Journal of Crohn's and Colitis, 2023, **17**, 1707–1722
https://doi.org/10.1093/ecco-jcc/jjad053
Advance access publication 18 April 2023
ECCO Scientific Workshop Paper

Results of the Eighth Scientific Workshop of ECCO: Prevention and Treatment of Postoperative Recurrence in Patients With Crohn's Disease Undergoing an Ileocolonic Resection With Ileocolonic Anastomosis

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Abstract

Despite the introduction of biological therapies, an ileocolonic resection is often required in patients with Crohn's disease [CD]. Unfortunately, surgery is not curative, as many patients will develop postoperative recurrence [POR], eventually leading to further bowel damage and a decreased quality of life. The 8th Scientific Workshop of ECCO reviewed the available scientific data on both prevention and treatment of POR in patients with CD undergoing an ileocolonic resection, dealing with conventional and biological therapies, as well as non-medical interventions, including endoscopic and surgical approaches in case of POR. Based on the available data, an algorithm for the postoperative management in daily clinical practice was developed.

Key Words: Crohn's disease; postoperative; recurrence; prevention; treatment

1. Introduction

Despite the introduction of biological therapies, the majority of patients with Crohn's disease [CD] will need to undergo a bowel resection throughout the course of their disease. Although endoscopic remission can more frequently be achieved with biological therapies, whether this may alter the natural history of CD remains of debate.[1] Although recent data suggest a decrease in primary resection rates, a clear link with the introduction of biological therapies has not been established.[2–9]

As the terminal ileum and right colon are involved in many patients with CD, the most commonly performed surgical procedure is an ileocaecal or ileocolonic resection [ICR] with ileocolonic anastomosis.[10] Unfortunately, such a procedure is not an ultimate cure for CD, as many patients will develop postoperative recurrence [POR] that may have a major influence on their personal and socioeconomic life. Therefore, interventions that decrease the risk of further bowel damage are needed.[10,11]

A major question from both an economic and safety point of view is the selection of patients who would benefit most from immediate postoperative prophylactic therapy.[12] The few validated clinical predictors of postoperative CD recurrence [active smoking, penetrating disease and previous ICRs] only have modest predictive power.[13–15] Some gastroenterologists discontinue CD-related therapy in the immediate postoperative phase and introduce immunosuppressive [mostly thiopurines or biological] therapy only after demonstrating endoscopic POR 6–12 months after surgery [endoscopy-driven postoperative prophylactic therapy]. However, an increasing number of gastroenterologists start prophylactic immunosuppressive therapy in the immediate postoperative phase [systematic postoperative prophylactic therapy]. The European Crohn's and Colitis Organisation [ECCO] guidelines state that prophylactic treatment is recommended after an ICR in patients with at least one risk factor for POR.[13] The presence of risk factors is also included as guidance for postoperative management in the French, Spanish and British guidelines.[16–18] In contrast, the American Gastroenterology Association [AGA] suggests early pharmacological prophylaxis in all patients with surgically induced remission of CD, regardless of the presence of risk factors.[19] However, in a commentary to this statement that was based on a very low quality of evidence, the authors mention that prophylactic therapy might be withheld in patients with a lower risk of recurrence, especially if these patients want to avoid the potential risk, even low, of adverse events linked to pharmacological prophylaxis. Indeed, increased use of biological therapy will not only lead to higher healthcare costs, but also serious adverse events associated with these treatments. The latter also makes it difficult to convince a patient to start such therapy after a surgical intervention with no residual inflammation. In this paper, we present an expert review of the available scientific data on both prevention and treatment of POR in patients with CD undergoing an ICR. We refer to data on conventional and biological therapies, as well as to non-medical interventions, including endoscopic and surgical approaches in the case of POR. Finally, we propose a postoperative strategy for CD patients undergoing ICR. Of note, if not specifically mentioned, endoscopic POR was regarded as a Rutgeerts score ≥i2, severe endoscopic recurrence as a Rutgeerts score ≥i3 and endoscopic remission as a Rutgeerts score <i2.[20] However, it must be mentioned that this postoperative endoscopic recurrence score has never been validated.

