

Predicting, treating and preventing postoperative recurrence of Crohn's disease: The state of the field

Anna M Borowiec MD¹, Richard N Fedorak MD FRCPC²

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The majority of patients diagnosed with Crohn's disease eventually require surgical intervention. Unfortunately, postsurgical remission tends to be short lived; a significant number of patients experience clinical relapse and many require additional operations. The pathogenesis of this postoperative recurrence is poorly understood and, currently, there are no reliable tools to predict when and in whom the disease will recur. Furthermore, the postoperative prophylaxis profiles of available Crohn's disease therapeutic agents such as 5-aminosalicylates, immunomodulators, steroids and probiotics have been disappointing. Recently, the combination of antibiotics and azathioprine in selected high-risk patients has demonstrated some potential for benefit. The goal of the present article is to provide a coherent summary of previous and new research to guide clinicians in managing the challenging and complex problem of postoperative Crohn's disease recurrence.

Key Words: Azathioprine; Corticosteroids; Crohn's disease; Ileocolonic resection; Infliximab; Mesalamine; Postoperative recurrence; Probiotics

Crohn's disease (CD) is a chronic inflammatory gastrointestinal (GI) disorder that can affect any portion of the GI tract. At diagnosis, 47% of patients have localized disease in the terminal ileum, and 21% experience involvement of the ileocolon (1). CD is most prevalent in North America and Europe, with an estimated occurrence of 0.2% in the United States and central Canada; peak incidence occurs in the second decade of life (2,3). The etiology of CD remains unclear; however, a combination of genetic predisposition, several bacterial agents and environmental factors are most likely responsible for disease onset and progression.

There is no cure for CD – the goal of medical and surgical therapies is symptom relief. Medical management is the first line of therapy, while surgery is reserved for patients who experience refractory symptoms despite optimized medical management, and for the treatment of complications. The most common indications for surgery are failure of medical management and obstruction (4). It has been estimated that 75% of CD patients eventually require surgery within 20 years of symptom onset (5). The goal of the present review is to discuss the available surgical management options, postoperative recurrence rates and patterns, tools for predicting recurrence and, finally, postoperative preventive and therapeutic choices.

SURGICAL MANAGEMENT OF CD

The goals of surgical therapy for CD are to alleviate symptoms while limiting or preventing bowel resection, and to minimize the risk of complications such as short bowel syndrome.

The most commonly performed operations are stricturoplasties and bowel resections. A stricturoplasty conserves bowel length by widening a narrowed lumen without bowel resection. A common indication for stricturoplasty is a short segment stricture within the jejunum and ileum (6).

Prédire, traiter et prévenir la récurrence postopératoire de maladie de Crohn : l'état de la situation

La majorité des patients ayant un diagnostic de maladie de Crohn finissent par devoir se faire opérer. Malheureusement, la rémission postchirurgicale tend à être de courte durée. En effet, de nombreux patients font une rechute clinique et bon nombre doivent subir de nouvelles opérations. La pathogenèse de cette récurrence postopératoire est mal comprise et, à l'heure actuelle, il n'existe aucun outil fiable pour prédire quand la maladie récidivera et qui cette récurrence touchera. De plus, les profils prophylactiques postopératoires des agents thérapeutiques offerts contre la maladie de Crohn, tels que les 5-aminosalicylates, les immunomodulateurs, les stéroïdes et les probiotiques, sont décevants. Récemment, l'association d'antibiotiques et d'azathioprine chez des patients à haut risque sélectionnés a démontré un certain potentiel de bienfaits. Le présent article vise à fournir un sommaire cohérent des recherches passées et nouvelles, afin d'orienter les cliniciens dans la prise en charge du problème difficile et complexe de la récurrence de maladie de Crohn.

Of patients referred for surgery, 40% to 50% have disease of the terminal ileum, which requires resection due to perforation, fistulas or a long strictured segment (4). The estimated probability of ileocolonic resection after an average of 13 years of disease activity in the terminal ileum is 91.5% (7).

