

TOPIC HIGHLIGHT

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Postoperative Crohn's disease recurrence: A practical approach

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Abstract

Crohn's disease is a chronic inflammatory condition that may involve any segment of the gastrointestinal tract. Although several drugs have proven efficacy in inducing and maintaining disease in remission, resectional surgery remains as a cornerstone in the management of the disease, mainly for the treatment of its stenosing and penetrating complications. However, the occurrence of new mucosal (endoscopic) lesions in the neoterminal ileum early after surgery is almost constant, it is followed in the mid-term by clinical symptoms and, in a proportion of patients, repeated intestinal resections are required. Pathogenesis of postoperative recurrence (POR) is not fully understood, but luminal factors (commensal microbes, dietary antigens) seem to play an important role, and environmental and genetic factors may also have a relevant influence. Many studies tried to identify clinical predictors for POR with heterogeneous results, and only smoking has repeatedly been associated with a higher risk of POR. Ileocolonoscopy remains as the gold standard for the assessment of appearance and severity of POR, although the real usefulness of the available endoscopic score needs to be revisited and alternative techniques are emerging. Several drugs have been evaluated to prevent POR with limited success. Smoking cessation seems to be one of the more beneficial therapeutic measures. Aminosalicylates have only proved to be of marginal benefit, and they are only used in low-

risk patients. Nitroimidazolic antibiotics, although efficient, are associated with a high rate of intolerance and might induce irreversible side effects when used for a long-term. Thiopurines are not widely used after ileocecal resection, maybe because some concerns in giving immunomodulators in asymptomatic patients still remain. In the era of biological agents and genetic testing, a well-established preventive strategy for POR is still lacking, and larger studies to identify good clinical, serological, and genetic predictors of early POR as well as more effective drugs (or drug combinations) are needed.

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Key words: Crohn's disease; Postoperative recurrence; Smoking; Aminosalicylates; Nitroimidazolic antibiotics; Thiopurines

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory intestinal disease that frequently requires surgical bowel resection due to refractory activity in spite of medical treatment or complications such as stenosis or fistulae. Approximately, 80% of patients need intestinal resection during their lifetime^[1]. Nevertheless, resectional surgery is not definitively curative and disease frequently reappears at the site of the anastomosis and/or proximally. The term recurrence defines the presence of new objective intestinal lesions of CD after a radical or curative resection. Radical resection is considered as a complete excision with a sufficient length (5-15 cm) of macroscopic normal margins from both ends of the diseased bowel segment, together with local lymph nodes, to remove the whole involved gut^[2]. Although some alternative surgical techniques such as stricturoplasty are emerging, according to the European consensus on definitions and diagnosis of CD, *recurrence* is best used to define the reappearance of lesions after surgical resection while *relapse* refers to

the reappearance of symptoms^[3]. Early studies by the Leuven group showed a symptomatic recurrence rate of 20%-30% one year after ileal or ileocolonic resection, with a 10% increase in each subsequent year^[4]. Moreover, the same group reported an endoscopic and histological recurrence rate of 72% within one year of the operation^[5]. These key studies marked the basis of knowledge about postoperative recurrence (POR) in CD.

DEFINITION OF POSTOPERATIVE RECURRENCE

POR rates vary according to the criteria used for its definition: clinical, endoscopic, morphologic, or surgical (Figure 1). *Morphological* POR refers to the occurrence of new lesions assessed by imaging techniques; since radiological explorations are less accurate in detecting small or superficial mucosal lesions, morphological POR has been replaced by *endoscopic* POR. The occurrence of new mucosal (endoscopic) lesions in the neoterminal ileum early after surgery is almost constant, and it is followed in the mid-term by clinical symptoms and, in a proportion of patients repeated intestinal resections are required. As recently reviewed, *clinical* POR rates, assessed by conventional clinical activity indexes, varies between 17%-55% at 5 years, 32%-76% at 10 years and 72%-73% at 20 years^[6], whereas *surgical* POR rates (patients requiring re-operation) are of 11%-32% at 5 years, 20%-44% at 10 years and 46%-55% at 20 years^[6-8].

