IBD REVIEWS REVIEW ARTICLE

Prevention of Endoscopic Postoperative Recurrence in Crohn's Disease

Rogério Saad-Hossne[1], Paulo Gustavo Kotze[2]*, Fábio Teixeira[1,3] and Anderson Omar Damião[4]

[1]Digestive Surgery Unit, UNESP, Botucatu, São Paulo; [2]Colorectal Surgery Unit, Catholic University of Parana, Curitiba; [3]Gastrosaúde Clinics, Marilia; [4]Gastroenterology Department, University of São Paulo, São Paulo. Brazil

Abstract

Surgery still has an important role in the treatment of Crohn's disease, and more than 70% of patients will require surgery at some time in their disease course, even with the best therapeutic options. Unfortunately, these patients have an increased risk of future reoperations in the long term (8-10 years). Recurrence is a common event after surgery and occurs in up to 90% of patients after one year. The natural history of postoperative recurrence of Crohn's disease demonstrates that endoscopic recurrence precedes clinical symptoms and bowel damage that can lead to future reoperations. Several risk factors are associated with recurrence of Crohn's disease, mainly smoking, perforating disease, and previous resections. The different strategies of prevention of endoscopic postoperative recurrence lead to better disease control after surgery. In this review the authors describe the risk factors associated with recurrence and debate the therapeutic options for prevention of postoperative endoscopic recurrence. (IBD Rev. 2016;2:13-21)

Corresponding author: *Paulo Gustavo Kotze, pgkotze@hotmail.com*

Key words: *Crohn's disease. Recurrence. Postoperative.*

Introduction

Over the last 15 years we have seen great progress in the medical management of inflammatory bowel diseases (IBD), ulcerative colitis (UC), and Crohn's disease (CD). Despite these advances, surgery is still needed in the care of these patients. Unfortunately, approximately 70-75% of CD patients will require surgery at some time in their lives, even with the best treatment options[1-3]. Thus, surgery has an important role in the management of CD. The main indications for surgery are based on complications associated with the disease: fibrotic strictures, abscesses, and fistulae that often require a partial intestinal resection[2-6].

For many years, after intestinal resections, these patients received no therapy for a long time

Corresponding author:
*Paulo Gustavo Kotze
E-mail: pgkotze@hotmail.com

Received for publication: 03-03-2016
Accepted for publication: 06-04-2016

and started to receive proper treatment only after clinical recurrence. This concept has changed over the years and endoscopic recurrence is currently an important feature to be prevented[5,6].

Nowadays, there is enough evidence that these patients have an increased risk of future reoperations and 30-70% will require a new procedure within 8-10 years[3,4,6]. This interval depends on some risk factors: smoking, perforating disease, and previous resections, which are considered features with an associated high risk of recurrence[2-6]. These factors have been used as parameters to guide the proper medication for prevention of recurrence.

Postoperative recurrence is defined by clinical, endoscopic, histological, radiological, and surgical characteristics. It is very important to highlight that postoperative endoscopic recurrence (PER) precedes symptoms and the severity of endoscopic lesions predicts the likelihood of subsequent development of clinical and surgical recurrences[4,6-10].

Rutgeerts, et al.[4,5] initially described the classification of PER after ileocolic resection with ileocolonic anastomosis. Currently, this classification is the most important point in the standardization of postoperative endoscopic findings as early detection of endoscopic signs of inflammation can lead to treatment optimization and better disease control.

In this review, the authors will describe the definition of PER, how it can be accessed, and describe the most important risk factors and the best strategies to prevent it.

Definition of postoperative endoscopic recurrence

In 1984 Rutgeerts, et al.[5] carried out a study to describe the findings in 114 patients after ileocolic resection. The endpoint was to correlate endoscopic findings near the anastomosis, with histopathological findings and the natural history of recurrent CD. After one year, 72% of patients had recurrent CD in the neoterminal ileum. Early endoscopic signs of recurrence were defined as small aphthous ulcers in the neoterminal ileum and the authors emphasized: "clinical manifestations were often absent in the early stage of recurrence and could not be detected in radiological examinations". The authors proposed a classification based on these findings (Rutgeerts score)[4,5] that is summarized in table 1. This classification was described only for endoscopic findings in ileocolonic anastomosis, and is to date the best validated method to grade PER.

