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REVIEW ARTICLE

Pharmacological Prevention of Postoperative Recurrence in Crohn's Disease

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Abstract
Despite increasing use of immunosuppressants and anti-tumor necrosis factor (TNF) agents, approximately half of Crohn's disease (CD) patients still require surgery within 10 years after diagnosis. Surgery is not curative as postoperative relapse is very frequent in the absence of prophylactic treatment. Screening for known risk factors for postoperative recurrence allows patients to be stratified in order to consider appropriate therapy. A subsequent endoscopic evaluation and reassessment of treatment is currently the best strategy. Analyses of pooled data indicate that 5-aminosalicylic acid and thiopurines have only slight efficacy to prevent postoperative recurrence in CD. Nitroimidazole antibiotics are modestly effective, but long-term toxicity limits their use in clinical practice. Recently, anti-TNF agents have demonstrated the best efficacy profile to prevent endoscopic recurrence after surgery. As new treatment algorithms evolve towards increasing use of anti-TNF agents, this drives increased costs of management. However, this may be offset by the more widespread use of biosimilar versions of the anti-TNF agents. The increasing number of patients with previous exposure to numerous immunosuppressants and biologics at the time of surgery is a new challenge in postoperative management of CD, for which further data on new biologics are eagerly awaited.

Key Points

Half of Crohn's disease patients require surgery within 10 years after diagnosis. Surgery is not curative; relapse is very frequent in the absence of prophylactic treatment.

Screening for risk factors for recurrence so that the appropriate pharmacological prevention can be considered, with subsequent endoscopic evaluation and reassessment of treatment, is currently the best strategy.

New treatment algorithms evolve towards the increasing use of anti-TNF agents to prevent postoperative recurrence.

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1 Introduction

Crohn's disease (CD) is a longstanding inflammatory bowel disease that often requires surgical resection of intestinal macroscopic lesions. Rates of resection remain high despite the increasing use of anti-tumor necrosis factors (anti-TNF) and the recent release of new pharmacological options. Unfortunately, surgery is not curative, as the vast majority of the patients will experience endoscopic and eventually clinical recurrence of the disease a few years later [1], in the absence of appropriate postoperative management. Thus, in current CD guidelines [2], considering 'prophylactic treatment' is advised in patients who undergo surgery, even in the setting of complete postoperative remission. Herein we discuss the epidemiology of CD surgery and subsequent recurrence, its risk factors and diagnosis, before reviewing data on current therapeutic options for the prevention of postoperative recurrence.

2 Natural Course of Crohn's Disease: Surgery and Recurrence

Despite wide use of immunosuppressants and biologics for 20 years, the need for surgery remains high in CD [3]. In population-based studies, roughly half of CD patients

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underwent surgery within 10 years after the initial diagnosis [4]. Data from the Olmsted county cohort showed a cumulative probability of intestinal resection of 38% and 48% at 5 and 10 years after diagnosis, respectively [5]. Recently, a trend towards reduced rates of surgery was observed [6], which might be driven by the more intensive and early use of anti-TNF agents [7], as demonstrated in the prospective REACT (Randomised Evaluation of an Algorithm for Crohn's Treatment) trial [8].

Recurrence is the rule after surgical resection in CD. The most relevant study to understand the natural course of postoperative recurrence was performed in the 1980s [9] when no treatment was proposed after surgery for CD. Rutgeerts et al. [9] prospectively followed 114 patients after ileal or ileocolic resection with anastomosis, and monitored them annually with colonoscopies. This study showed a rate of recurrence of 72% after 1 year, > 80% after 10 years, and demonstrated that the lesions were located more often in the neoterminal ileum and at the anastomosis [9]. Early endoscopic signs of recurrence were small aphthous ulcers in the neoterminal ileum; more advanced lesions were observed in patients examined several years after surgery, consisting of larger ulcers, nodular thickening of folds, and stenosis of anastomose [9].

The postoperative recurrence rates vary depending on whether clinical, endoscopic, or surgical recurrence is considered. Endoscopic recurrence precedes clinical recurrence, and is predictable of CD clinical course. Severe endoscopic recurrence predicts a poor prognosis [1]. Following these observations, Rutgeerts et al. [1] developed an endoscopic postoperative scoring system, still unvalidated, but used worldwide, that divides patients into five groups (i0–i4) according to endoscopic findings and further prognosis (Table 1). An endoscopic score of i0 or i1 correlated with a low risk of endoscopic progression and had clinical recurrence rates of < 10% over 10 years [1]. In contrast, 92% of patients with severe lesions (i3 or i4) had progressive or severe evolution at 3 years. A third group consisted of patients with intermediate severity of disease (i2); some of these patients remained asymptomatic, but others developed symptoms and showed progression of the lesions at follow-up examinations [1]. Thus, subsequent to this study, clinical trials generally used i2 or above as a cut off for defining endoscopic recurrence.

Results from referral center studies and randomized controlled trials indicated that more than half of patients (48–93%) and 85–100% of patients experienced endoscopic recurrence (Rutgeerts' score ≥ i2) during the first year after surgery, and at 3 years, respectively [10]. In a pooled analysis from referral centers, the clinical postoperative recurrence rate ranged from 20% to 37% and from 34% to 47% at 1 and 5 years, respectively [10]. Surgical recurrence rates from a Norwegian population-based cohort indicated that 9% of CD patients required two or more surgeries over a 10-year follow-up [11]. Similarly, in Denmark, 13% of the patients were operated on two or more times [12]. In the Olmsted county cohort, 65 and 32 of 152 operated patients required second and third surgeries, respectively [5].

3 Diagnosis of Crohn's Disease Recurrence

3.1 Clinical Diagnosis

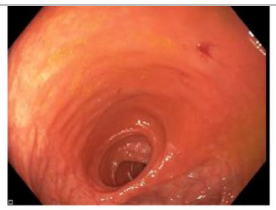
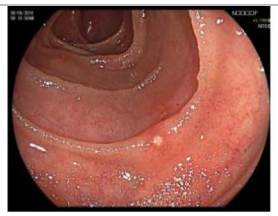
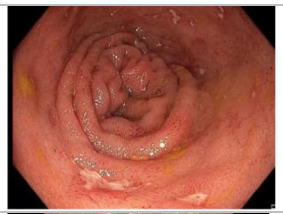
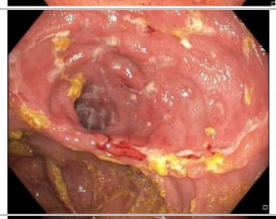
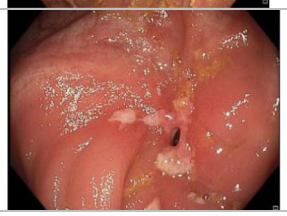
Clinical recurrence is defined by the emergence of CD digestive symptoms, which may be difficult to assess in the postoperative period given the anatomic changes and the subsequent potential diarrhea induced by biliary salts. On the other hand, the symptoms may be delayed and appear only when severe intestinal lesions have already emerged [9]. Thus, clinical indices such as the Crohn's Disease Activity Index (CDAI) have a low sensitivity to discriminate between patients with or without postoperative recurrence and have not been validated after surgery [13].

