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Risk of postoperative recurrence and postoperative management of Crohn's disease

Antonino Spinelli, Matteo Sacchi, Gionata Fiorino, Silvio Danese, Marco Montorsi

Antonino Spinelli, Matteo Sacchi, Marco Montorsi, Department and Chair of General Surgery, University of Milan, Istituto Clinico Humanitas IRCCS, Via Manzoni 5620089, Rozzano, Milan, Italy
Gionata Fiorino, Silvio Danese, IBD Unit, Department of Gastroenterology, Istituto Clinico Humanitas IRCCS, Via Manzoni 5620089, Rozzano, Milan, Italy

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Correspondence to: Antonino Spinelli, MD, PhD, Department and Chair of General Surgery, University of Milan, Istituto Clinico Humanitas-IRCCS, Via Manzoni 5620089, Rozzano, Milan, Italy. antonino.spinelli@humanitas.it

Telephone: +39-2-82244772 Fax: +39-2-82244590

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Abstract

Crohn's disease (CD) is a chronic inflammatory disease of the digestive tract with systemic manifestations. Etiology is unknown, even if immunological, genetic and environmental factors are involved. The majority of CD patients require surgery during their lifetime due to progressive bowel damage, but, even when all macroscopic lesions have been removed by surgery, the disease recurs in most cases. Postoperative management represents therefore a crucial mean for preventing recurrence. Several drugs and approaches have been proposed to achieve this aim. Endoscopic inspection of the ileocolic anastomosis within 1 year from surgery is widely encouraged, given that endoscopic recurrence is one of the greatest predictors for clinical recurrence. A strategy should be planned only after stratifying patients according to their individual risk of recurrence, avoiding unnecessary therapies when possible benefits are reduced, and selecting high-risk patients for more aggressive intervention.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the digestive tract with associated several systemic manifestations. Etiology of CD seems to be multifactorial, which results from an interaction of genetic susceptibility, immunological dysregulation of the mucosal immune system, gut microflora and environmental factors, but the final cause remains still unknown. Pathologically, CD is characterized by non-caseating granulomas and transmural inflammation, which can affect all the digestive tract from the mouth to the anus^[1]. The most commonly affected sites are the ileum and ascending colon and the disease recurs in most cases after surgical resection of macroscopically affected segments^[1]. For this reason, almost all studies on postoperative recurrence are primarily focused on ileocolic disease. CD patients have a high likelihood of undergoing repeated surgery for disease recurrence during their lifetime, with risk for short bowel syndrome: surgery in these patients is as conservative as possible in order to reduce this risk. Two distinct approaches are possible in clinical practice for postoperative CD management: starting prophylactic medical therapy after surgery, which aims to avoid or postpone recurrence;

or waiting for endoscopic recurrence, and eventually starting or adapting medical therapy before the patient becomes symptomatic. Both these strategies are rational and can be indicated in specific situations. Recurrence risk assessment after surgery is critical for correct decision making about medical prophylaxis and surveillance, and has to consider many different variables. Regueiro *et al*^[2] have considered three grades of recurrence risk: (1) very low, defined as long-standing, first surgery, short stricture; (2) low-moderate, i.e. < 10-year-long history of CD, presence of a long stricture or any case of inflammatory CD; and (3) high risk, defined as presence of penetrating disease or patients with repeated intestinal resection (more than twice). Those patients may require a more aggressive approach^[2]. This review provides an overview on this relevant and debated clinical topic.

NATURAL HISTORY

Schofield introduced the definition of "natural history" for ulcerative colitis first and later for regional enteritis^[3]. The natural history of CD is characterized by the progression of bowel injury, which leads to surgery in up to 80% of patients during their lifetime^[4]. Surgery in CD is not curative, even when all of the macroscopic disease has been removed. Disease recurrence typically presents at an anastomotic site, mostly in the preterminal ileum in patients with previous ileal involvement^[4]. Endoscopic surveillance programs for operated CD patients has led to identification of endoscopic lesions (endoscopic recurrence) that, in most cases, precede clinical symptoms (clinical recurrence). Clinical recurrence rates and reoperation rates increase over the years: about 80% of patients will experience clinical recurrence within 20 years from surgery, and about 50% will undergo repeated surgery during the same time in most series^[4,5].