Table 1. Detailed description of Rutgeerts score

Rutgeerts score	Endoscopic description of findings
i0	No lesions
i1	≤ 5 aphthoid ulcers
i2	> 5 aphthoid ulcers with normal mucosa in between, or normal areas between larger ulcers, or ulcers limited to ileocolic anastomosis
i3	Diffuse aphthoid Ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, nodulations, or stenosis

Postoperative endoscopic recurrence is defined according to the Rutgeerts score as i2, i3 or i4. Patients with i0 or i1 are defined with normal mucosa, without endoscopic recurrence. Thus, early PER is common after resection and can occur in up to 90% of patients after one year[6-11]. Over time, clinical recurrence usually occurs after 2-4 years and surgical recurrence after 8-10 years. *Adapted with permission from Rutgeerts, et al.*[5]

Accessing endoscopic recurrence

The gold standard method to diagnose PER is ileocolonoscopy with the possibility of performing biopsies. With this method, physicians can scope the neoterminal ileum, the anastomosis, and the colon. Biopsies are taken from inflamed areas to chase histologic recurrence. There is controversy regarding the best moment to perform an ileocolonoscopy, but there are data suggesting it can be performed from 6-12 months after surgery.

The POCER randomized, double blind, prospective study[11] had a primary endpoint of PER rates 18 months after ileal resection, comparing a group using individualized therapy (active arm, based on colonoscopy at six months with

the possibility of optimization) versus the best available therapy (control arm, with colonoscopy only after 18 months with a single preventive treatment). PER was defined as Rutgeerts score i2-i4. The conclusions were that individualized treatment, with the possibility of colonoscopy based optimization six months after surgery, was superior than the fixed treatment with the best drug based on risk factors after 18 months. This study was essential to confirm that all patients after ileocolic resection for DC can have an optimized management based on an ileocolonoscopy after six months.

As ileocolonoscopy can only access colonic and terminal ileum recurrence, other procedures are needed in order to analyze recurrence in other sites. There are few papers analyzing enteroscopy and PER. Naganuma, et al.[12] analyzed 20 patients in postoperative CD (6-12 months after surgery) and evaluated the lesions in the small bowel. An interesting finding was that the inflammatory lesions were in the anastomosis, but also in the middle and/or upper ileum, which demonstrates the importance of an adequate study of the whole small bowel, and how these findings could change the treatment strategy for recurrence. More data with a large number of patients is needed to better demonstrate the importance of enteroscopy in PER management.

Other noninvasive methods can be used to follow these patients, mainly faecal calprotectin and lactoferrin. Yamamoto[13], in a recent review, analyzed 10 studies in which the value of faecal calprotectin was measured after surgery for CD. A total of 665 patients were included and the results showed an excellent correlation between endoscopic findings and faecal calprotectin levels. The conclusion of these papers showed a good and sufficient sensitivity and specificity (> 90%) for this method to monitor PER in CD. They also demonstrated that predictive values can be used to identify patients with higher risk of recurrence. Another important conclusion was that calprotectin could be used to monitor response after the treatment for recurrence.

Capsule endoscopy, another tool to chase recurrence in the small bowel, also has contradictory data in terms of sensibility and specificity when compared to ileocolonoscopy. Beltran et al.[14] concluded that capsule endoscopy is better than ileocolonoscopy in the detection of PER. The authors evaluated 19 patients, and capsule endoscopy detected recurrence in 68 vs. 25% by ileocolonoscopy. Bourreille, et al.[15] prospectively compared ileocolonoscopy to capsule endoscopy in 32 patients, with two different observers. Ileocolonoscopy could detect recurrence with 90% sensitivity and 100% specificity, while capsule endoscopy had 76% sensitivity and 90% specificity. More studies with wider samples are also needed in order to elucidate the real importance of capsule endoscopy in the management of PER.