3.2 Endoscopic Diagnosis

The recent POCER (randomised postoperative Crohn's endoscopic recurrence) trial demonstrated the superiority of treatment decision making based on a systematic colonoscopy 6 months after surgery over clinical management alone [14]. Currently, a systematic evaluation of the anastomosis and the neoterminal ileum by ileocolonoscopy is recommended between 6 and 12 months after surgical resection [2], whatever the postoperative treatment.

Rutgeerts' scores of i0 and i1 are considered in clinical trials as endoscopic remission in the postoperative setting [15], whereas Rutgeerts' scores of ≥ i2 are commonly considered as recurrence (Table 1). Currently, there is a debate on whether i2-type lesions (Table 1) should be considered as predictors of recurrence as, in the pivotal publication by Rutgeerts, the i2 category, including aphthous lesions in the terminal ileum as well as anastomotic lesions, harbored heterogeneous recurrence risks. A modified Rutgeerts score includes a distinction between i2a lesions—ulcers confined to the anastomosis—and i2b lesions—more than five aphthous ulcers in the ileum with normal mucosa in between, with or without anatomic lesions [16]. However, in two retrospective studies, the rates of clinical postoperative recurrence were not different in i2a and i2b patients [16, 17]. Also, in a recent study, anastomotic ulcers at the first postoperative colonoscopy were associated with further disease recurrence in 182 CD patients after ileal resection [18]. Prospective studies are needed to address the relevance of treatment

Table 1 Rutgeerts' score of postoperative lesions in Crohn's disease

Endoscopic score	Definition	Endoscopic features
i0	No lesion.	
i1	≤ 5 aphthous lesions in the neoterminal ileon.	
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.	

i0 and i1scores are considered as remission.

step-up in case of i2-type lesions. In case of endoscopic remission (i0, i1), no further treatment is advised [2], but recent data indicating subsequent clinical and/or surgical recurrence in the follow-up [19] prompt continuous monitoring of these patients.

3.3 Radiologic and Biologic Diagnosis

Less invasive techniques are emerging as alternative tools for recurrence screening, such as magnetic resonance imaging [20, 21], small bowel capsule endoscopy [22, 23], and fecal calprotectin [24, 25]. In a sub study from the POCER trial, fecal calprotectin data collected from 135 participants were analyzed [24]. Levels of fecal calprotectin above 100 µg/g indicated endoscopic recurrence with 89% sensitivity and 58% specificity, and a negative predictive value of 91% [24]. In another prospective multicenter cohort, in 86 patients following surgical resection, fecal calprotectin levels differed significantly in patients with or without endoscopic recurrence [25]. The cutoff point for fecal calprotectin to distinguish between endoscopic remission and recurrence was also 100 µg/g, with 95% sensitivity, 54% specificity, and a negative predictive value of 77% [25].

Currently, endoscopic evaluation is the gold standard to assess postoperative recurrence in clinical practice. In addition, given recent data, an early measurement of fecal calprotectin at 3 months after surgery could be proposed to capture early postoperative recurrence and bring forward adequate management.

4 Risk Factors for Postoperative Recurrence

The European Crohn's and Colitis Organization (ECCO), in its latest consensus on the diagnosis and management of CD in 2016 [2], considered the following factors as predictors of early postoperative recurrence after ileocolonic resection: smoking, prior intestinal surgery, absence of prophylactic treatment (evidence level [EL] 1), penetrating disease at index surgery, perianal location (EL2), granulomas in resection specimen (EL), and myenteric plexitis (EL3) (Table 2). Smoking is the strongest predictor for postoperative recurrence [26], consistently reported in clinical trials. In two randomized controlled trials (RCTs), there were a 2.1- and a 2.4-fold increase in recurrence rates in smokers compared with non-smokers at the time of surgery [14, 27]. A meta-analysis of 13 studies including 3044 patients found that penetrating phenotype was associated with more frequent postoperative recurrence than non-penetrating phenotype (odds ratio [OR] 1.5) [28]. Numerous observational studies have shown that a history of prior resection is associated with recurrence [29, 30]. Recently, in the French prospective REMIND cohort [31] of 225 patients operated on for CD, endoscopic recurrence was analyzed within 1 year following surgery. In multivariate analysis, male gender (OR 2.48), active smoking at surgery (OR 2.65), and previous resection (OR 3.03) were associated with higher odds of endoscopic recurrence [31]. Inversely, post-operative anti-TNF treatment decreased the risk of endoscopic recurrence (OR 0.50) [31], as demonstrated also in the POCER trial [14]. So far, data are conflicting and/or inconclusive concerning gender [2, 26]. While perianal disease and extensive small bowel resection (> 50 cm) are usually considered as risk factors, data are conflicting on the strength of their association with postoperative recurrence [2, 26, 32, 33]. However, in clinical practice, patients with perianal disease and/or history of extensive resections are considered as 'high risk' patients and candidates for postoperative treatment to avoid bowel damage. Recently, several studies looked at histological predictors of recurrence. A meta-analysis found significantly higher recurrence and reoperation rates in patients with granulomas [34]. Myenteric and submucosal plexitis at the proximal margin of the ileocolonic resection were identified as risk factors for postoperative recurrence in five studies [35–39], although one study failed to demonstrate a significant difference in clinical postoperative recurrence between patients with or without plexitis in the proximal resection margin [40]. In the French prospective postoperative cohort [41], CD transmural lesions at the resection margin (defined by mucosal ulceration or cryptitis, submucosal fibrosis, and lymphoplasmacytic infiltrate of the subserosa), were independently associated with early endoscopic recurrence (OR 3.83) and clinical recurrence (OR 2.04) [41]. All these data support the inclusion of histologic features of the ileal margin in the decision process about postoperative therapy (Table 2).