Regarding location, CD tends to be stable, since only about 6.5% of the patients will experience a change of site in disease involvement over time^[4]. Henriksen has investigated the changes in disease location in the Inflammatory Bowel South-Eastern Norway (IBSEN) population-based study. Of 200 CD patients, only 14% changed affected site after 5 years^[6].

It has to be underlined that biological therapies are relatively new in the management of CD, and most of the studies on CD natural history refer to an era when the efficacy of medication was lower compared to the present. Anti-tumor necrosis factor (TNF)- α antibodies like infliximab and adalimumab show strong efficacy in inducing mucosal healing; they could possibly modify the natural history of the disease, but data on reduction of the need for repeated surgery in the long-term are still not available. Data from clinical trials in inflammatory bowel diseases (IBD) patients treated by anti TNF- α show that scheduled therapy significantly reduces the risk of hospitalization and surgery related to CD up to 55 mo on average^[7,8]. There is then a reasonable perspective that scheduled therapy by infliximab or adalimumab might prevent or delay postoperative recurrence in high-risk patients, with a significant change in the natural his-

tory of the disease, although further large prospective studies focused on this topic are needed.

Today, surgery remains part of the clinical history of CD patients^[9,10]. In recent years, laparoscopic surgery is gaining a place in the surgical treatment of CD, especially for ileocecal disease^[4].

The assessment of activity, severity and complications of CD that may require surgical procedures remains a big challenge for physicians. Different kinds of objective measures of those parameters are available, but none of them is comprehensive for all aspects of the disease. The Crohn's disease activity index (CDAI)^[11] and the Harvey-Bradshaw index^[12] are commonly used to assess the activity and severity of the disease, but they can be affected by other non-CD gastrointestinal or extraintestinal disorders that may affect the correct evaluation of the disease. These scores do not include the endoscopic features of the disease that can be measured using two other different scores: the Crohn's Disease Endoscopic Index of Severity^[13] and the Simplified Endoscopic Score-Crohn's Disease^[14]. Other methods to assess disease activity include the level of fecal markers, such as fecal calprotectin, fecal lactoferrin and polymorphonuclear neutrophil elastase, which are produced in the course of bowel inflammation, and that can be detected in fecal samples. They have been shown to be more sensitive, specific and accurate than C-reactive protein in differentiating active from inactive disease, and to distinguish between CD-related symptoms and irritable bowel syndrome^[15]. These non-invasive biomarkers can also be used in the postoperative follow-up in order to distinguish bowel symptoms related to mechanical causes (such as shortening of the small bowel, colonic resection, bile salt diarrhea) from a clinical recurrence of CD. None of these tools is comprehensive for all aspects of CD; therefore, a new global score that considers clinical, endoscopic, radiological parameters and surgical history to assess the disease activity, severity and organ damage is urgently needed.

CD RECURRENCE

Definition

Recurrence is defined as reappearance of lesions after complete surgical resection^[16]. Recurrence can be assessed by endoscopy, radiology or surgery. Clinical recurrence is defined as the appearance, after complete resection of macroscopic disease, of CD symptoms, which confirms recurrence of the lesions^[16]. This confirmation is important because postoperative recurrence-like symptoms may be due to causes other than CD, such as motility disturbances or bile malabsorption.