Magnetic resonance imaging (MRI) has a solid role in the diagnosis of CD and complications. However, novel MRI techniques, such as motility studies, PET-MRI, molecular imaging, and diffusion-weighted MRI, are being investigated, whether for diagnosis or management of CD. Ordas, et al.[16], in a prospective, multicenter study, followed 48 CD patients with active disease and compared ileocolonoscopy findings with MRI findings 12 weeks after the start of the treatment and observed "90% accuracy for reporting ulcer healing and 84% accuracy for evaluating endoscopic remission". Grand, et al.[17] analyzed 310 patients, comparing MRI and ileocolonoscopy for CD, and observed that the sensitivity and specificity of MRI were 85 and 80%, respectively (kappa = 0.65), whereas the sensitivity for detection of severe disease was 87% in the terminal ileum. These findings put MRI as a promising method to detect recurrence after proximal small bowel surgery and more data, specifically in the postoperative scenario, are needed.

Risk factors for postoperative endoscopic recurrence

Patient-related factors

Smoking has consistently emerged as a very strong, modifiable risk factor for PER, and

physicians must make a determined effort to convince these patients to stop smoking. The support for this comes from several randomized trials.[11] Reese, et al.[18] in a meta-analysis (16 studies, 2,962 patients) showed that smokers had a higher clinical recurrence rate when compared with nonsmokers (OR: 2.15; 95% CI: 1.42-3.27; $p < 0.001$). The influence of gender, family history of IBD, and oral contraceptives remains controversial, so their role as risk factors cannot be fully addressed.

Disease-related factors

Penetrating disease, perianal involvement, and prior intestinal resections are the most important and consistent disease-related risk factors for recurrence. Other factors that are less consistent and controversial are described, such as granulomas and myenteric plexus. These are not universally accepted, probably due to controversial results in different studies[3,19,20].

Penetrating disease, defined as abdominal fistulas, abscesses, or free perforation, is considered an independent risk factor for recurrence, even clinical or surgical[1]. Reese, et al.[18] in a meta-analysis (13 studies) demonstrated that the probability of surgical recurrence was significantly higher in patients with penetrating disease as compared to those with a non-penetrating phenotype (HR: 1.50; 95% CI: 1.16-1.93). Another import point is that penetrating disease tends to recur again as penetrating and non-perforating as non-perforating disease; recurrence tends to be similar in accordance to the disease phenotype and requires repeated surgery for similar indications[21,22].

As shown and evidenced in penetrating disease, perianal disease (fistulizing or luminal) has also been associated with higher rates of recurrence[22]. Buisson, et al.[20] demonstrated that perianal disease is the only independent risk factor for postoperative recurrence, and concluded that prior intestinal resection is an established risk factor for recurrence. Furthermore, patients with a previous resection required more intensive follow-up and treatment to prevent clinical and surgical recurrences[23].

Histological features have also been studied. Bressenot and Peyrin-Biroulet[24] in a meta-analysis of 21 studies (n = 2,236 patients) reported that the number of patients with recurrence associated with further operations was higher in patients with granulomas as compared to those without this histological finding (OR: 1.37; 95% CI: 1.02-1.84 and OR: 2.38; 95% CI: 1.43-3.95, respectively). Unfortunately there is still controversy if granulomas can be fully associated to recurrence, probably due to differences in sampling and methods.

Myenteric plexitis has been considered another histological feature to predict recurrence, even with controversial results. Four well-designed studies have independently found this characteristic to be a good predictor. Another important aspect is that the severity of the plexitis can be correlated with the severity of PER[25].