Currently, physicians face a new challenge as many patients undergoing surgery for CD have been previously exposed to anti-TNFs. Previous exposure to anti-TNF agents was associated with postoperative therapeutic failure. In the PREVENT (Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in CD Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence) RCT [42], patients who received anti-TNF therapy pre-surgery were more likely to have a clinical recurrence. In a retrospective analysis [43] of CD patients who underwent surgical bowel resection with anastomosis and prophylactic treatment with anti-TNF therapy, cumulative rates of postoperative endoscopic recurrence at 2 years were 45.5% in patients exposed to two or more anti-TNF agents, as compared with 29.1% in patients exposed to no or one anti-TNF agent before surgery ($p = 0.07$). Multivariable analysis identified smoking and previous exposure to two or more anti-TNFα as risk factors for CD clinical or endoscopic postoperative recurrence in this study [43]. Thus, previous anti-TNF exposure, and especially documented failure, should now be considered in clinical practice, in the postoperative setting.

Table 2 Summary of risk factors for postoperative recurrence

	Risk factors		
	Clinical	Surgical	Histological resection margins
Strong predictor	Active smoking		
Probable predictors	Penetrating disease (B3)	Previous intestinal resection	Myenteric/submucosal plexitis Transmural lesions
Possible predictors	Perianal disease	Extensive resection (> 50 cm)	

B3 penetrating disease according to Montreal's classification

5 Pharmacological Prevention

Given the high level of evidence regarding the risk of postoperative recurrence in smokers, tobacco withdrawal must always be encouraged, with a dedicated council and support, before surgical resection. Also, prophylactic therapy for CD should always be discussed after surgery, and treatment is advised in patients with at least one risk factor for recurrence, to be started within 4 weeks of surgery [2]. Numerous pharmacological drugs have been investigated to prevent postoperative endoscopic or clinical recurrence in CD with various efficacy profiles (Table 3).

5.1 5-Aminosalicylic Acid (5-ASA)

5.1.1 Mesalazine (Mesalamine)

Mesalazine was compared with placebo in five RCTs. In the study by Brignola et al. [44], 87 patients were treated with mesalazine 3 g daily or placebo; the overall endoscopic or radiologic rates of severe recurrence at 12 months were 24% and 56%, respectively ($p < 0.004$). In the study by McLeod et al. [45], 163 patients were randomized. The recurrence rate (symptoms and endoscopic and/or radiological disease) in the treatment group (mesalamine 1.5 g twice daily [bid]) was 31% compared with 41% in the control group ($p = 0.031$) [45]. The French trial from the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) included 126 patients after resection, and reported an endoscopic recurrence in 50% and 63% in the mesalazine (1 g bid) and placebo groups, respectively ($p = 0.16$) at 12 weeks [46]. A large multicenter European trial enrolled 318 patients and found no significant difference in cumulative clinical relapse rates after 18 months in the mesalamine 4 g and placebo groups: 24.5% and 31.4%, respectively ($p = 0.1$) [47]. Hanauer et al. [48] evaluated the effect of either 6-mercaptopurine (6-MP) or mesalazine (3 g) compared with placebo and found no difference between mesalazine and placebo for endoscopic recurrence rate at 24 months (63% vs 64%, not significant [NS]). In a multicenter, randomized trial from Italy, endoscopic recurrence rates at 24 months were 52% and 85% in the mesalamine 2.4 g/day group compared with the no-treatment group (NS) [49]. Regarding the dose, a trial compared the effect of a high dose of mesalamine (4 g/day) versus a low dose of mesalamine (2.4 g/day); no difference was observed between the two groups for the rate of severe endoscopic outcomes or clinical recurrence [50]. More recently, a randomized, prospective, three-armed, unblinded study compared adalimumab (160/80/40 mg every other week [eow]), azathioprine (2 mg/kg/day), and mesalamine (3 g/day) [51]. The rate of endoscopic recurrence at 2 years was significantly lower in adalimumab (6.3%) compared with the azathioprine (64.7%) and mesalamine groups (83.3%), as was the quality of life [51].

In an updated meta-analysis from Cochrane [52], there was moderate certainty evidence suggesting that 5-ASAs are more effective for preventing clinical relapse than placebo. During a follow-up period of 12–72 months, 36% (131/361) of 5-ASA-treated patients relapsed compared with 43% (160/369) of placebo-treated patients (relative risk [RR] 0.83, 95% CI 0.72–0.96) [52]. The number needed to treat (NNT) to prevent one recurrence was 13 patients. The evidence for endoscopic remission was uncertain [52]. The risk of serious adverse events or patient withdrawal was not increased with mesalazine [52]. In a previous meta-analysis from Cochrane [53], the RR of severe endoscopic recurrence (Rutgeerts' score $\geq$ i3) was significantly lower with mesalazine (0.50; 95% CI 0.29–0.84) with an NNT of 8; however, the RR of any endoscopic recurrence was not significantly reduced (0.93; 95% CI 0.76–1.13) [53]. In a network meta-analysis of RCTs by Singh et al. in 2015 [54], mesalazine did not reduced the risk of endoscopic relapse compared with placebo (RR 0.67; 95% CI 0.39–1.08).

5.1.2 Sulfasalazine

The effect of sulfasalazine 3 g/day versus placebo on postoperative recurrence was studied by Ewe et al. [55] in 1989 in 232 patients. At 1 year, they observed a difference in the rate of recurrence (either clinical, radiologic, or endoscopic) with sulfasalazine over placebo (16 vs 28%) [55]. Bias in the definition of recurrence and significant loss to follow up and withdrawals made results difficult to interpret.

Altogether, despite being the most studied drugs for this indication, 5-ASAs have only demonstrated a very minor effect for postoperative recurrence prevention in some of the different meta-analyses conducted in this regard [52, 53, 56].

5.2 Corticosteroids

Two trials examined the effect of oral budesonide on rates of postoperative recurrence in CD. In a German multicenter, randomized, double-blind, placebo-controlled trial, 83 patients received either placebo or budesonide after ileal and/or colonic resection. The recurrence rate after 1 year based on endoscopic findings was not statistically different in the two groups [57]. Similarly, in the Swedish study by Hellers et al. [58], 129 patients were randomized to either oral budesonide or placebo; the frequency of endoscopic recurrence did not differ between the groups at 3 and 12 months.

According to these results, budesonide has no benefit in the prevention of endoscopic recurrence and is not recommended in this indication.