Although the real relevance of endoscopic POR is yet to be known, the emergence of mucosal healing as one of the most important therapeutic targets in CD increases the interest for endoscopic POR prevention as the main goal after resectional surgery, at least in the setting of clinical trials.

NATURAL HISTORY OF POSTOPERATIVE RECURRENCE

The physiopathology of POR still remains unknown and its course is unpredictable. Reasonably, pathogenic mechanisms of recurrence should be the same of CD itself, but even a more relevant role of luminal microorganisms is suspected. It is known that if ileocolonic anastomosis is protected by a proximal ileostomy and no faecal stream passes through the anastomosis, mucosal lesions rarely appear^[9]. The infusion of intestinal luminal contents into the excluded ileum results in inflammatory mucosal changes, as shown in a classical interesting study by the Leuven group in 3 CD patients who were studied by histopathology and electron microscopy^[10]. The authors demonstrated that, as soon as 8 d after the reinfusion of intestinal fluids, focal infiltration of mononuclear cells, eosinophils, and polymorphonuclear cells in the lamina propria, small vessels, and epithelium appeared in the previously normal excluded neoterminal ileum. Furthermore and considering this hypothesis, the same group showed some years later that nitroimidazolic antibiotics are efficient in preventing POR, as will be

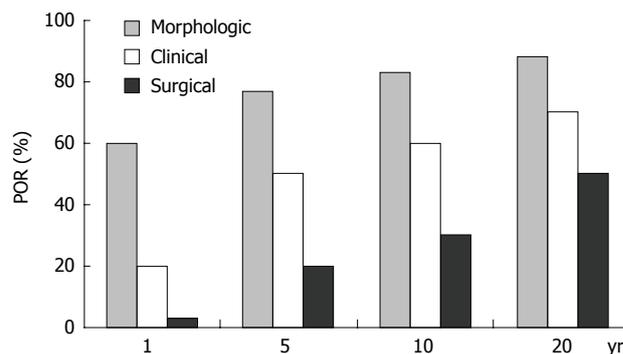


Figure 1 Mean rates of postoperative recurrence of Crohn's disease assessed by clinical relapse, imaging techniques (morphologic), and re-operation (surgical).

later discussed^[11,12].

The onset of disease recurrence begins by the appearance of new mucosal lesions (morphologic recurrence) that can be assessed by means of radiological or endoscopic techniques and the evolution of these lesions mimics the previous phenotypic pattern in every particular patient, as shown when the indication for reoperation is evaluated^[13].

Ileocolonoscopy is a very useful diagnostic tool for examination of neoterminal ileum after ileocolonic resection and it determines the presence or absence of new lesions. There is a sequence of endoscopic lesions in the anastomotic and preanastomotic regions followed by the development of clinical symptoms. The earliest lesions detected are aphthoid ulcers and it is possible to detect a disruption of capillary basement membrane with haemorrhaging and rails of fibrinogen in the surrounding lamina propria emptying into the bowel lumen^[14]. The presence of extensive lesions in the neoterminal ileum by endoscopic examination within some months after surgery predicts a rapid evolution to recurrent symptoms and eventual complications, and there is evidence that these early lesions do not originate from microscopic inflammation prior to surgery^[15].

RISK FACTOR FOR POSTOPERATIVE RECURRENCE

Even though the determinants for disease recurrence remain as speculative as for the initial CD lesions, several risk factors for POR have been reported. The identification of such factors is very important in order to select those patients who may benefit the most from active preventive measures. Clinical parameters that influenced outcome are listed in Table 1, and they can be grouped in those related to the patient's and disease's characteristics, and those that depend on surgical questions. However, it has to be pointed out that most studies evaluating risk factors for POR are retrospective, and that prospective RCTs designed to evaluate different preventive treatment for POR (mostly with a smaller sample size than retrospective studies) have not confirmed these results.