Postoperative recurrence of CD

Surgical management of CD offers immediate resolution of acute symptoms; however, surgical success tends to be short lived. Despite advances in the medical treatment of CD, the overall reported postoperative recurrence rates remain high, with clinical relapses of 17% to 55% at five years, 32% to 76% at 10 years, and 70% at 20 years (8). Furthermore, a considerable number of patients with recurrent CD will require subsequent operations, which are more complex procedures and are associated with an increased risk of morbidity (9). The estimated overall incidence of reoperation is 11% to 32% at five years, 20% to 44% at 10 years, and 46% to 55% at 20 years (8).

Both the site of the initial operation and the surgical procedure performed influence the pattern and rate of recurrence. A large meta-analysis of 1112 patients who underwent 3259 stricturoplasties (94% of cases) involving the jejunum and/or ileum (6) revealed recurrence rates requiring reoperation in 14% of patients at five years. By comparison, patients with surgically treated ileocolonic disease tended to experience a higher frequency of reoperation at the same time interval (53%) (10). Interestingly, the site of recurrence among 90% of these stricturoplasty patients was remote from the original site of operation (6). In contrast, a retrospective study of 78 CD patients who underwent reoperation (11) found recurrence at the previous anastomosis in 70% of bowel resection cases. In addition, the disease recurred at the anastomosis site for 83% of patients who had previously undergone ileocecal resection, and the inflammation extended into the proximal limb of the neoterminal ileum.

¹Department of Surgery, Division of General Surgery; ²Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton, Alberta
Correspondence: Dr Anna M Borowiec, Department of Surgery, Division of General Surgery, University of Alberta, Ziedler Ledcor Building, Edmonton, Alberta T6G 2X8. Telephone 780-492-6941, fax 780-492-8121, e-mail amb1@ualberta.ca

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For ileocecal resection, the pathogenesis leading to clinical symptoms appears to occur in the immediate postoperative period. Up to 72% of patients show endoscopic evidence of disease such as aphthous ulcers in the neoterminal ileum in the first postoperative year; however, only 20% experience symptoms (12). Clinical follow-up and endoscopy at three and 10 years show progressively more severe bowel wall disease activity, and a progressive increase in CD symptoms (12). These early postoperative changes present an opportunity for early intervention.

Risk factors for postoperative recurrence of CD

Patient factors: Patient factors such as age at disease onset, sex and use of oral contraceptives have been investigated; however, none of these factors are currently considered to be predictors of disease recurrence (13-16). Strikingly, a large volume of evidence indicates that tobacco smoking is an independent risk factor for endoscopic, clinical and surgical recurrence (14,16-21). The data on smoking were summarized in a recent, large meta-analysis of 2962 patients (22) in which CD patients who were smokers were shown to have 2.5-fold increased risk of surgical recurrence and a twofold increased risk of clinical recurrence compared with nonsmokers. This high risk of postoperative relapse and reoperation is significantly reduced if a patient quits smoking (22).

Disease factors: Disease-associated factors that have been implicated in early postoperative recurrence include the duration of disease before initial surgical therapy and the presence of perforating disease activity. Based on mixed results from studies conducted both in adults and children (13,23-27), the relationship between the duration of disease and its recurrence remains inconclusive.

CD follows one of the three following behaviour patterns: non-stricturing and nonperforating; stricturing; or perforating (least common) (1). Perforating CD is characterized by the development of acute-free perforations, abscesses or fistulas, and appears to represent a more complex and aggressive form of the disease that results in earlier postoperative recurrence. This is supported by a review of 770 patients (28) showing that individuals with perforating disease were more likely to require reoperation for recurrent perforation, and required reoperation two times earlier than did patients with nonperforating disease. However, the early recurrence of perforating disease has not been supported by several studies (23,29,30) including a meta-analysis of 3044 patients (31). Although the results of the meta-analysis showed significantly increased risk of reoperation for patients with perforating disease, these results must be interpreted with caution due to the significant differences in these studies' designs. However, one thing is certain: the type of disease requiring surgical intervention predicts the type of recurrent disease – perforating disease leads to perforating recurrence, while nonperforating disease recurs as a nonperforating disease (31).