Table 3 Characteristics of trials evaluating endoscopic and/or clinical recurrence after surgery in Crohn's disease, according to pharmacological prophylactic treatments

Study	Drug regimen	Patients, *n*	Endoscopic recurrence *n* (%)		Clinical recurrence *n* (%)
			Any	Severe	
5-ASAs					
Ewe et al., 1989 [55]	Sulfasalazine 3 g/d vs placebo	232			18 (16) vs 34 (28) S
Caprilli et al., 1994 [49]	Mesalazine 2.4 g/d vs no treatment	110	M24: (52) vs (85) S	M24: (17) vs (38) S	M24: (18) vs (41) S
Brignola et al., 1995 [44]	Mesalamine 3 g/d vs placebo	87		M12: (24) vs (56) S	M12: 7 vs 17
McLeod et al., 1995 [45]	Mesalamine 3 g/d vs placebo	163	RR 0.635		27 (31) vs 31 (41) S
Florent et al., 1996 [46]	Mesalazine 2 g/d vs placebo	126	M3: (50) vs (63) ns		
Lochs et al., 2000 [47]	Mesalamine 4 g/d vs placebo	318			M18: 152 (24) vs 166 (31) ns
Caprilli et al., 2003 [50]	Mesalazine 4 g/d vs mesalazine 2.4 g/d	101	M12: > i0 (46) vs (62) S > i1 ns	M12: > i2: ns	
Hanauer et al., 2004 [48]	6-MP 50 mg/d, mesalamine 3 g/d, or placebo	131	M24: (63), (64) ns		M24: (58), (77) ns
Savarino et al., 2013 [51]	ADA 160/80/40 mg eow or AZA 2 mg/kg/d or mesalazine 3 g/d	51	M24: > i1 1 (6) vs 11 (65) vs 15 (83) S		M24: 2 (12) vs 11 (65) vs 9 (50) S
Corticosteroids					
Ewe et al., 1999 [57]	Budesonide 3 mg/d vs placebo	83	M12: 20 (57) vs 19 (70) ns		(19) vs (28) ns
Hellers et al., 1999 [58]	Budesonide 6 mg/d vs placebo	129	M12: (32) vs (65) ns		
Antibiotics					
Rutgeerts et al., 1995 [59]	Metronidazole (20 mg/kg) vs placebo	60	M3: 12 vs 21 (75) S	M3: 3 (13) vs 12 (43) S	
Rutgeerts et al., 2005 [60]	Ornidazole 1 g/d vs placebo	80	M12: 15 (54) vs 26 (79) S		M12: 3 (8%) vs 15 (38%) S
Herfarth et al., 2013 [62]	Ciprofloxacin vs placebo				
Thiopurines					
Hanauer et al., 2004 [48]	6-MP 50 mg/d, mesalamine 3 g/d, or placebo	131	M24: (43), (64) S		M24: (50), (77) S
Ardizzone et al., 2006 [63]	AZA 2 mg/kg/d vs mesalamine 3 g/d	142			M24: OR: 2.04; 95% CI 0.89–4.67, ns
Herfarth et al., 2006 [64]	AZA 2–2.5 mg/kg/d vs 5-ASA 4 g/d	81	M12: 9 (21) vs 9 (23) ns	M12: 2 (5) vs 6 (15)	M12: 2 (5) vs 5 (13) ns
D'Haens et al., 2008 [65]	AZA (100 mg/d < 60 kg or 150 mg/d > 60 kg) + metronidazole 250 mg tid 3 M vs placebo + metronidazole 250 mg tid 3 M	81	M12: 22 (55) vs 32 (78) S	M12: 6 (15) vs 8 (19.5)	M12: 3 (7.5) vs 7 (17)
Nos et al., 2000 [66]	AZA 50 mg/d vs mesalamine 3 g/d	39	M24: (64) vs (69) ns		M24: (36) vs (37) ns
Mowat et al., 2016 [67]	6-MP (1 mg/kg) vs placebo	240	M36: 29 (43) vs 28 (49) ns		M36: 16 (13) vs 26 (23) ns

Table 3 (continued)

Study	Drug regimen	Patients, *n*	Endoscopic recurrence *n* (%)		Clinical recurrence *n* (%)
			Any	Severe	
Biologics					
IFX					
Sorrentino et al., 2007 [75]	IFX 5 mg/kg and oral methotrexate 10 mg/w vs mesalamine 2.4 g/day	23	M24: (0) vs (75) S		
Regueiro et al., 2009 [71]	IFX 5 mg/kg vs placebo	24	M24: 1(9) vs 11 (85) S		M24: ns
Yoshida et al., 2012 [74]	IFX 5 mg/kg vs no treatment	31	M12: (21) vs (81) S		M12–M36: ns
Regueiro et al., 2016 [42]	IFX 5 mg/kg vs placebo	297	M16: (31) vs (60) ns	M16: (> i2) (19) vs (81)	M16: (13) vs (20) S
ADA					
Aguas et al., 2012 [77]	ADA 160/80/40 mg eow (observational)	29	M12: 6 (21)		M12: 4 (14)
Papamichael et al., 2012 [78]	ADA 160/80/40 mg eow (observational)	8	M6:1 M12: 2		
Savarino et al., 2013 [51]	ADA 160/80/40 mg eow or AZA 2 mg/kg/d or mesalazine 3 g/d	51	M12: 1 (6); 11 (65); 15 (83) S		
De Cruz et al., 2015 [69]	ADA 160/80/40 mg eow or AZA + metronidazole 3 M	101	M6: 6 (21) vs 33 (45) S	M6: (> i2) 1 (4) vs 6 (8)	M6: 5 (18) vs 16 (22) ns
López-Sanromán et al., 2017 [70]	ADA 160/80/40 mg eow or AZA + metronidazole 3 M	84	M12: 19 (42) vs 23 (59) ns		M6: ns M12: ns
VDZ					
Yamada et al., 2018 [79]	VDZ (observational)	22	M6–12: (≥ i1) (75)		

6-MP 6-mercaptopurine, *ADA* adalimumab, *AZA* azathioprine, *d* day, *eow* every other week, *IFX* infliximab, *M* month, *ns* non-significant, *OR* odds ratio, *RR* relative risk, *S* significant, *tid* three times a day, *VDZ* vedolizumab, *w* week