Endoscopic assessment

The severity of recurrence assessed by endoscopy is the best predictor of clinical outcome in postoperative CD^[17-21]. In order to correlate the endoscopic findings with the risk of clinical recurrence, Rutgeerts has validated an endoscopic scoring system to be assessed at the first ileocolonoscopy, 6-12 mo after surgery: it divides patients into

Table 1 Endoscopic recurrence score as reported by Rutgeerts *et al.*^[17]

Endoscopic score	Definition
i0	No lesions
i1	≤ 5 aphthous lesions
i2	> 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already large ulcers, nodules, and/or narrowing

Remission: Endoscopic score i0 or i1; Recurrence: Endoscopic score of i2-i4.

five groups (i0-i4, see Table 1)^[17], according to the severity of endoscopic lesions; in the i0-i1 group, there is < 5% recurrence at 3 years; in i2, about 15%; in i3, 40%; and i4, > 90%^[17]. The most common endoscopic lesions are aphthous ulcerations that are located in the neoterminal ileum near to the anastomotic area^[17]. In the absence of treatment, such lesions can evolve into large ulcerations or tight strictures: Rutgeerts has reported that only 20% of these patients become clinically symptomatic within 1 year after surgery^[17]. Symptoms develop only after a lesion has been established, and it is not uncommon to find endoscopic severe lesions in an asymptomatic patient. Clinical scoring systems such as the CDAI may therefore be of little help in identifying patients with postoperative recurrence^[22].

Risk factors

Most patients experience disease recurrence over time, but long-term medical strategies for prevention of recurrence can carry various risks: risk-benefit analysis should be individualized to each patient. Identification of risk factors for CD recurrence is therefore extremely important in order to identify high-risk patients, who are more likely to benefit from an aggressive therapeutic strategy.

Several factors have been studied as possible contributors to CD recurrence, including age, sex, cigarette smoking, age at onset of disease, duration of disease, anatomical site, extent and severity of disease, previous surgery, and disease phenotype, disease-free margins, anastomotic technique, blood transfusion, and occurrence of complications.

Among these many factors, the following have been shown to predict early recurrence in the majority of studies: smoking^[23], prior intestinal surgery (including appendectomy)^[24], penetrating disease behavior^[25], perianal involvement, and extended small bowel resection (> 100 cm)^[26]. Absence of prophylactic therapy is associated with early relapse (defined as a flare of symptoms)^[27].

Reese *et al.*^[28] in a recent meta-analysis have reported that clinical relapse occurred in 58.3% of smoking patients, compared with 39% of non-smokers ($P < 0.005$). The 5-year reoperation rate was higher among smokers, but not significantly (34.2% *vs* 31.1%); however, this difference becomes significant when considering the 10-year reoperation rates: 55.5% in smokers and 17.5%

in non-smokers ($P < 0.04$)^[28]. No differences were noted between ex-smokers and non-smokers^[28].

Data about sex, age at onset of the disease, duration of the disease, resection margins, type of surgery are discordant and inconclusive^[27].

POSTOPERATIVE MANAGEMENT STRATEGIES

General management

Postoperative management of CD represents a hard challenge. Stratifying patients according to their risk is essential: not all the patients benefit from maintenance therapy, and a patient at high risk of recurrence requires a different, stronger therapy than others. Cigarette smoking is consistently correlated with CD recurrence and, among the known related risk factors, it is the only potentially modifiable factor^[29]. Therefore, as a first step for preventing recurrence, it should be stressed to every patient the importance to stop smoking after surgery for CD^[29]. Smoking cessation decreases risk to the level of that of non-smokers^[28].

Drug prophylaxis of recurrence

Prophylactic drugs have considerable costs and risks, with limited efficacy^[4]. It has to be underlined that there is currently no evidence that, in terms of reduction of hospitalization or need for surgery, prophylactic therapy gives any advantage over a strategy of surveillance with prompt treatment of recurrence^[4]. An overview of the most important drugs used to prevent recurrence follows.