Surgical factors: The risk factors associated with surgical technique have been explored in depth, thereby enabling advances in surgical procedures and techniques that optimize postoperative outcomes. Factors such as the length of bowel resected, resection of microscopically positive margins, number of resections, presence of granulomas in the resected specimen and postoperative complications have not been consistently shown to be predictive of disease recurrence (15,23,32-36).

Most surgeons use a minimalist philosophy in the surgical treatment of CD by removing grossly diseased bowel and leaving behind margins that may harbour microscopic disease. The adequacy of this approach was confirmed in a prospective trial (37) in which no difference in recurrence was noted between patients randomly assigned to undergo 2 cm versus 12 cm resection margins. This approach minimizes bowel loss to prevent short gut syndrome.

Disease recurrence at the anastomosis is a well-recognized fact, which has prompted close examination of surgical anastomosis techniques (11). Retrospective studies (14,38-41) have provided conflicting evidence on the best anastomotic technique (staples versus hand sewn) and configuration (end-to-end versus side-to-side). However, a recent prospective trial (42) comparing stapled side-to-side anastomosis

with hand-sewn end-to-end anastomosis showed no difference between the two groups with respect to endoscopic and clinical recurrence at 12 months, thus making either choice appropriate.

An advance in the surgical management of CD in the past couple of decades has been the introduction and widespread use of laparoscopic bowel resections. This approach is best suited to patients undergoing elective operations, and should be used with caution or avoided completely in the setting of diffuse peritonitis, complex fistulae, dense adhesions or emergency. Laparoscopy offers multiple benefits including lower postoperative morbidity, faster GI functional recovery, reduction in blood transfusions, reduction in postoperative narcotic use, and shorter length of hospital stay, in addition to a more desirable cosmesis without increase in recurrence rates as demonstrated in short-term and long-term follow-up studies (43-47).

Predicting postoperative recurrence of CD

Currently, there are no clear guidelines for postoperative prophylaxis or follow-up. The lack of standard postoperative care guidelines stems from an incomplete understanding of the pathogenesis of postoperative CD recurrence, the limited number of efficacious prophylactic interventions available and an inability to reliably risk-stratify patients. Identification and risk stratification of patients are key steps in postoperative care for individuals who need treatment, and to avoid lifelong treatment and its potential adverse events in those who do not. A countless number of attempts at solving this dilemma were – and continue to be – made in the areas of radiology, genetics and immunology. Examples include imaging modalities such as ultrasound, virtual colonoscopy, capsule endoscopy and magnetic resonance, as well as the testing of fecal contents for alpha 1-antitrypsin and calprotectin, local and systemic production of proinflammatory cytokines such as tumour necrosis factor, interleukin-6 and interleukin-1 beta, the production of specific antimicrobial antibodies and genetic variability in the *NOD2/CARD15* gene (48-63). Although these studies contributed invaluable knowledge to the understanding of CD, their clinical applicability is presently limited.

MANAGEMENT OF POSTOPERATIVE CD

5-aminosalicylates (Table 1)

5-aminosalicylate (ASA) and its derivatives, mesalamine and sulfasalazine, are anti-inflammatory agents that decrease local bowel inflammation and can be formulated to target specific GI sites. The available evidence suggests that sulfasalazine has limited effectiveness in preventing postoperative recurrence. Two small randomized controlled trials using sulfasalazine at 5 g/day and 3 g/day versus placebo (64,65) showed no difference in terms of clinical recurrence at one year. A multicentre trial of 232 patients receiving daily sulfasalazine (3 g/day) or placebo (66) showed a reduction in the endoscopic, clinical and radiological recurrence rates in the treatment group at one year; however, no difference was observed at the three-year follow-up.