5.3 Antibiotics

Two studies from Leuven, Belgium, evaluated nitroimidazole antibiotics for the prevention of postoperative recurrence [59, 60]. The first study, in 1995, compared metronidazole (20 mg/kg) daily for 3 months versus placebo in 60 patients [59]. At week 12, 75% versus 52% of patients in the placebo group and the metronidazole group had endoscopic recurrent lesions in the neoterminal ileum, respectively ($p = 0.09$) [59]. Metronidazole therapy statistically reduced the clinical recurrence rates at 1 year (4% vs 25%). Reductions at 2 years (26% vs 43%) and 3 years (30% vs 50%) were not significant [59]. In a subsequent trial in 2005 [60], 80 patients were enrolled in an RCT to receive either ornidazole 1 g/day or placebo started within 1 week of resection and continued for 1 year. Ornidazole significantly reduced endoscopic recurrence at 12 months from 79% in the placebo group to 53.6% in the ornidazole group [60]. Patients withdrawal (RR 3.0) and adverse events (RR 2.4) were significantly greater with these nitroimidazole therapies relative to placebo [53]. More recently, in a retrospective single-center cohort in 70 patients with CD, the number of patients with ≥ i2 endoscopic recurrence within 12 months following ileal resection was significantly lower in patients who had received 3 months of metronidazole (7 of 35 patients; 20%) compared with the number in the control group (19 of 35 patients; 54.3%; $p = 0.0058$) [61].

In a pilot RCT [62], 33 patients with CD who had undergone surgery with ileocolonic anastomosis within the previous 2 weeks were randomized to treatment with ciprofloxacin (500 mg bid) or placebo for 6 months. Fourteen patients discontinued the study early. Endoscopic recurrence was observed in 3/9 (33%) patients in the ciprofloxacin group and 5/10 (50%) patients in the placebo group at 6 months after surgery ($p < 0.578$) [62]. Possible drug-associated adverse events occurred significantly more often in the ciprofloxacin group ($p < 0.043$) [62].

Nitroimidazole antibiotics are effective for preventing postoperative recurrence; however, short-term poor tolerance and long-term toxicity are limitations for their use in clinical practice. They may be useful as a bridge strategy shortly after surgery.

5.4 Thiopurines

Six controlled trials compared thiopurines (azathioprine or 6-MP) with placebo and/or mesalazine (Table 3). Hanauer et al. [48] found that 6-MP was more effective than placebo ($p < 0.05$) at preventing clinical and endoscopic recurrence over 2 years. In the study by Ardizzone et al. [63], no difference was observed in the efficacy of azathioprine and mesalamine in preventing clinical and surgical relapses after conservative surgery in 142 patients; no data were available regarding endoscopic recurrence. Herfarth et al. [64] published their results as a letter to the editor. Among 37 patients who completed the study, drug failure was found to be equally high in each group (azathioprine, 9 of 18; 5-ASA, 9 of 19; $p = 1.00$). Many patients withdrew because of adverse drug reactions [64]. A study by the Leuven team compared postoperative regimens with azathioprine or placebo in 81 patients who received metronidazole for the first 3 months in the two arms. Intention-to-treat analysis revealed endoscopic recurrence in 22 of 40 patients (55%) in the azathioprine group and 32 of 41 patients (78%) in the placebo group at 12 months ($p = 0.035$) [65]. Another randomized trial, only published in Spanish, studied 39 patients receiving either azathioprine (50 mg) or mesalazine; they failed to detect any significant difference between the two groups for endoscopic postoperative recurrence at 2 years [66]. Results should be interpreted with caution, as the dose of azathioprine was lower than recommended in CD [66]. More recently, the TOPPIC ('mercaptopurine versus placebo to prevent recurrence of CD after surgical resection') trial [67] enrolled 240 patients in 29 UK centers, randomly assigned to 6-MP or placebo. Over 3 years, 16 (13%) patients in the 6-MP group versus 26 (23%) patients in the placebo group had a clinical recurrence of CD and needed rescue treatment or surgical intervention (adjusted hazard ratio [HR] 0·54, 95% CI 0·27–1·06; $p = 0·07$); no difference was observed for endoscopic outcomes. In a subgroup analysis, three (10%) of 29 smokers in the 6-MP group and 12 (46%) of 26 in the placebo group had a clinical recurrence that needed treatment (HR 0·13, 95% CI 0·04–0·46) [67]. The authors concluded that 6-MP was effective in preventing postoperative clinical recurrence in smokers only.

Two meta-analyses were published in 2009, before the TOPPIC trial, with slight differences in the selection of the studies quoted above [53, 68]. The Cochrane meta-analysis [53] compared the effectiveness of azathioprine/6-MP with mesalamine and demonstrated no significant increase in the RR of clinical recurrence within 12 months (RR 1.43) with mesalamine but the RR of any endoscopic recurrence at 12 months was significantly increased with mesalamine relative to thiopurines (RR 1.45). This was not significant for more severe degrees of endoscopic recurrence [53]. In the meta-analysis by Peyrin-Biroulet et al. [68], in the overall analysis, thiopurines were more effective than control arms in the prevention of clinical recurrence at 1 year ($p = 0.021$; NNT 13) and in the prevention of severe endoscopic recurrence (i2–i4) at 1 year, but not effective in the prevention of more severe (i3–i4) recurrence at 1 year ($p = 0.13$). In the analysis restricted to comparisons with placebo arms, the efficacy of thiopurines was superior to that of placebo for clinical and endoscopic recurrence at 1 year ($p = 0.025$, RR 0.59, NNT 7; and $p = 0.0016$, RR 0.64, NNT 4, respectively) [53, 68]. Finally both meta-analyses highlighted the higher risk of adverse events compared with placebo or mesalazine [53, 68].

Few trials have compared thiopurines with drugs other than 5-ASA after surgery in CD patients. In the randomized study by Savarino et al. [51] comparing adalimumab, azathioprine, and mesalamine, adalimumab was significantly superior to thiopurines for endoscopic and clinical outcomes at 24 months. Moreover, no difference was observed in azathioprine-treated patients as compared with mesalamine-treated patients for endoscopic recurrence rates (OR 0.367; 95% CI 0.075–1.797) and clinical recurrence rates (OR 1.833; 95% CI 0.472–7.126) [51]. In a POCER study sub-analysis [69], efficacy of thiopurines and adalimumab was analyzed. Patients at high risk of recurrence (smokers, perforating disease, more than one operation) were treated after resection with 3 months of metronidazole together with either azathioprine 2 mg/kg/day or 6-MP 1.5 mg/kg/day [69]. Thiopurine-intolerant patients received adalimumab 160/80/40 mg eow. At 6 months, endoscopic recurrence (Rutgeerts score $\geq$ i2) occurred in 33/73 (45%) thiopurine-treated patients versus 6/28 (21%) adalimumab-treated patients (intention-to-treat; $p = 0.028$) [69]. In a recently published Spanish multicenter study [70], 84 patients were randomly assigned to receive either adalimumab 160/80/40 mg eow or azathioprine 2.5 mg/kg/day, both associated with metronidazole, after surgery. The inclusions were not restricted to patients with factors for high risk of recurrence [70], At 1 year, in the intention-to-treat analysis, therapy failed (endoscopic recurrence Rutgeerts i2b, i3 or i4) in 23/39 (59%) patients in the azathioprine group and in 19/45 (42%) patients in the adalimumab group ($p = 0.12$) [70].