5-Aminosalicylic acid: 5-Aminosalicylic acid (5-ASA) has been extensively studied in postoperative management of CD. Lochs *et al.*^[30] and Florent *et al.*^[31] have treated patients with 5-ASA (mesalazine 4 g/d) or placebo for > 18 mo postoperatively, and have shown that clinical recurrence rates are lower in the 5-ASA group (24.5% *vs* 31.4%), although the difference was not statistically significant. In a study by Florent *et al.*, mesalazine (2.4 g/d) did not significantly reduce endoscopic recurrence rates at 12 wk (50% *vs* 63%)^[27]. Ewe *et al.*^[32] have demonstrated that sulfasalazine (3 g/d) significantly reduces clinical recurrence rates at 1 year (16% *vs* 28%, $P < 0.01$), with effects maintained at 2 years. Endoscopic recurrence has been shown to occur more rarely after 12 mo mesalazine treatment (3 g/d); however the clinical recurrence rates were similar in the two groups^[33]. In a recent double-blind trial, two groups were randomized to receive 4 g or 2.4 g/d of mesalazine at 2 wk after surgery. At 12 mo, endoscopic recurrence was higher in the second group, although clinical recurrence rates were similar in both groups^[12]. The current evidence seems to indicate that 5-ASA is generally safe in postoperative CD prophylaxis, even if it seems to provide, at best, only a small reduction in clinical and endoscopic recurrence^[1].

Antibiotics: Two randomized clinical trials^[34,35] have

evaluated antibiotic therapy in the prevention of CD recurrence after surgery. In the first study, patients treated with metronidazole (20 mg/kg per day, for 3 mo after surgery) had a reduced incidence of severe endoscopic recurrence after a follow-up of 1 year (4% *vs* 25%), but experienced a three times higher incidence of side effects than the placebo group (23.3% *vs* 6.7%)^[56]. Similar results were obtained by another study by the same group on another nitroimidazole antibiotic, ornidazole (1 g/d), administered for 1 year: recurrence rates were reduced at 1 year, but not maintained at 2 and 3 years. The therapy in these studies was not well tolerated. Nitroimidazole antibiotics have shown efficacy in reducing severe endoscopic recurrence in the short- and medium-term and can be eventually associated with other treatments in the first postoperative period^[1]. The possible use of other more tolerable antibiotics such as rifaximin or ciprofloxacin has still to be evaluated.

Budesonide: Two large randomized clinical trials have found that oral budesonide is ineffective in reducing postoperative recurrence rates after surgery for CD^[57]. Ewe *et al*^[32] have found that endoscopic and clinical recurrences after 1 year were not significantly different when comparing budesonide to placebo treatment; Hellers *et al*^[38] have not found differences between the two groups at 3 and 12 mo regarding endoscopic recurrence rates.

Immunomodulators: The thiopurines azathioprine (AZA)/6-mercaptopurine (6-MP) have proven efficacy and are widely recommended for postoperative prophylaxis of recurrence after surgery for CD. Ardizzone *et al* have demonstrated that patients after surgical resection benefit more from AZA than mesalazine for prevention of clinical recurrence, despite the side effects experienced by patients in the AZA group (22% *vs* 8% compared to the mesalazine group)^[1]. Hanauer *et al*^[36] have found that clinical recurrence at 2 years was 50% in the 6-MP group, 58% in the mesalazine, and 77% in the placebo group. In this study, only 69% of patients assigned to 6-MP was able to complete the treatment, because of the significant side effects. A recent meta-analysis of four controlled studies of AZA for recurrence prophylaxis has demonstrated its efficacy for reducing the incidence of overall recurrence at 12 mo. On the other hand, the rate of adverse events leading to therapy withdrawal was higher in the AZA group than in the control groups^[39]. Thiopurines have been shown to be more effective than mesalazine for prevention of postoperative recurrence, despite the higher rate of side effects reported^[1].