Eight randomized controlled trials using mesalamine (67-74) have been conducted, seven of which compared mesalamine with placebo and one that compared it with 6-mercaptopurine (6-MP). The first two moderately sized, controlled studies of 110 and 163 patients, using 2.4 g/day and 3 g/day of mesalamine, respectively (67,68), reported positive effects. The patients using 2.4 g/day had lower rates of endoscopic and symptomatic recurrence at two years, while patients taking 3 g/day had lower symptomatic recurrence rates over the course of the six-year follow-up period. Two subsequent studies (69,70), however, did not show any statistical significance in favour of mesalamine, and a third study of 87 patients on 3 g/day of mesalamine (71) reported less severe lesions on endoscopy at 12 months. Three randomized, controlled trials that followed also failed to demonstrate strong benefits for mesalamine. One of these trials (72), the largest multicentre controlled trial to date, enrolled 318 patients who received 4 g/day of mesalamine, did not demonstrate a difference in the recurrence rates between the treatment and the placebo groups at 18 months. However, subgroup analysis showed lower relapse rates among the mesalamine

TABLE 1
Summary of evidence supporting the use of 5-aminosalicylates for the prevention of postoperative recurrence of Crohn's disease

Author (reference), year	Study type	n	Treatment	Primary outcome*	P
Wenckert et al (65), 1978	RCT	66	Sulfasalazine 3 g/day versus placebo	Clinical at 1 year	NS
Summers et al (64), 1979	RCT	28	Sulfasalazine 5 g/day versus placebo	Clinical at 1 year	NS
Ewe et al (66), 1989	RCT	232	Sulfasalazine 3 g/day versus placebo	Endoscopic at 1 year; radiological at 1 year; clinical at 1 year	<0.01
Caprilli et al (67), 1994	RCT	110	Mesalamine 2.4 g/day versus placebo	Endoscopic at 2 years; clinical at 2 years	<0.05
McLeod et al (68), 1995	RCT	163	Mesalamine 3 g/day versus placebo	Clinical at 6 years	0.03
Brignola et al (69), 1995	RCT	87	Mesalamine 3 g/day versus placebo	Endoscopic at 1 year; clinical at 1 year	NS
Florent et al (70), 1996	RCT	126	Mesalamine 3 g/day versus placebo	Endoscopic at 3 months	NS
Sutherland et al (71), 1997	RCT	66	Mesalamine 3 g/day versus placebo	Clinical at 1 year	NS
Lochs et al (72), 2000	RCT	318	Mesalamine 4 g/day versus placebo	Clinical at 18 months	NS
Caprilli et al (73), 2003	RCT	165	Mesalazine 4 g/day versus 2.4 g/day	Endoscopic at 1 year	NS
Hanauer et al (74), 2004	RCT	131	Mesalamine 3 g/day versus 6-MP 50 mg/day	Endoscopic at 2 years; radiological at 2 years; clinical at 2 years	NS

*Primary outcome = recurrence rates (endoscopic, radiological, clinical or surgical). 6-MP 6-mercaptopurine; AZA Azathioprine; NS Not statistically significant ($P>0.05$); RCT Randomized controlled trial

TABLE 2
Summary of evidence supporting the use of immunomodulators in the prevention of postoperative recurrence of Crohn's disease

Author (reference), year	Study type	n	Treatment	Primary outcome*	P
Cuillerier et al (76), 2001	Retrospective case series	38	AZA mean dose 2 mg/kg/day	Clinical at 1, 2 and 3 years Endoscopic at 1, 2 and 3 years	NA
Domenech et al (77), 2004	Retrospective case series	33	AZA vs mesalazine(variable doses)	Clinical and endoscopic during 4 years	<0.05
Hanauer et al (74), 2004	RCT	131	6-MP 50 mg/day vs mesalamine 3 g/day	Endoscopic at 2 years	<0.05
Ardizzone et al (81), 2004	Open-label prospective	142	AZA 2 mg/kg/day vs mesalamine 3 g/day	Clinical at 2 years	NS
D'Haens et al (79), 2008	RCT	81	Abx with AZA 100–150 mg/day vs Abx with placebo	Endoscopic at 1 year	<0.05