At present, evidence for routine use of thiopurines as a prophylactic therapy in postoperative CD is heterogeneous and unconvincing.

5.5 Anti-TNF Agents

5.5.1 Infliximab

In 2009, in a pilot RCT, the efficacy of infliximab was assessed in 24 patients in the prevention of postoperative recurrence [71]. Patients were randomly assigned to receive either infliximab (5 mg/kg) or placebo within 4 weeks after surgery, for 1 year. Half of the patients had concomitant immunomodulators in both groups, while there were more active smokers in the infliximab group. The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (1/11 patients; 9.1%) than in the placebo group (11/13 patients; 84.6%). It was not significant for clinical remission [71]. Moreover, the use of anti-TNF within 4 weeks after intestinal resection was not associated with postoperative complications [72]. In the long-term follow-up of this study [73] over 4 years, of the 12 patients who received postoperative infliximab for 1 year, five stopped infliximab. These five patients all had endoscopic recurrence and four had another surgery. Conversely, of the seven who continued infliximab, none required surgery and all maintained the same endoscopic score; two of these patients (i0) ultimately stopped infliximab and had endoscopic recurrence (i3) [73].

In a Japanese trial, 31 patients were randomly assigned after surgery to receive infliximab (5 mg/kg every 8 weeks for 36 months) or no treatment [74]. There was no significant difference for the primary CDAI endpoint at 1 year; however, the infliximab group achieved higher endoscopic remission at 12 months: 78.6% versus 18.8% ($p = 0.004$) [74]. In an open-label trial, Sorrentino et al. [75] studied seven CD patients treated with infliximab (5 mg/kg) and oral methotrexate 10 mg/week after surgery, compared with 16 patients treated with mesalamine 2.4 g/day. At 2 years, none of the infliximab/methotrexate-treated patients had clinical or endoscopic recurrence, 75% of the patients in the mesalamine group had clinical or endoscopic recurrence [75]. The same group observed in the long-term follow-up of these patients that discontinuation of infliximab after 3 years of treatment caused endoscopic recurrence after 4 months in 10/12 patients (83%) [76]. All ten patients were re-treated successfully with infliximab. More recently, the PREVENT phase III study [42] randomly assigned 297 patients with at least one risk factor for recurrence to infliximab (5 mg/kg) or placebo every 8 weeks. The primary endpoint was clinical recurrence. A smaller proportion of infliximab-treated patients had a clinical recurrence before or at week 76 compared with placebo-treated patients, but this difference was not statistically significant (12.9% vs 20.0%; $p = 0.097$) [42]. However, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based on Rutgeerts score $\geq$ i2 (22.4% vs 51.3%; $p < 0.001$) [42].

5.5.2 Adalimumab

In a first Spanish multicenter prospective observational trial [77], 29 CD patients considered at high risk (two or more risk factors) received adalimumab (160/80/40 mg eow) after resection, half of whom had previously received infliximab. Of the 29 patients, six (20.7%) developed endoscopic recurrence after 1 year. During follow-up, five patients needed adalimumab dose intensification (40 mg/week) [77]. Another, open-label study included eight high-risk patients who had undergone ileocecal resection to receive adalimumab from postoperative day 14. At 6 months, endoscopic postoperative recurrence was seen in only one of eight patients, and a second patient developed endoscopic relapse at 24 months of treatment in the follow-up [78]. Three studies compared the efficacy of adalimumab and thiopurines in the postoperative setting [51, 69, 70]. In the randomized but unblinded and small sampled study by Savarino et al. [51], 1/16 (6.3%) patients treated with adalimumab had endoscopic recurrence over 2 years (score $\geq$ i2), compared with 11/17 (64.7%) patients in the azathioprine group (OR 0.036; 95% CI 0.004–0.347). In the analysis of adalimumab versus thiopurine-treated high-risk patients of the POCER trial, endoscopic recurrence at 6 months was significantly less frequent in patients treated with adalimumab, as stated above [69]. Complete mucosal endoscopic normality (Rutgeerts' score i0) occurred in 17/73 (23%) patients in the adalimumab group versus 15/28 (54%) in the azathioprine group ($p = 0.003$). The most severe recurrence (Rutgeerts' score i3 and i4) occurred in 8% versus 4%, respectively [69]. Thirdly, in the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis ulcerosa (GETECCU) study, at 1 year after surgery, in all patients regardless of their recurrence risk, in the intention-to-treat analysis, adalimumab was not superior to azathioprine to prevent endoscopic recurrence [70].

There is no RCT that evaluated adalimumab for the prevention of recurrence after surgery for CD.

Overall, in the network meta-analysis based on Bayesian analyses combining direct and indirect treatment comparisons, anti-TNF monotherapy was the most effective pharmacologic intervention for postoperative prophylaxis, with large effect sizes relative to all other strategies (clinical relapse: RR 0.02–0.20; endoscopic relapse: RR 0.005–0.04) [54]. Taken together, anti-TNF agents are currently the most potent drug class to prevent endoscopic postoperative recurrence in CD patients at risk of postoperative recurrence.