The presence of granulomas in the mesenteric lymph nodes was studied by Li, et al.[26]. From 194 included patients, in 23 (11.9%) the presence of granuloma was positive as a risk factor for PER ($p = 0.015$) as well as surgical recurrence ($p = 0.035$). The granulomas in the bowel wall were also analyzed, with no association to endoscopic recurrence ($p = 0.94$) or surgical recurrence ($p = 0.56$). The authors analyzed Cox proportional hazards regression analysis and concluded that granulomas in mesenteric lymph nodes were independently associated with an increased risk for PER (HR: 1.91; 95% CI: 1.06-3.45; $p = 0.031$) and surgical recurrence (HR: 3.43; 95% CI: 1.18-9.99; $p = 0.023$).

Surgery related factors

The extension of the resected specimen is associated with higher rates of PER[3,27]. A controversial point is the definition of “extensive small bowel resection”, commonly referred to as segments longer than 50 cm, this meaning

a high risk for recurrence. Limited resections used to be associated with similar clinical and surgical recurrence rates when compared to wider resections, as shown by Fazio, et al.[28]. No difference in clinical and surgical recurrences was detected between patients randomly assigned to undergo 2 cm (limited) versus 12 cm (extended) resection margins. Moreover, no significant difference in recurrence rates was noted among those with residual microscopic disease.

Other operation-related factors, such as perioperative blood transfusion postoperative complications, hand sewn end-to-end anastomosis versus stapled side-to-side anastomosis, and laparoscopic versus open surgery, have conflicting data regarding the influence on recurrence rates, but are usually considered as non influential factors on recurrence[3,19,20].

Prevention of endoscopic recurrence

Conventional therapy

Aminosalicylates

Sulphasalazine was not proved to be effective in preventing PER in CD[29]. Regarding mesalazine, at least five randomized controlled trials (versus placebo) were performed (time of follow-up 3-24 months). Only in two of them a significant statistical benefit was seen. The largest trial enrolled 318 patients and found no difference in clinical PER rates between mesalazine (4 g/day) and placebo after 18 months (24.5 vs. 31.4%, respectively; p = 0.10). Pooled data of these five trials were evaluated in a meta-analysis[7]. Compared with placebo, mesalazine was associated with a significantly reduced risk of clinical recurrence (RR: 0.76; 95% CI: 0.62-0.94; number needed to treat [NNT] = 12), and severe (Rutgeerts score i3 and i4) endoscopic recurrence (RR: 0.50; 95% CI: 0.29-0.84; NNT = 8). However, any endoscopic recurrence was not significantly reduced by mesalazine. Moreover, mesalazine was inferior to azathioprine/6-mercaptopurine (AZA/6-MP) in preventing any endoscopic recurrence, but had a lower risk of serious adverse effects. Thus, the current evidence indicates that mesalazine provides, at best, a mild reduction in PER rates, and seems not to be cost-effective.

Thiopurines: azathioprine and 6-mercaptopurine

In general, thiopurines have been shown to be more effective than placebo and mesalazine for prevention of postoperative recurrence in CD[27]. One meta-analysis showed that thiopurines were associated with a significantly reduced risk of clinical recurrence (RR: 0.59; 95% CI: 0.38-0.92; NNT = 7), and severe endoscopic recurrence (RR: 0.64; 95% CI: 0.44-0.92; NNT = 4), when compared to placebo[7]. A second meta-analysis[30] confirmed the superiority of AZA/6-MP over placebo or mesalazine in preventing one-year clinical and endoscopic recurrence, with an NNT of 13 and 7, respectively. Long-term maintenance therapy (≥ 36 months) seems to be beneficial in those who can tolerate the drug[31]. Overall, AZA/6-MP have modest efficacy in preventing PER in CD. There is also controversy if immediate use of AZA after surgery may be superior to an endoscopic-driven approach, as studied in a prospective trial from the IOIBD (International Organization of Inflammatory Bowel Diseases). In this study, no difference was found between the two strategies, but the sample was limited and the study was interrupted due to slow patient recruitment[32].

