low or moderate?

MR Categorizing patients' risk of recurrence as low, moderate, or high is somewhat arbitrary, but I think most clinicians would agree that patients have a low risk of recurrence if they have had CD for a long time (at least 10 years), have not had previous surgeries, and have a short stricture without active inflammation. In such cases, I would not start any treatment following surgery; instead, I would perform a colonoscopy within 1 year to see if the patient has developed a recurrence and then initiate treatment if needed.

I would classify patients as having a moderate risk of recurrence if they have some risk factors—such as shorter disease duration (less than 10 years), active inflammation, and intestinal narrowing—but lack additional risk factors, such as penetrating or fistulizing disease or a history of multiple surgeries. I would recommend that these patients receive 6-MP or azathioprine to prevent recurrence, and

I would perform a repeat colonoscopy 6–12 months after surgery. If a recurrence is detected on colonoscopy, then I would add an anti-TNF agent to their treatment regimen.

Probably the biggest recent change in the way I manage postoperative CD has been the way I approach patients who are at a high risk for recurrence. For these patients, I initiate postoperative anti-TNF treatment after surgery and perform a colonoscopy within 1 year.

G&H How do different medications compare in terms of their efficacy for preventing postoperative recurrence?

MR A couple of studies have evaluated 5-ASA—comparing it to azathioprine, 6-MP, and placebo—and have found that 6-MP and azathioprine seem to be more effective than 5-ASA for preventing CD after surgery. Another study compared treatment with azathioprine and metronidazole to treatment with azathioprine alone after surgery, and the 1-year data suggest that the metronidazole combination group achieved better outcomes. There are currently no head-to-head studies comparing immunomodulators and anti-TNF agents, nor are there any studies comparing different anti-TNF agents, although I think both will be areas of future interest.

G&H Why do clinicians need to address postoperative recurrences promptly?

MR Addressing recurrences promptly is especially important in high-risk patients, as these individuals often develop complications if their disease is left unchecked. These complications can include strictures with bowel obstruction, fistulas, perforations, or other penetrating complications—all of which can ultimately lead to additional hospitalization and surgery. After the first surgery, the clinician's main goal is to prevent CD recurrence and the need for further surgery; thus, recurrences must be adequately addressed as soon as possible. As has been previously discussed, probably the best strategy is to start treatment after surgery in order to prevent recurrence. If preventative treatment is not appropriate, then clinicians must monitor for recurrence after surgery and promptly treat recurrence when it is identified.

G&H How frequently should colonoscopy be performed following surgery?

MR Typically, I perform a colonoscopy 6–12 months after surgery to check for CD recurrence, and some physicians are starting to perform colonoscopy as early as 3 months following surgery. I recommend a 3-month colonoscopy for moderate- to high-risk patients who

decline preventative treatment; if there is recurrence of disease at 3 months, then these patients should be started on treatment. In most cases, however, I start patients on treatment after surgery and then perform a colonoscopy at 6–12 months. Depending on what I see, I can then alter treatment accordingly; if a patient has a recurrence while on medication, I may adjust the dose and/or add a second agent.

G&H What other tools can clinicians use to detect postoperative recurrences?

MR This is an area of intense research and interest. Right now, Crohn's Disease Activity Index (CDAI) scores do not appear to be a good modality for predicting or monitoring recurrence. In a recent article published in *Inflammatory Bowel Diseases*, my colleagues and I analyzed postoperative CDAI scores and did not find a correlation with recurrence. This finding supports an earlier study by Rutgeerts and colleagues in which no correlation was found between clinical symptoms and postoperative recurrence.

The use of inflammatory markers to detect recurrence is appealing, but C-reactive protein and sedimentation rate testing are probably of limited value, as these tests may detect only a small percentage of recurrences. Fecal calprotectin and lactoferrin testing may also be used to detect early recurrence after surgery, but this possibility needs to be further researched in the postoperative setting. Similarly, small bowel ultrasound is an exciting possibility, but it needs to be further developed; this technology is currently being studied in several centers but is not yet ready for prime time. In the future, clinicians may be able to perform noninvasive ultrasound and reliably detect recurrences; for now, however, the gold standard is to perform a colonoscopy and visually examine the mucosa at and above the site where the surgery was performed.

G&H How does a postsurgical recurrence differ from the initial disease presentation?

MR Within the first 1–2 years after surgery, recurrence often presents as ulcers and inflammation just above the anastomosis in the ileum (assuming the patient's surgery involved resecting the terminal ileum with an ileocolonic anastomosis). Otherwise, the recurrence is often similar to the patient's initial presentation. Patients who had strictures in the past will often develop another stricture, especially if they are not treated after surgery. If they had a fistula or perforation in the past, that complication will often present again if the patient is left untreated. However, a difference between the initial presentation and the recurrence is that the recurrence often affects a

shorter area of the intestine. Another important difference is that the recurrence is clinically silent in most cases, meaning that most patients do not experience symptoms of inflammation until their disease has progressed to the point where complications necessitate another surgery. Thus, we should not wait for patients to feel sick; we need to perform colonoscopies to look for recurrence even if patients are asymptomatic.

G&H What further research is needed regarding prevention and treatment of postoperative CD?

MR First, we need studies comparing different preventative strategies. One study that would be of high interest would be a comparison between an immunomodulator, such as 6-MP or azathioprine, and an anti-TNF agent, such as infliximab, adalimumab (Humira, Abbott), or certolizumab pegol (Cimzia, UCB). A second interesting study would be a comparison among anti-TNF agents to determine whether all the agents in this class have equal efficacy for preventing postoperative recurrence. Finally, we need data to guide the decision about when to start

therapy. Is it better to start treatment immediately after surgery to prevent recurrence, or should we wait for an endoscopic recurrence before initiating therapy?

Suggested Reading

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