5.6 New Biologic Agents

The use of vedolizumab was investigated in a referral center in the postoperative setting [79] among a cohort of 203 patients that underwent a CD-related surgery between 2014 and 2016. In this time frame, 22 of these patients

Table 4 Summary of guidelines on postoperative prophylactic treatments after surgery in Crohn's disease from major gastroenterology bodies

Pharmacologic agent	ECCO, 2016	AGA, 2017	ACG, 2018	NICE, 2019
Mesalazine	High-dose mesalazine is an option for patients with an isolated ileal resection	Suggests against using mesalamine	Limited benefit, but is an option for patients with an isolated ileal resection and no risk factors	No guideline on mesalazine
Antibiotics	Imidazole antibiotics have been shown to be effective after ileocolic resection but are less well tolerated	Patients at lower risk or who place a higher value on avoiding the small risk of adverse events of thiopurine or anti-TNF treatment may choose nitroimidazole antibiotics	Imidazole antibiotics at doses between 1 and 2 g/day can be used after small intestinal resection	Consider azathioprine in combination with up to 3 months' postoperative metronidazole
Thiopurines	The drugs of choice are thiopurines or anti-TNFs	Suggests using anti-TNF therapy and/or thiopurines over other agents	May be used, more effective than mesalamine or placebo Not effective at preventing severe endoscopic recurrence	Consider azathioprine in combination with up to 3 months' postoperative metronidazole if tolerated
Anti-TNF agents	The drugs of choice are thiopurines or anti-TNFs	Suggests using anti-TNF therapy and/or thiopurines over other agents	Should be started in high-risk patients Although data are lacking, should be combined with an immunomodulator	Do not offer biologics to maintain remission

ACG American College of Gastroenterology, *AGA* American Gastroenterological Association, *ECCO* European Crohn's and Colitis Organization, *NICE* National Institute for Health and Care Excellence (UK), *TNF* tumor necrosis factor

received vedolizumab and 58 received anti-TNF agents as postoperative treatment. The rate of endoscopic remission at 6–12 months (defined as a simple endoscopic score for CD of 0) in the vedolizumab group was significantly lower than in the anti-TNF agent group (25% vs 66%, $p = 0.01$) [79]. Vedolizumab use was the only factor that was associated with an increased risk of endoscopic recurrence on both univariate ($p = 0.005$) and multivariate analysis (OR 5.77; 95% CI 1.71–19.4; $p = 0.005$). To lower confounding factors, a propensity score-matched analysis was performed and indicated lower rates of endoscopic remission (25% vs 69%, $p = 0.03$) in patients treated with vedolizumab compared with anti-TNF agents [79]. However, as described before [39], the presence of submucosal lymphocytic plexitis in the proximal surgical margin has been significantly associated with higher risks for postoperative recurrence after ileocolonic resection. These observations warrant further prospective trials with vedolizumab, which may block lymphocytic trafficking in the postoperative bowel. No study has evaluated the use of ustekinumab in the postoperative setting so far.

5.7 Interventions on Microbiota

There is scientific evidence that may support interventions on microbiota after intestinal resection in CD. In the REMIND cohort study, at the time of surgery, several bacterial taxa associated with endoscopic recurrence were identified [80]. Also, endoscopic recurrence was associated with strong changes in ileal mucosa-associated microbiota, consistent with those observed in ileal CD compared with healthy subjects with a reduction in alpha diversity, and a decrease in several members within the Firmicutes phylum [80]. However, unlike nitroimidazole antibiotics, *probiotics* failed to demonstrate their superiority over placebo to maintain postoperative remission in CD. Five studies evaluated the effect of probiotics, respectively, *Lactobacillus johnsonii* [81, 82], *L. rhamnosus* [83], and probiotic cocktails Synbiotic 2000 [84] and VSL#3 [85]. The trials were negative. Accordingly, two meta-analyses concluded that probiotics were ineffective to prevent postoperative recurrence in CD [53, 86]. A phase II randomized trial (NCT02417974) is currently ongoing to investigate if *fecal microbiota therapy* can reduce the risk of endoscopic recurrence of CD in patients after intestinal resection.

5.8 Nutritional Supplements

The efficacy of *curcumin*, known for its anti-inflammatory properties, was investigated in a French multicenter RCT [87]. Sixty-two consecutive patients with CD undergoing bowel resection received azathioprine (2.5 mg/kg) and were randomly assigned to groups given oral curcumin (3 g/day,

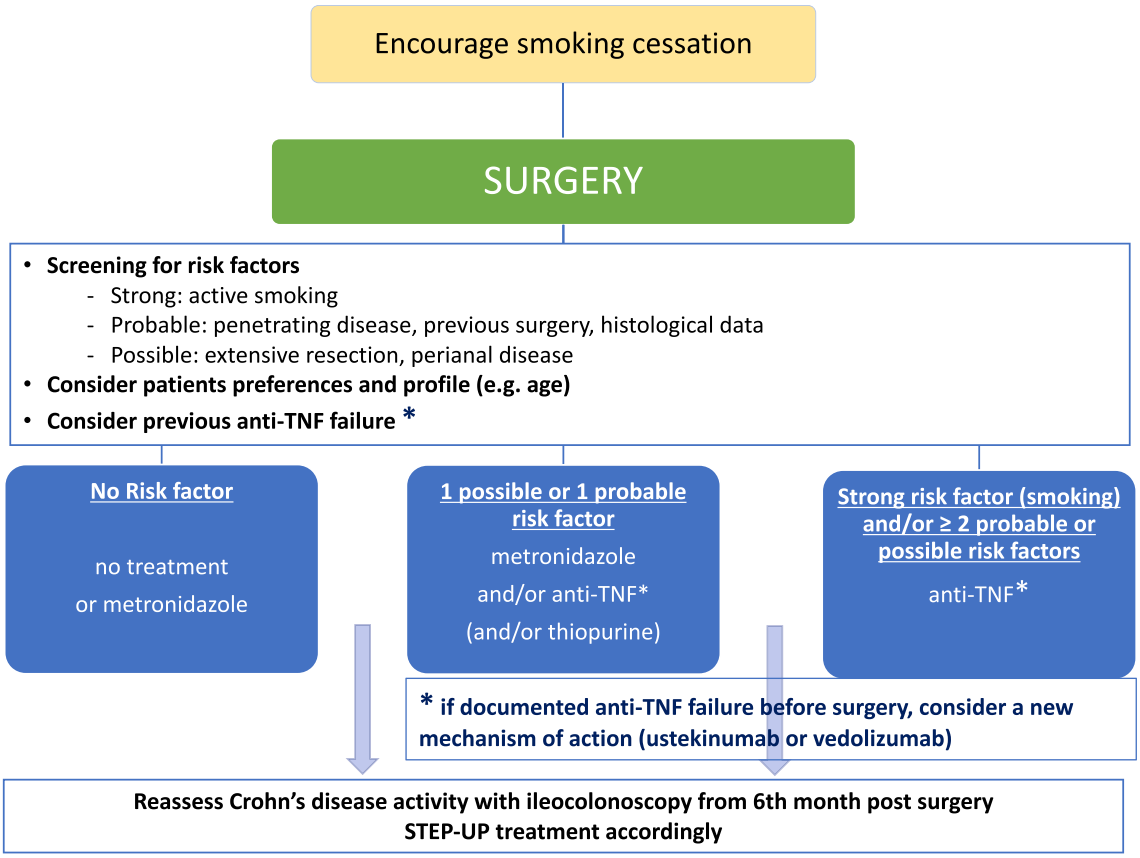


Fig. 1 Decision algorithm for prevention of postoperative recurrence in Crohn's disease in clinical practice (expert opinion)