Antibiotics

A placebo-controlled trial of metronidazole (20 mg/kg) for three months showed reduced prevalence of severe PER at three months[33]. Adverse events were three times more common in the metronidazole group. Moreover, metronidazole for three months at a lower

dose (750 mg/day) in combination with AZA for 12 months was superior to metronidazole (three months) associated with placebo (12 months) in reducing PER, pointing to a possible synergic effect[34]. Metronidazole at this lower dose was well tolerated. The same positive effect was seen with another imidazole antibiotic, ornidazole (1 g/day), in a trial that showed a significant reduction in both clinical and severe endoscopic recurrence rates at one year[35]. Again, adverse events were more common in the ornidazole group. Thus, metronidazole and ornidazole were more effective than placebo in preventing PER, but their effect is not long-standing (beyond one year) and poor tolerability may preclude their use in some patients beyond three months. In a recent randomized, double-blind, placebo-controlled pilot study with oral ciprofloxacin (500 mg twice daily), the drug was not more effective than placebo in preventing PER in patients with CD at six months after surgery (65% in the ciprofloxacin group vs. 69% in the placebo group; $p < 0.805$)[36]. Drug-associated adverse events occurred significantly more often in the ciprofloxacin group.

Corticosteroids

Traditional steroids (prednisone, methylprednisolone) are not recommended either for maintenance therapy in CD or for postoperative prophylaxis owing to both adverse events and ineffectiveness[37]. In addition, a meta-analysis with budesonide showed no benefit for reduction of either endoscopic or clinical postoperative recurrence[38].

Probiotics

Since dysbiosis plays a crucial role in CD recurrence, it is reasonable to think that modification of the microbiota with a probiotic may be effective in preventing PER[19]. Unfortunately, the results have been disappointing with several strains and cocktails (*Lactobacillus rhamnosus* strain GG, *L. johnsonii* [LA1], Synbiotic 2000, and VSL#3)[6]. Accordingly, a meta-analysis showed that probiotics were of no benefit in preventing PER in CD[39]. A recent prospective study also demonstrated that there was no difference in using VSL#3 or placebo in endoscopic recurrence rates, evaluated at three and 12 months[40].

Biological therapy

Biological agents, mainly adalimumab (ADA) and infliximab (IFX), are mostly indicated after surgical resection in CD in selected patients with high risk for recurrence. Some patients have a quite clear indication for postoperative biological therapy, such as patients submitted to previous intestinal resections in the past that are submitted to repeated operations and who may be at risk to develop short bowel syndrome. Patients with penetrating CD as well are good candidates for this kind of therapy after resection[3]. It is also clear that anti-tumor necrosis factor (anti-TNF) agents cannot be used in all patients with high risk for recurrence due to limitations in costs and access to these medications. Decisions should be individualized as to when to indicate biological agents, mainly if not used preoperatively.

In patients under these conditions that had conventional treatment before surgery, biological therapy can be started usually 2-4 weeks after the procedure, once surgical and infectious complications are ruled out. On the other hand, most patients at high risk for recurrence are already using biological agents before the procedures. In these cases, restarting the medication without re-induction doses is usually the best strategy, again once complications are not seen in 2-4 weeks after surgery. This is a common situation, mostly because several patients would still have residual disease (active CD in another location, for example, perianal or proximal small bowel) that still needs to be treated properly. In this case, proper treatment is continued after surgery, not meaning a strategy of prevention of recurrence.

In patients with "curative resection" (no residual disease and no macroscopic CD in other locations), the strategy to interrupt biological therapy (that was used before the operation) has not been studied to date. In these particular cases, a specific prospective trial, comparing patients with continuous use after surgery versus patients with treatment interruption, could elucidate several questions regarding these issues.

Data that demonstrate the efficacy of biologics are mostly based on the experience with IFX and ADA. There are no specific studies published to date, defining the role of certolizumab pegol or vedolizumab in the postoperative scenario. Regueiro, et al.[9] demonstrated 9.1% of PER with IFX as compared to 84.6% in patients with placebo infusions after a follow-up period of one year after ileocecal resections. In a longer follow-up of these same patients (at least five years), the authors demonstrated that patients on long-term use of IFX had lower rates of endoscopic and surgical recurrences, as well as longer time until reoperation when needed[41].