Table 1 Clinical parameters that may influence the development of postoperative recurrence

Age (at onset of disease)
Gender
Family history of CD
Smoking
Duration of disease before surgery
Location
Genetic factors
Involvement of disease at the resection margin
Indication for surgery
Length of resected bowel
Anastomotic technique
Histological findings

Patient and disease characteristics

Smoking: It is known that smoking habits play an important role in the pathogenesis of inflammatory bowel diseases and it is maybe the only environmental factor extensively evaluated in both CD and ulcerative colitis. The effect of smoking and its cessation on disease location, behaviour, and disease progression in CD has been recently analyzed through a systematic *Medline* research^[16]. The conclusions were that smoking duplicates the risk of recurrence after surgery and smoking cessation should be encouraged as one of the most useful measures for the management of the disease. Cigarette smoking may not be only a risk factor for development of CD but also may influence disease activity following surgery^[17]. The risk of surgery as well as the risk for further resections during disease course is increased among smokers in most studies. The first study that analyzed the effect of cigarette smoking on POR (defined by the need for repeated surgery) in a historical cohort of 174 CD patients who had been operated on, found that the rate of reoperation after 5 and 10 years was significantly different for smokers (36% and 70%, respectively) that for nonsmokers (20% and 41%, respectively). When patients were stratified by gender, this increased risk was more apparent in women^[18]. In another study, significant differences in surgical recurrence rates between smokers and non-smokers and for both male and female were also found. Five and 10-year recurrence rates were 43% and 64%, respectively, for smokers, with corresponding figures for non-smokers of 26% and 33%^[19]. In addition, it has been shown that macroscopic lesions at the neoileum are present in 70% of smokers one year after surgery, for only 35% in non-smokers and 27% in ex-smokers. Finally, an Italian study correlated the risk of recurrence to the severity of smoking habits, with a more marked increase in the risk of symptomatic POR among heavy smokers than among mild smokers^[20]. No interventional study evaluating the impact of smoking cessation has been performed and it is unlikely to occur.

Genetic factors: *NOD2/CARD15* gene variants play an important role in the susceptibility to CD. Studies of genotype-phenotype relationship suggest that these variants are associated with ileal location and the development of intestinal strictures. In a study evaluat-

ing the influence of *NOD2/CARD15* variants on CD outcomes including 170 patients (70 of who had been operated on), Alvarez-Lobos and co-workers found that those patients carrying gene variants had a higher risk of surgical POR^[21]. Recently, in another Mediterranean area study including a total of 110 patients, although these findings were not completely reproduced, those patients the L1007fs mutation also had higher rates of reoperation^[22].

Disease phenotype-related factors: Early onset of CD might be associated to a higher recurrence rate. However, results were controversial in the largest series in which this item was evaluated, and age at diagnosis should not be considered as a definitive predictive factor. Similar results have been found regarding family history of CD^[23].

Clinical parameters that have been associated to post-operative outcomes are preoperative disease activity^[14] and location of disease at diagnosis^[24]. When recurrence was defined by the need for reoperation, patients with disease affecting only large bowel had a higher risk when compared to those with isolated small bowel involvement or ileal and colonic disease^[24]. The presence of jejunal CD is associated with a higher rate of early disease recurrence as compared to ileocecal disease, but long-term recurrence rates do not differ significantly^[25]. In a European study, phenotype at diagnosis had a strong predictive value for clinical relapse or recurrence, upper gastrointestinal disease being the most important positive predictor; although the study did not focus on POR, it seems that these results agree with those obtained in the Japanese study^[13].

Perforating disease seems to be associated with a more rapid or aggressive POR. In a recent meta-analysis, a trend for earlier reoperation in patients who were firstly operated on for perforating complications as compared to patients operated on for non-perforating indications was found^[26]. However, there was a significant heterogeneity among the included studies, limiting the value of the results.

Histopathological factors: Although microscopic involvement of the resection margins was not associated to a higher risk of surgical POR in a RCT in which patients were randomized to have a limited or an extended resection from the macroscopically affected margin^[27], recent data suggest that the presence of myenteric plexitis in the resection margins may be a relevant predictor of POR. Ferrante and colleagues studied the surgical specimen and the clinical and endoscopic outcome of 59 patients who were operated on and included in the placebo arm of two RCTs for POR prevention. Those patients with myenteric plexitis in the surgical specimen had significant higher rates of endoscopic POR at both 3 and 12 mo after surgery^[28].

Surgery-related factors: Several prognostic factors related to surgical aspects have been investigated. The length of resected bowel does not appear to be a predis-

posing factor to POR^[29,30]. As long as recurrence rate is unaffected by the presence of microscopic active disease at the surgical margins, the current surgical approach is that only macroscopically affected tissue must be removed in order to minimize the risk of a further short bowel syndrome.