$n = 31$) or an identical placebo ($n = 31$) for 6 months. At 6 months, endoscopic recurrence (score ≥ i2) occurred in 18 (58%) patients receiving curcumin and 21 (68%) patients receiving placebo ($p = 0.60$) [87]. A clinical recurrence of CD was observed in 45% of patients receiving placebo and 30% of patients receiving curcumin ($p = 0.80$). The study was discontinued after interim analysis due to futility [87].

The potential anti-inflammatory effects of *vitamin D* were explored in a prospective, multicenter, placebo-controlled clinical trial including 143 CD patients with at least one risk factor for recurrence [88]. Patients were randomized to receive weekly 25.000 international units (IU) of vitamin D3 (cholecalciferol) or placebo for 6 months, without other CD medication. No difference was observed in the incidence and severity of endoscopic recurrence at 6 months between the two groups (Rutgeerts' score ≥ i2 in 87% and 82%, respectively, in vitamin D and placebo groups; $p = 0.22$). The cumulative clinical recurrence rates at week 26 were also comparable [88].

6 Current Management

The latest guidelines from the ECCO [2], from the American Gastroenterological Association (AGA) [89] Institute, and from the American College of Gastroenterology (ACG) [90] were published in 2016, 2017, and 2018, respectively (Table 4). All major bodies agree on tobacco cessation. Otherwise, recommendations on pharmacological drugs may vary regarding practical advice and levels of evidence. In patients with surgically induced remission of CD, the AGA suggests against using 5-ASA (conditional recommendation). High-dose mesalazine is an option for patients with an isolated ileal resection (EL2) in the ECCO consensus, and is an option for patients with an isolated ileal resection and no risk factors for recurrence in the ACG guidelines (conditional recommendation, moderate level of evidence). The AGA (moderate quality of evidence) and the ECCO (EL2) suggest anti-TNF therapy and/or thiopurines are the drugs of choice to prevent postoperative recurrence in patients with at least one risk factor, while, in high-risk patients, anti-TNF agents are proposed over thiopurines by the ACG (conditional recommendation, low level of evidence). Finally, the ECCO consider imidazole antibiotics have been shown to be effective after ileocolic resection but less well tolerated

(EL1); the ACG consider imidazole antibiotics can be used after small intestinal resection in CD patients to prevent recurrence (conditional recommendation, low level of evidence), and the AGA state that patients at lower risk for disease recurrence or who place a higher value on avoiding the small risk of adverse events with thiopurines and/or anti-TNF treatment may reasonably choose nitroimidazole antibiotics (for 3–12 months) (moderate level of evidence). The National Institute for Health and Care Excellence (NICE) guidelines from the British Society of Gastroenterology on "maintaining remission in Crohn's disease after surgery" were updated very recently in May 2019 [91] (Table 4). To maintain remission in people with ileocolonic CD who have had complete macroscopic resection within the last 3 months, they recommend to "consider azathioprine in combination with up to 3 months' postoperative metronidazole", and they advise against biologics: "do not offer biologics to maintain remission after complete macroscopic resection of ileocolonic Crohn's disease" [91]. Thiopurines are certainly cost effective. In a recent cost-utility analysis [92], the strategy of thiopurines immediately post-surgery plus endoscopy-guided biological step-up therapy dominated the other two strategies of endoscopy-guided full step-up therapy and combination therapy immediately post-surgery. However, long-term analyses would be necessary to properly address the costs in view of rehospitalization and recurrent surgery costs, specifically for each country. Current strategies should also be balanced with the significant cost savings induced by the spread of biosimilars of infliximab and adalimumab [93].

New treatment algorithms to prevent postoperative recurrence are needed, considering the following parameters: growing knowledge on the efficacy and safety profiles of the treatments previously reviewed, stratification of patients according to their risk factors, new profiles of patients going to surgery (previous exposure to more treatments, especially anti-TNF agents), release of biosimilars and new biologics, and patients' age and preferences (Fig. 1).

Given the efficacy profile of anti-TNF agents, we are moving towards their increasing use to prevent postoperative recurrence. In the proposed algorithm, according to our clinical practice, we divided patients into three groups depending on the presence and weight of risk factors, while also considering previous anti-TNF failure (Fig. 1). In the postoperative setting, primary non-response before surgery may potentially not be due only to pharmacodynamics failure of anti-TNF but also to an established fibro-stenotic disease, potentially making the drug a good option after resection. On the other hand, when documented anti-TNF failure despite appropriate drug management was observed, vedolizumab (scarce, disappointing data) or ustekinumab (no data) may be considered. As very few data are available on new biologic agents with other mechanisms of action, we cannot provide more rigorous evidence. Also, strategies based on risk stratification and previous treatments await validation in clinical trials. Whatever the choice of prophylactic therapy, a step-up approach based on endoscopic evaluation (and optional early fecal calprotectin), and reassessment of treatment choice, accordingly, is the best strategy. On the other hand, in the near future, given the wider use of biologics in the postoperative setting, we may move towards top-down strategies in remitters. These new approaches will require clinical trials to validate their efficacy.

Compliance with Ethical Standards

Conflicts of interest LV has received lecture fees from Abbvie, Ferring, Mayoli, MSD, Pfizer, Janssen, and Takeda; consulting fees from Abbvie, Ferring, Gilead, Janssen, and Takeda; research grants from MSD, Pfizer, and Takeda. LPB has received consulting fees from AbbVie, Amgen, Biogaran, Biogen, Boerhinger-Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Forward Pharma, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lycera, Merck, Lilly, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilège, Samsung Bioepis, Sandoz, Takeda, Therakos, Tillots, UCB Pharma, and Vifor, and lecture fees from AbbVie, Ferring, H.A.C. Pharma, Janssen, Merck, Mitsubishi, Norgine, Takeda, Therakos, Tillots, and Vifor.

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