In a prospective trial, Armuzzi, et al. showed no significant difference between the use of IFX or AZA in a small sample of 21 patients, but a tendency towards better results with IFX could be demonstrated[42]. In a multicenter, prospective randomized study, presented at the Digestive Disease Week in 2015, entitled the PREVENT trial, the role of IFX in preventing clinical recurrence was studied[43]. The primary endpoint was not met, and no significant difference between IFX and placebo was found regarding clinical recurrence after 76 and 104 weeks. The secondary endpoint of this study was endoscopic recurrence, and a significant difference was observed between patients in the IFX group (22.4%) as compared to placebo (51.3%), with $p < 0.001$[43].

Savarino, et al., from Italy, described the higher efficacy of ADA in preventing PER, as compared to AZA and mesalazine, in a prospective trial with two years of follow-up[44]. A meta-analysis was also published recently, including all studies that compared biological agents with conventional therapy, and the conclusion was that anti-TNF agents were more effective than the control arms in prevention (seven studies included) and treatment of PER (two studies included)[45].

Other prospective studies, such as the POCER trial, also demonstrated the efficacy of tailoring prevention of PER with biological therapy, when needed, based on findings of a colonoscopy performed six months after the resection, in a follow-up period of 18 months[11]. The main results of this interesting trial showed that tailoring the management of recurrence (active arm) with a six-month colonoscopy presented lower PER rates after 18 months than just using a fixed strategy, without the possibility of optimization of therapy (control arm). The rates of PER at the end of the trial (18 months) were 49% in the active arm and 67% in the control arm, with statistical significance ($p = 0.028$)[13]. Thus, the strategy of properly selecting the patients for each therapy, based on an interventional colonoscopy, lead to lower PER rates than patients treated with the best therapy defined immediately after the operation.

Kotze, et al. also retrospectively studied if any difference between the two main anti-TNF agents (IFX and ADA) could exist in the postoperative scenario. In a multicentric international database, with 96 patients submitted to ileocecal resections, with postoperative colonoscopies performed up to 12 months after surgery, that were on biologics postoperatively, there was no difference in PER rates between IFX and ADA (27.12 vs. 24.32%; $p = 0.815$)[46]. The same findings were observed prospectively in a smaller sample (20 patients) in a comparative study from Tursi, et al.[47] In this small open-label trial, there was also no significant difference between IFX and ADA in terms of postoperative endoscopic, clinical, or histologic recurrence in a follow-up of 12 months.

Another matter of debate is the use of combination therapy (biologics and immunomodulators)

versus monotherapy after surgery. There is a significant lack of data in the literature regarding this important issue. In a subanalysis of a multicentric international database, no difference in terms of PER rates was found in the use of biologics with or without concomitant immunomodulators. However, the groups were not fully comparable in this retrospective study[46]. Another interesting topic is the association between endoscopic recurrence and serum levels of biological agents. An Italian study demonstrated that lower serum levels of adalimumab were associated with higher rates of endoscopic recurrence in a case series recently published[47].

Thus, biologics are indicated mainly in patients with high risk for recurrence, independently of their preoperative use. To base the indication in colonoscopy findings seems to be the best strategy. The selection of the anti-TNF agent can be made specifically for each patient, according to personal preferences, convenience, reimbursement, and access to infusion clinics, as no significant difference between both anti-TNF agents has been observed to date.

Final considerations

As seen, PER occurs in the majority of patients and usually is the first detected signal of recurrence in CD. Detailed protocols are still needed in order to define the best timing for the first postoperative colonoscopy, but current data from the POCER trial suggests that six months can be an adequate period. Operations performed in the proximal small bowel need different tests to detect early recurrence, such as capsule endoscopy, MRI enterography or fecal biomarkers such as calprotectin. Prevention of PER is essential for disease control, mainly in patients with high risk factors. The choice of the adequate medication after surgery depends on serial factors and needs to be individualized in a case-by-case analysis.

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