2. Medical Prevention of Postoperative Recurrence

The potential of a wide variety of drugs in preventing POR has been evaluated in randomized controlled trials [RCTs] [Table 1]. The primary endpoint for most of these studies was endoscopic POR, as assessed by the Rutgeerts score.[20] From a conceptual point of view, one should 'avoid the development of new endoscopic lesions' after a 'curative' resection. Studies that have assessed the development of endoscopic POR showed that it may occur even a few weeks after surgery.[20,21] Therefore, preventive therapy may have to start soon after surgery to limit the development of endoscopic postoperative lesions.[22]

2.1. Antibiotics

The predominant microorganisms in the ileocolic region after an ICR are anaerobic and it is believed that bacterial antigens have a role in the pathogenesis of POR.[23] Nitroimidazolic antibiotics have a high antimicrobial activity against anaerobes and induce changes in the colonic microbiota.[21,24] The efficacy of metronidazole [given at 20 mg/kg/day for the first 3 months after ICR] was assessed in a placebo-controlled RCT in which patients were followed endoscopically at 3 months.[25] A nominally lower rate of endoscopic POR [52% vs 75%, $p = 0.09$], and a significantly lower rate of both severe endoscopic [13% vs 43%, $p = 0.02$] and histological POR [17% vs 54%, $p = 0.008$] was noted in the metronidazole group compared to the placebo group. However, a high rate of adverse events [57% vs 20%] was observed with metronidazole, including gastrointestinal intolerance, metallic taste and paraesthesia. In a similar placebo-controlled RCT, the same group evaluated ornidazole, another nitroimidazolic antibiotic, at a dose of 1 g/day for 1 year.[26] Significantly lower rates of endoscopic [54% vs 79%, $p = 0.037$] and clinical POR [8% vs 38%, $p = 0.0046$] at 1 year were observed in the ornidazole group, but adverse events were common and more patients in the ornidazole group dropped out from the study because of side effects [32% vs 13%, $p = 0.041$]. Of note, metronidazole has also been used in association with thiopurines and anti-tumour necrosis factor [anti-TNF] agents, as will be discussed below.[27–30]

Finally, ciprofloxacin has also been evaluated for prevention of POR in a pilot randomized, double-blind, placebo-controlled trial in 33 patients with CD who underwent ICR.[31] A similar endoscopic POR was observed for treatment and placebo groups after 6 months [65% vs 69%, $p < 0.805$] and a high rate of adverse events was described [58%].

2.2. Mesalazine

Although different doses of mesalazine have been used in the available studies,[32–35] the last meta-analysis from the Cochrane Library suggested that mesalazine is more effective than placebo in preventing clinical POR.[36] During a follow-up period of 12–72 months, 36% [131/361] of patients treated with mesalazine relapsed compared with 43% [160/369] of patients treated with placebo (relative risk [RR] 0.83, 95% confidence interval [95% CI] 0.72–0.96). The number needed to treat to prevent one recurrence was 13. However, for the prevention of endoscopic POR the evidence was uncertain. Similar findings were reported in a network meta-analysis, showing less clinical relapse but no difference in endoscopic POR compared with placebo [RR 0.67; 95% CI 0.39–1.08].[37]

Interestingly, studies using higher doses of mesalazine or with an earlier initiation of mesalazine after ICR did not show a higher efficacy.[38] However, the therapeutic effect of mesalazine may depend on the site of drug release. Indeed, it has been observed that mesalazine concentrations at the level of the ileocolic anastomosis are lower in patients with an end-to-end anastomosis as compared to patients with a side-to-side anastomosis.[39]

2.3. Corticosteroids

Oral budesonide was evaluated as prophylactic treatment for POR in two RCTs.[40,41] Hellers et al. randomized 129 patients who underwent ICR to budesonide 6 mg daily or placebo.[41] The frequency of endoscopic POR did not differ between

Table 1. Effectiveness of pharmacological interventions for the prevention and treatment of postoperative recurrence in patients with Crohn's disease. Only the most relevant supporting data are shown; placebo-controlled studies [or meta-analyses including placebo arm] are mentioned were available; if placebo-controlled studies were lacking, comparative evidence [to other treatment options] is shown.