*Primary outcome = recurrence rates (endoscopic, radiological, clinical or surgical). 6-MP 6-mercaptopurine; Abx Antibiotic (metronidazole 250 mg three times daily or ornidazole 500 mg twice daily); AZA Azathioprine; NA Not applicable because recurrence rate was reported, but no P value was calculated; NS Not statistically significant ($P>0.05$); RCT Randomized controlled trial; vs Versus

patients whose disease was isolated to the small bowel. A more recent meta-analysis from the Cochrane Collaboration examining mesalamine versus placebo (75) reported a reduction in the RR of clinical recurrence, but no effect on overall endoscopic recurrence. This particular meta-analysis confirmed good compliance with mesalamine and a low risk of adverse events.

Immunosuppressants (Table 2)

The immunosuppressors 6-MP and azathioprine (AZA) are purine analogues that interfere with DNA, RNA and protein synthesis, causing global downregulation of the immune system. In combination with an antibiotic, the use of these agents currently comprise the best evidence supporting their prophylactic use in the prevention of CD relapse following surgery.

A few small retrospective studies (76-78) reported that immunosuppressors may be of benefit in lowering postoperative clinical and endoscopic recurrence rates. However, only two randomized controlled trials have been conducted to date (74,79), one comparing 6-MP (50 mg/day) with mesalamine (3 g/day) and placebo, and the second examining a combination of antibiotic (metronidazole 250 mg three times daily or ornidazole 500 mg twice daily) for the first 12 weeks along with AZA (100 mg/day to 150 mg/day) or placebo for one year. The first study (74) found 6-MP to be more effective in reducing postoperative endoscopic and clinical recurrence than were mesalamine or placebo

at two years; however, these results must be interpreted with caution. The study was criticized for overestimating clinical relapse in the placebo group, having a high dropout rate, a lack of primary outcome measure definition, a flawed statistical analysis and a dose of 6-MP that was possibly too low (80).

In the second study examining the combination of an antibiotic and AZA (79), 81 high-risk patients (with more than one of the following risk factors: younger than 30 years of age; active smoker; corticosteroid used in the three-month preoperative period; second, third or fourth resection; and perforating disease) who had undergone ileal or ileocolonic resection were treated with daily metronidazole or ornidazole for three months plus AZA or placebo then, after three months, continued on AZA or placebo for 40 weeks. The primary outcomes were defined as endoscopic recurrence with a Rutgeerts' score of greater than 2 at three and 12 months (79). There was no difference in endoscopic recurrence between the two groups at three months; however, patients treated with AZA experienced a significantly lower rate of endoscopic recurrence at 12 months (55%) than did the patients who received placebo (78%).

An open-label prospective trial comparing AZA (2 mg/kg/day) with mesalamine (3 g/day) (81) did not reveal a difference with respect to clinical and surgical recurrence rates at two years following conservative surgery for CD. However, subgroup analysis did show that, among the patients who underwent a previous bowel resection, those treated with AZA had lower relapse rates. Similarly, the potential benefit

TABLE 3
Summary of evidence for the use of steroids for the prevention of postoperative recurrence of Crohn's disease

Author (reference), year	Study type	n	Treatment	Primary outcome*	P
Bergman et al (85), 1976	RCT	97	Sulfasalazine with prednisolone versus placebo	Clinical at 1, 2 and 3 years	NS
Hellers et al (86), 1999	RCT	129	Budesonide 6 mg/day versus placebo	Endoscopic at 3 months, 1 year	NS
Ewe et al (87), 1999	RCT	83	Budesonide 3 mg/day versus placebo	Endoscopic at 3 months, 1 year	NS