Anti-TNF agents: There is only one randomized, double-blind, placebo-controlled trial that has assessed the efficacy of infliximab for reducing postoperative recurrence rates after ileocolic resection^[2]: 24 patients were randomized to receive 5 mg/kg infliximab with a standard three-dose induction and a maintenance dose once every 8 wk, for 1 year, versus placebo. In the infliximab group, 9.1% developed endoscopic recurrence compared with

84.6% in the placebo group ($P = 0.0006$). Infliximab patients experienced a significantly lower risk of endoscopic, histological and clinical recurrence at 1 year^[2]. No data are available about other anti-TNF agents for preventing CD recurrence after surgery.

Other therapies

Different types of probiotics have been evaluated, but none of them has showed a significant effect over placebo in preventing recurrence. There is no evidence for the use of other agents such as synbiotics or interleukin-10 for preventing CD recurrence after surgery^[40-44].

Endoscopic surveillance strategy

Surgery for CD treats complications such as strictures, abscesses or fistulae, but it cannot interrupt the course of the disease. Postoperative recurrence rate in absence of treatment reaches 65%-90% within 12 mo and 80%-100% within 3 years from surgery^[27], with an increase of 22%-25% per year^[19,45]. Moreover, about 50% of the patients will need reoperation within 10 years after the first bowel resection^[9,16,24-26,46,47]. It is therefore important to plan a surveillance of the patient after having assessed their risk of recurrence and chosen the most indicated treatment.

The CDAI can be used to assume the possible activity of the disease, but in postoperative settings it does not reach a sufficient sensitivity to predict disease recurrence accurately: patients with a high CDAI may be completely asymptomatic^[22]. Fecal markers can play a role, but their use for this particular indication needs further investigation.

Rutgeerts *et al*^[47] have developed a validated endoscopic score to measure the postoperative recurrence and stratify patients, according to their endoscopic findings, in five categories, already described (see Table 1 for details). The severity of endoscopic lesions correlates with the risk of disease progression. Endoscopic signs of recurrence do appear before symptomatic disease, which allows early treatment that may be effective in modifying the natural course of the disease, preventing clinical recurrence and possibly, the need for new surgery.

Patients presenting with no or minimal endoscopic lesions (endoscopic score i0-2) may not benefit from therapy; on the contrary, severe endoscopic recurrence (endoscopic score i3-4) should promote aggressive therapy. Based on correlation data between endoscopic lesions and clinical recurrence, and on data about risk factors for postoperative CD recurrence, patients can be considered at low risk if their disease is long-standing, mainly fibrostenotic, and involves a limited bowel segment; on the other hand, all other patients, especially active smokers, with prior intestinal surgery, perianal disease, perforating and inflammatory disease, who have undergone extensive bowel resection should be considered at high risk for recurrence. It can be a rational strategy to wait to treat low-risk patients until performing the first ileocolonoscopy, 6 mo to 1 year postoperatively, and reserving the immediate start of postoperative prophylactic therapy (with thiopurines or anti-TNF) for high-risk patients. For low-risk patients, if there is endoscopic recurrence at ileocolonoscopy, im-