Based on data suggesting that anastomotic stapling techniques result in a localized ischemic injury that might increase disease recurrence, the studies evaluating this topic show different results^[31]. Firm conclusions are difficult to achieve because of the retrospective nature and heterogeneity of studies. Recently, a meta-analysis evaluated the incidence of recurrence and indication for reoperation between patients undergoing end-to-end anastomosis and patients with another anastomotic configuration after intestinal resection^[32]. Eight studies (only two were prospective and randomized) reported data from 661 patients who underwent 712 anastomosis. Almost half the patients had end-to-end anastomosis and recurrence rate was significantly reduced in those patients who had other anastomotic configurations.

Laparoscopic resection is more adequate in CD since patients are usually young, with cosmetic and working concerns. This technique can be performed safely and effectively and it shows a faster resumption of oral feeds, lesser postoperative pain, and shorter hospital stay when compared to open surgery. No differences were found in the recurrence rate or the disease-free interval when laparoscopic technique was compared with open surgery in a retrospective analysis of 61 consecutive patients performed in a tertiary Canadian centre^[33]. Similar results were obtained in a retrospective study involving a larger cohort of 113 patients^[34]. Recently, long-term results of laparoscopic-assisted or open ileocolic resection for Crohn's disease have been compared in terms of surgical recurrence, quality of life, body image, and cosmetics^[35]. Although surgical recurrence and quality of life were comparable, a better body image and cosmetic appearance favored laparoscopy.

ASSESSMENT OF POSTOPERATIVE RECURRENCE

Clinical monitoring should be the easiest way to assess the occurrence of POR (clinical recurrence). However, ileocecal resection (especially in cases of extensive ileal resection) may be associated with the development of abdominal symptoms such as diarrhoea or abdominal cramps secondary to bacterial overgrowth, bile salts malabsorption, or short bowel syndrome, and these might be misinterpreted as a disease recurrence. Unfortunately, no clinical activity index has been validated for patients with previous ileocolonic resection, and the value of the changes in the CDAI or the Harvey-Bradshaw indices in this clinical setting is still to be established.

Histology (histological recurrence) could also be used to diagnose POR, but microscopic inflammatory mucosal changes have been described to occur early after

surgery^[10] and the relationship with the timing or severity of clinical recurrence has not been adequately evaluated.

As mentioned before, Rutgeerts and colleagues showed that the severity of mucosal lesions correlated with the likeliness to develop clinical recurrence. Although these lesions should be detected radiologically or endoscopically, the higher accuracy of endoscopy to detect small lesions makes ileocolonoscopy the gold standard for POR assessment. Moreover, these authors proposed an endoscopic index to specifically describe and grade POR^[15]. Since then, the so called Rutgeerts' endoscopic index has been used to define the primary endpoint in most RCTs evaluating preventive strategies for POR performed in the last decade, as a surrogate for clinical recurrence. This index scores recurrent ileal lesions as i0 (no lesions), i1 (less than 5 aphthous lesions), i2 (more than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to < 1 cm from the ileocolonic anastomosis), i3 (diffuse aphthous ileitis with diffusely inflamed mucosa), and i4 (diffuse inflammation with larger ulcers, nodules, and/or narrowing). Although POR was initially defined as a Rutgeerts score \geq i1, most RCTs use i2 as the cut-off to define endoscopic recurrence and i3 for defining "significant" or "severe" endoscopic recurrence, suggesting that i1 and i2 are of low value to predict clinical recurrence in the short-term.

The meaning of those endoscopic lesions confined to the anastomosis is still under debate. These lesions, although included in the Rutgeerts index as i2, have been questioned by some authors who claimed that they could be related to staples and/or ischemia^[36]. In a recent prospective study, when considered apart, these lesions did not become symptomatic and showed a low probability to progress to more severe endoscopic lesions in the mid-term (22% and 42% after 3 and 5 years of surgery, respectively)^[37]. Certainly, some authors already had not considered these lesions as disease recurrence in the setting of clinical trials^[38]. Moreover, a careful reading of the initial paper by Rutgeerts *et al* in which the index was first defined, shows that whereas the clinical outcome was markedly different in patients with an endoscopic index greater or lesser than i2, patients with i2 had an unpredictable outcome. Therefore, the possibility that these lesions may be a confounding factor rather than a 'true' disease recurrence should be kept in mind, and their clinical relevance should be revisited.