*Primary outcome = recurrence rates (endoscopic, radiological, clinical or surgical). NS Not statistically significant ($P>0.05$); RCT Randomized controlled trial

TABLE 4
Summary of evidence for the use of antibiotics and probiotics for prevention of postoperative recurrence of Crohn's disease

Author (reference), year	Study type	n	Treatment	Primary outcome*	P
Rutgeerts et al (89), 1995	RCT	60	Metronidazole 20 mg/kg versus placebo	Endoscopic at 3 months	NS
Rutgeerts et al (90), 2005	RCT	80	Ornidazole 1 g/day versus placebo	Endoscopic at 1 year, clinical at 1 year	<0.05
Prantera et al (92), 2002	RCT	45	<i>Lactobacillus GG</i>	Endoscopic at 1 year	NS
Marteau et al (93), 2006	RCT	98	<i>Lactobacillus johnsonii</i> LA1	Endoscopic at 6 months	NS
Van Gossum et al (94), 2007	RCT	70	<i>Lactobacillus johnsonii</i> LA1	Endoscopic at 3 months	NS
Chermesh et al (95), 2007	RCT	30	Synbiotic 2000 versus placebo	Endoscopic at 3 months	NS
Madsen et al (96), 2008	RCT	120	VSL#3 [†] vs placebo	Endoscopic at 3 months, endoscopic at 1 year	NS <0.05

*Primary outcome = recurrence rates (endoscopic, radiological, clinical or surgical); [†]VSL Pharmaceuticals Inc, USA. NS Not statistically significant ($P>0.05$); RCT Randomized controlled trial

of AZA and 6-MP in patients who had undergone multiple bowel surgeries was shown in a small retrospective study in which patients treated with these immunosuppressants were found to be less likely to undergo a third intestinal resection (82). In a more recent open-label prospective study (83), 56 patients who underwent curative intestinal resection were treated with daily AZA (2 mg/kg/day to 2.5 mg/kg/day) starting immediately after surgery. The cumulative probabilities of endoscopic postoperative relapse based on this study were 44%, 53%, 69% and 82% at one, two, three and five years, respectively. The authors interpreted these results to indicate that early initiation of postoperative AZA treatment delayed endoscopic recurrence. The importance of this 'delay' depends on what one considers to be the natural postoperative recurrence rate. For example, the classical study conducted by Renna et al (84) in 1984 showed evidence of endoscopic recurrence in 70% of patients at one year; however, a recent meta-analysis of postoperative placebo treatment reported a pooled estimate of 50.2% for the one-year severe endoscopic recurrence rate, with significant heterogeneity being exhibited among the studies used (12,83). In addition, 36% of patients in this 56-patient study experienced adverse effects from the AZA – the most common being lymphopenia (84).

The evidence supporting the use of immunosuppressants in the postoperative setting is summarized in a recent Cochrane Collaboration meta-analysis by Doherty et al (75). The authors concluded that AZA/6-MP therapy was associated with a significantly reduced risk of clinical and severe endoscopic recurrence compared with placebo. However, one must be reminded of the potential adverse effects associated with the use of these agents.

Steroids (Table 3)

Steroids play a very limited role in the maintenance of medically induced CD remission, and have no documented role in preventing the postoperative recurrence of CD (85-88).

Antibiotics and probiotics (Table 4)

The commensal GI bacteria have been implicated in the pathogenesis of CD, and agents targeting bacterial flora, in theory, should have an effect on the disease itself. Two randomized controlled trials examining antibiotic treatment in the postoperative context have been conducted (89,90). In the first study (89), 60 patients were randomly assigned to metronidazole (20 mg/kg) or placebo for three months immediately after ileocolonic resection surgery. Patients receiving the antibiotic were found to have significantly less severe endoscopic disease

at 12 weeks postoperatively and lower recurrence rates at one year, but no improvement in relapse rates at two and three years – findings suggesting that antibiotics delay postoperative recurrence.