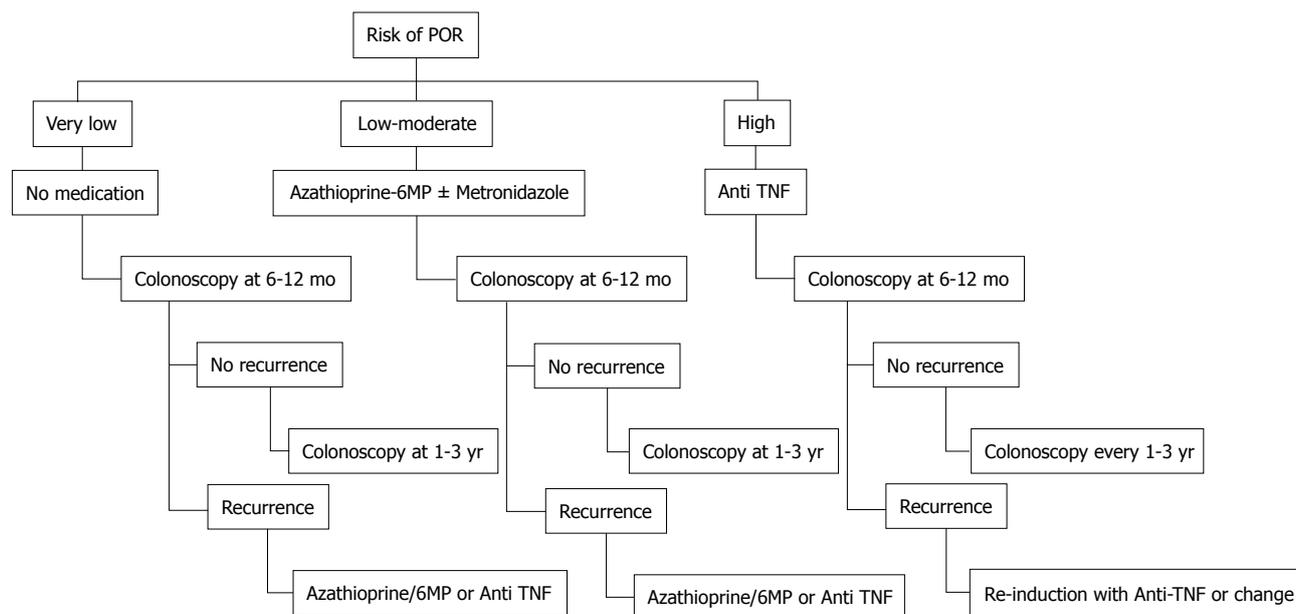


Figure 1 Flow-chart for treatment of postoperative recurrence of CD (adapted from Regueiro^[29]). 6-MP: 6-mercaptopurine; TNF: Tumor necrosis factor; POR: postoperative recurrence.

munomodulatory or anti-TNF therapy could be started; if negative, only a new endoscopic surveillance can be performed 1-3 years later. Further optimization or modification of therapy could be performed according to the severity of endoscopic lesions, repeating ileocolonoscopy after another 6-12 mo. For patients at high risk of recurrence, thiopurines or anti-TNF treatment is recommended, starting a few weeks after surgery; if endoscopic controls during surveillance reveal recurrence of disease, it is possible to intensify the dose or switch to another agent^[29].

Surgical strictureplasty represents a valid treatment for most patients with small bowel strictures, while its role in duodenal and colonic disease remains debated^[48]. A recent meta-analysis by Yamamoto *et al*^[48] has shown that younger age, short duration of the disease, and short interval from previous resection can increase the risk of recurrence. Differently from what previously reported^[49], the most recent evidence has shown that the number of strictures and strictureplasties do not affect the risk of recurrence^[48]. Except for the duodenum and the last ileal loop, small bowel is difficult to be explored endoscopically; therefore, data regarding the CD recurrence are focused on ileocecal resection, and there is no evidence that medical management or timeline for surveillance after strictureplasty is different than in patients undergoing ileocecal resection.

CONCLUSION

CD recurrence after surgery is very frequent. Identification of risk factors for recurrence is extremely important in order to stratify patients according to their risk, identifying those who can benefit from an aggressive medication regimen, possibly modifying the natural course of the disease. If postoperative prophylaxis of recurrence is indicated, then thiopurines (eventually with metronidazole) and anti-

TNF agents are the most effective choices. Ileocolonoscopy within 1 year of surgery, regardless of the eventual postoperative treatment, is widely recognized as the best tool for early detection of CD recurrence, allowing tailoring the appropriate therapy to the individual patient. A summary of the suggested management of postoperative recurrence is shown in Figure 1. Cooperation between gastroenterologists, endoscopists and surgeons is desirable in order to assess the risk of recurrence, to plan postoperative surveillance (not limited to symptomatic flares), and to offer the most appropriate treatment strategy to the patient. Which approach would be better for treating and preventing postoperative recurrence of CD remains debatable.

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