Finally, although POR usually occurs at the neoterminal ileum after ileocecal resection, some patients (mostly after segmentary colonic resections) may develop mucosal lesions in the colon. This is not considered in the Rutgeerts score, and in a recently published RCT a modified version of this index including recurrent lesions in the colon has been used^[39]. For all these reasons, and despite a Rutgeerts' index of \geq 3 has been strongly associated with a poor prognosis, many authors do not recommend its use neither in clinical practice nor in the setting of RCTs since data supporting its clinical relevance are still lacking^[36].

Table 2 Characteristics of available preventive measures of post-operative recurrence

Preventive measure	Pros	Cons
Smoking cessation	Many colateral beneficial effects Synergistic effect with thiopurines?	Lack of specifically designed prospective studies and RCTs (data coming from retrospective studies) Low adherence
Enteral nutrition	Excellent safety profile	Preliminary results Adherence?
5ASA compounds	Safety profile	Marginal benefit (high number needed to treat -NNT-)
Nitroimidazolic antibiotics	Proven efficacy in RCTs	High rate of intolerance/side effects (not applicable in a long-term basis)
Thiopurines	Strong positive results in open and retrospective studies Proven efficacy in RCT when combined with metronidazole Particularly efficient after second resection? Synergistic effect with smoking cessation?	Safety profile/intolerance Efficacy in monotherapy not conclusive (RCTs)

Alternative non-invasive imaging techniques to assess POR have been evaluated in recent years. Wireless capsule endoscopy (WCE) has potential advantages over ileocolonoscopy: it is more comfortable and better tolerated by patients, it does not need sedation, and it is less influenced by technical limitations (impossibility to access the neoterminal ileum). In small-sized controlled trials, WCE demonstrated a similar efficacy to ileocolonoscopy to detect mucosal lesions in the neoterminal ileum^[38,40,41]. Furthermore, WCE is able to detect mucosal lesions one year after surgery in 60%-70% of patients in upper segments of the gastrointestinal tract that are outside the scope of ileocolonoscopy. The significance of these lesions is uncertain; whereas some authors defend that they must be considered as disease recurrence, the lack of a careful assessment of the upper gastrointestinal tract prior to surgery makes impossible to know if they were already present before surgery. In the early nineties, Lescut *et al* performed a perioperative retrograde endoscopy through the enterotomy and up to the angle of Treitz in 20 CD patients undergoing ileal and/or colonic resections, and found that 65% of patients had mucosal lesions^[42]. Furthermore, a prospective endoscopic evaluation of these patients did not find any relationship between endoscopic recurrence 12 wk after surgery and the presence of small bowel lesions left in place after a "curative" surgery^[43]. The spreading use of WCE for POR assessment may be additionally restricted by two major concerns: first, there are no studies evaluating the correlation between those mucosal lesions seen at WCE and the clinical outcome and, second, WCE interpretation is associated to a significant interobserver variability^[44].

Abdominal ultrasonography is an attractive alternative to assess POR. It has the advantage over ileocolonoscopy to be non-invasive and well-tolerated, and it is cheaper than WCE. However, conventional transabdominal ultrasonography has the inherent technical limitations of the virtual lumen and the presence of gas in the intestinal loops for assessing intestinal lesions. To overcome these limitations, the administration of polyethylene glycol as an anechoic luminal contrast (the so called small intestine contrast ultrasonography -SICUS-) has proven to be able to dissociate intestinal loops, thus al-

lowing the measurement of the bowel wall thickness and lumen diameter. In a recently published study in which SICUS was compared to ileocolonoscopy and WCE, even though it was found to be useful in assessing POR, it had a low diagnostic specificity and there was a poor correlation between wall thickness evaluated by SICUS and the Rutgeerts index^[38]. In addition, it has to be kept in mind that, even when using improved modifications of abdominal ultrasonography, an experienced sonographer is always required to detect small intestine lesions.