Ornidazole (1 g/day) was also shown to be more effective than placebo in a randomized controlled trial of 80 patients (90) in which the treatment group experienced significantly lower postoperative endoscopic and clinical recurrences at 12 months after ileocolonic resection. Despite these positive findings, there was a high dropout rate for both studies due to adverse treatment side effects including metallic taste and GI upset. The recent study (79) that combined three months of lower dose metronidazole (250 mg three times daily) with continuous AZA demonstrated a reduction in endoscopic recurrence, and may have solved the issue of high-dose antibiotic use.

Probiotics are nonpathogenic gut bacteria that can improve intestinal microbial balance. Studies of probiotics in recent years have revealed a variety of mechanisms through which these microbes benefit the host including modulation of epithelial cell-barrier function and epithelial cytokine secretion, as well as exertion of antibacterial effects through the secretion of antimicrobial peptides and competition with other microbes for colonization (91). To date, however, four of five randomized controlled trials (92-96) have not provided supporting evidence encouraging the use of probiotics in the prevention of postoperative recurrence. For example, endoscopic recurrence was not prevented at one year after bowel resection using a 12-month administration of *Lactobacillus GG*, or at three and six months in patients receiving *Lactobacillus johnsonii* LA1 (92-94). Similarly, treatment with a combination of prebiotics and probiotics (Synbiotic 2000 [a mixture of prebiotics and probiotics, including four lactic acid bacteria and four fermentable fibres. The four lactic acid bacteria are as follows: 1010 *Pediococcus pentosaceus*, 1010 *Lactococcus raffinolactis*, 1010 *Lactococcus paracasei* subsp *paracasei* 19 and 1010 *Lactococcus plantarum* 2362. The four fermentable fibres are 2.5 g beta-glucans, 2.5 g inulin, 2.5 g pectin and 2.5 g resistant starch]) did not result in improved endoscopic injury scores at three and 24 months after surgery (95). In contrast, one study that used a combination of probiotics (VSL#3, VSL Pharmaceuticals Inc, USA) (96) showed a trend toward decreased severity of endoscopic CD recurrence at one year among patients receiving the probiotic, which was not statistically significant. Furthermore, in the same study, VSL#3 had a marked downregulating effect on mucosal proinflammatory cytokine expression. Presently, there is no evidence to support the routine use of probiotics in the postoperative setting.

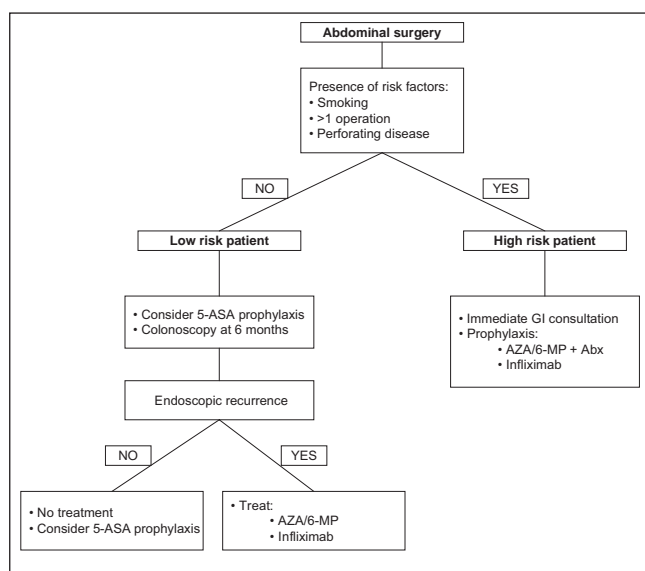


Figure 1 Recommended approach to patients undergoing surgery for Crohn's disease. 6-MP 6-Mercaptopurine; Abx Antibiotic; 5-ASA 5-Aminosalicylate; AZA Azathioprine; GI Gastroenterological