Granulocyte-labelled scintigraphy has also been evaluated in a small study to assess POR suggesting that, although with a lower specificity, this technique might be useful^[45]; nevertheless, it is time-consuming and it is not available in all centres.

The usefulness of inflammatory faecal markers for early and non-invasive evaluation of POR is still to be established. Recently, faecal markers have shown to be superior to CDAI and CRP in predicting endoscopic disease activity as measured by the CDEIS^[46]. However, although promising results in pilot studies are available^[47,48], the role of inflammatory faecal markers has not been appropriately evaluated in the post-operative setting.

PREVENTION OF POSTOPERATIVE RECURRENCE

Several different approaches have been unsuccessfully evaluated in the prevention of POR (Table 2). The preventive use of conventional drugs such as budesonide has not proven efficacy^[49], although one single study suggested that this drug might be beneficial in those patients operated on for refractory inflammatory activity^[50].

Despite they may be more appealing from a pathogenic point of view, neither the administration of anti-inflammatory cytokines such as interleukin-10^[51], nor the use of probiotics^[39,52,53] or a cocktail of probiotics and prebiotics^[54], have demonstrated to be superior to placebo in preventing POR in RCTs.

As in many other clinical scenarios in CD, the role of mesalazine in the prevention of POR remains controversial. Many RCTs have been published, some of them with a large sample size, but with heterogeneous results.

Repeated meta-analyses suggest that 5-ASA compounds offer just a marginal benefit in this setting^[55,56] and their use is only advised in patients with low-risk of POR or in non-treated patients with grade i1-i2 of endoscopic recurrence^[2,57].

Enteral nutrition, although with a lesser effect than conventional steroids, is able to induce remission in up to 50% of patients with active CD with almost no associated serious adverse effects^[58]. In fact, enteral nutrition is considered as the treatment of choice at the onset of paediatric CD. Some studies suggest that supplementation with enteral nutrition may also be beneficial for maintaining clinical remission^[59]; however this strategy has been poorly explored after surgically-induced remission. Yamamoto and colleagues found in a prospective, controlled, open, pilot study that long-term nocturnal enteral nutrition administered by nasogastric self-intubation resulted in a significant reduction in the 12-mo rates of clinical and endoscopic POR^[60].

Similarly, the efficacy of biological agents in this setting has not been assessed yet. Sorrentino and colleagues reported the results of a prospective, parallel, non-randomized study in which 7 patients were treated with a conventional dosing of infliximab plus low-dose oral methotrexate and compared to 16 patients treated with 2.4 g/d of mesalazine, to prevent POR. None of the infliximab-treated patients had evidence of disease recurrence by means of endoscopy, MRI and small-bowel enteroclysis 2 years after surgery, whereas 75% of the patients in the mesalazine group had endoscopic recurrence, 25% of them with concurrent clinical recurrence^[61].

Even though it is well established that smokers have an increased risk of POR in comparison to non-smokers, the impact of smoking cessation on the risk of developing POR has only been evaluated in retrospective studies in which patients who quit smoking had a reduced risk for both clinical^[62] and surgical^[63] recurrence. Prospective, controlled studies evaluating the usefulness of smoking cessation to prevent POR will never be performed but, taking into account that the impact of this therapeutical measure has been compared to the start of immunomodulator therapy^[64], it should be the first line therapy for POR prevention.

Nitroimidazolic antibiotics are the only drugs with clearly proven efficacy at preventing endoscopic and clinical POR. However, side effects are a major drawback for their long-term administration. In the two RCTs that evaluated metronidazole (for 3 mo) and ornidazole (for 12 mo) in the prevention of POR, almost one half of the patients developed unequivocal drug-related side effects, leading to treatment discontinuation in 13% and 21% of patients, respectively^[11,12]. Therefore, nitroimidazolic antibiotics are not appropriate as monotherapy for maintaining postoperative remission.

Many arguments suggest that thiopurines may work in preventing CD recurrence. First, thiopurines (azathioprine and 6-mercaptopurine) are, together with infliximab and adalimumab, the only drugs that have proven efficacy for maintaining CD in remission^[65-67].

Second, Rutgeerts *et al.*, in the ornidazole trial, already found that discontinuation of immunomodulators at the time of operation was the only clinical parameter predicting clinical recurrence, irrespective of the treatment during the trial. This led the authors to suggest that patients receiving thiopurines before surgery should continue on these drugs after intestinal resection^[12]. Finally, azathioprine may lead to healing or improvement of endoscopic lesions in a great proportion of patients with severe postoperative recurrence, as described by D'Haens *et al.*^[68]. However, thiopurines have not been appropriately evaluated in this clinical setting. Several retrospective studies reported good results with AZA to prevent POR^[69-72]. The largest RCT published up to date compared thiopurines to mesalazine and placebo, and found that 6-mercaptopurine was more effective than placebo for preventing both endoscopic and clinical POR over 2 years^[73]. Nevertheless, the study was strongly criticized because of a lower than expected efficacy of 6-mercaptopurine (maybe related to the low dose used) and the high rate of dropouts from the study. A previous small-sized RCT did not demonstrate any superiority of low-dose azathioprine over mesalazine 3 g/d^[74]. In addition, the use of thiopurines seems to merely delay but not avoid the development of mucosal lesions in the neoterminal ileum, as stated in two recently published prospective, open studies^[38,72], suggesting that the efficacy of these drugs should be improved. Despite that, thiopurines are the best drugs to prevent and treat POR and they are still considered the first line treatment in patients with severe endoscopic lesions or at high risk.

Given the limited efficacy and/or applicability of the available preventive measures, alternative or combined strategies must be investigated. Recently, D'Haens and colleagues reported positive results with azathioprine when associated to metronidazole for the first 3 mo after surgery in patients at high risk for POR. Such an association resulted to be better than metronidazole alone, with 12-mo endoscopic recurrence rates of 44% and 69%, respectively^[75]. Smoking cessation might have a synergistic effect with thiopurines on the prevention of POR. In a retrospective study, Papay and co-workers found that treatment with thiopurines and non-smoking were the only factors associated with a lower risk of surgical recurrence in a large cohort of CD patients who had been operated on, although non-smoking did not reach statistical significance in the multivariate analysis (OR 1.6, 95% CI 0.99-2.7)^[76].

A PRACTICAL APPROACH: WHICH PATIENTS MUST START PREVENTION TREATMENT AFTER SURGERY?

Whether POR must be prevented in all patients after intestinal resection and how, is still under debate. Even though everyone agrees in treating those patients at "high risk", it is difficult (if not impossible) in clinical practice to classify patients as being at "low" or "high" risk; therefore, this is not applicable in most instances.

As long as smoking is harmful not only for Crohn's evolution (and, of course, for the risk of developing POR) but also for developing cardiovascular and neoplastic diseases, smokers have to be earnestly encouraged to give up smoking once surgery have been planned. Those patients who continue smoking despite medical advice should be considered as being at high risk and, consequently, treated with thiopurines. It also seems clear that patients with previous intestinal resections must follow active prevention; in this setting, azathioprine has shown to be superior to no-treatment^[71] or high-dose of mesalazine^[77] at preventing clinical recurrence. There are no other clinical or epidemiological factors clearly associated with a high risk of POR; thus, studies in large cohorts of patients evaluating not only clinical and epidemiological but also genetic and serological factors are warranted. In the meantime, some authors are prone to endoscopically monitor or even prescribe mesalazine to those patients with no risk factors (mainly smoking, second resection, and/or penetrating disease pattern). Our opinion is that all patients must be given thiopurines. Crohn's disease is a chronic condition with a relapsing course and most patients will develop penetrating or stenosing complications within the first 5 to 10 years from diagnosis. This has led to the thought that maintenance treatment must be started right from the diagnosis of CD, and it has been already shown that early introduction of thiopurines is beneficial in both paediatric^[78] and adult^[79] CD patients. From this point of view, it makes no sense to leave untreated those patients who already had a complication of the disease. Even if this policy is chosen, many questions remain unanswered: must thiopurines be started together with a 3-mo course of metronidazole? Which are the alternatives in those patients intolerant to thiopurines or with a previous failure of these drugs to prevent POR? Can we stop thiopurines in smokers some months after smoking cessation?

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