Biologicals

Although promising, the evidence supporting the use of infliximab in the postoperative setting is still based on limited experience consisting of one case report, a small nonrandomized prospective study and two small randomized controlled trials (97-100). In the case report (97), a 23-year-old woman remained free of endoscopic and clinical recurrence at four years postsigmoid resection while on a combination treatment of intravenous infliximab (5 mg/kg) every eight weeks and a low weekly dose of oral methotrexate (10 mg/week). Following the same regimen after various surgical interventions (ileal, ileocolonic and sigmoid resections), seven patients experienced no endoscopic or clinical recurrence at two years after surgery compared with a control group of 16 patients receiving daily mesalamine (2.4 g/day) that experienced a 75% recurrence rate at the time of follow-up (98). To date, the best evidence supporting the postoperative use of infliximab comes from a study of 24 patients randomly assigned to 5 mg/kg intravenous injections of infliximab or placebo for one year (99). The patients receiving infliximab had significantly lower endoscopic and histological recurrence rates at one year postileocolonic resection; however, clinical recurrence, although lower in the treatment group, did not reach statistical significance. Infliximab was also proven to be more effective than mesalamine and AZA in salvage therapy once endoscopic recurrence was confirmed at six months after surgery (100). In a small study of 26 patients (100), eight patients with endoscopic recurrence randomly assigned to infliximab did not progress to clinical recurrence over the next six months, and showed improvement in mucosal inflammation over the same period. By comparison, 38% and 70% of patients developed clinical recurrence when treated with AZA and mesalamine, respectively.

Other strategies

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that ameliorates inflammation in an IL-10-deficient murine model of CD. In addition, low levels of ileal IL-10 messenger RNA in humans at the time of surgery has been shown to predict early recurrence (101). The subcutaneous administration of recombinant human IL-10 (Tenovil, Schering-Plough, USA) in a randomized controlled trial of 58 patients after ileocolonic resection (102) did not prevent endoscopic recurrence at 12 weeks.

SUMMARY AND CLINICAL APPLICATION

Despite ongoing efforts, there remains a lack of firm, evidence-based guidelines for the surveillance and management of CD patients following surgery.

Based on the evidence reviewed in the present document, we recommend the approach presented in Figure 1 to patients undergoing surgery for CD. First, in considering the management of postoperative CD, it is important to distinguish true prophylaxis – ie, preventive therapy started immediately after surgery – from early treatment, defined as therapy started six to 12 months after surgery when active disease is demonstrated on endoscopy. Second, patients must be stratified into groups with a low risk or high risk of recurrence as defined below:

Low-risk group

The low-risk group is comprised of patients with no risk factors for recurrence (eg, nonsmokers, first abdominal operation or stricturing disease). This group most likely does not require prophylaxis but, rather, treatment when there is evidence of recurrence. This group should be followed clinically at six months and at one year postsurgery with colonoscopy between six and 12 months, and treated accordingly depending on the clinical and colonoscopic findings.

High-risk group

The high-risk group includes patients who are smokers, have undergone multiple abdominal surgeries and experienced more complex disease (eg, perforating or fistulizing). These patients should be managed more aggressively. All patients should be encouraged to stop smoking and started on a prophylactic regimen (immediately after surgery) using immunomodulators (eg, AZA, 2.5 mg/kg/day or 6-MP 1.5 mg/kg/day) in combination with a short course (three months) of metronidazole (250 mg three times/day).

CD patients requiring surgical intervention represent a subset of complex patients, and one cannot sufficiently stress the importance of the multidisciplinary approach to these patients. For these proposed management strategies to be implemented and effective, there is a need for an ongoing dialogue between the surgical and gastroenterology teams such that the candidates for prophylaxis are, ideally, identified preoperatively, and that all patients receive appropriate postoperative follow-up and care.

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