	Prevention of POR			Treatment of POR		
Antibiotics						
Nitroimidazolic antibiotics	**Effective**			**No data**		
	RCT, $n = 60$ [Rutgeerts *et al.*, 1995][25]	Metronidazole [20 mg/kg/day] vs placebo	Reduced endoscopic [52% vs 75%, $p = 0.09$], severe endoscopic [13% vs 43%, $p = 0.02$] and histological [17% vs 54%, $p = 0.008$] POR at month 3			
	RCT, $n = 80$ [Rutgeerts *et al.*, 2008][26]	Ornidazole [1 g/day] vs placebo	Reduced clinical [8% vs 38%, $p = 0.0046$] and endoscopic [54% vs 79%, $p = 0.037$] POR at year 1			
Ciprofloxacin	**Not effective**			**No data**		
	RCT, $n = 33$ [Herfarth *et al.*, 2013][31]	Ciprofloxacin [500 mg/twice daily] vs placebo	Similar endoscopic [65% vs 69%, $p < 0.805$] POR at month 6			
Mesalazine	**Uncertain**			**Uncertain**		
	Network meta-analysis, 6 studies, $n = 811$ [Singh *et al.*, 2015][37]	Mesalazine/sulfasalazine vs placebo	Reduced clinical [RR 0.60, 95% CI 0.37–0.88] POR	RCT, $n = 78$ with endoscopic POR [Reinisch *et al.*, 2010][90]	Mesalazine vs azathioprine	No difference in treatment failure [11% vs 22%, $p = 0.19$] at year 1, but clinical POR more often with mesalazine; endoscopic improvement less frequent with mesalazine [34.4% vs 63.3%, $p = 0.023$]
	Network meta-analysis, 7 studies, $n = 766$ [Singh *et al.*, 2015][37]	Mesalazine/sulfasalazine vs placebo	Similar endoscopic [RR 0.67, 95% CI 0.39–1.08] POR	RCT, $n = 46$ with endoscopic POR [Orlando *et al.*, 2020][91]	Mesalazine vs azathioprine	No difference in treatment failure [21% vs 14%, $p = 0.702$] at year 1, but clinical POR more often with mesalazine; endoscopic improvement less frequent with mesalazine [8.3% vs 36.4%, $p = 0.035$]
	Meta-analysis, 5 studies, $n = 730$ [Gjuladin-Hellon *et al.*, 2019][36]	Mesalazine vs placebo	Reduced clinical [36% vs 43%, RR 0.83, 95% CI 0.72–0.96] POR after 12–72 months			
	Meta-analysis, 3 studies, $n = 537$ [Gjuladin-Hellon *et al.*, 2019][36]	Mesalazine vs placebo	Similar endoscopic [70% vs 73%, RR 0.83, 95% CI 0.56–1.23] POR after 12–72 months			
Corticosteroids	**Not effective**			**No data**		
	RCT, $n = 62$ [Ewe *et al.*, 1999][40]	Budesonide 1 mg 3×/day vs placebo	Similar clinical and/or endoscopic [57% vs 70%, p = ns] POR at year 1			

Table 1. Continued

	Prevention of POR			Treatment of POR		
	RCT, n = 129 [Hellers *et al.*, 1999][41]	Budesonide 6 mg/day vs placebo	Similar endoscopic POR at month 3 [31% vs 52%, p = ns] and month 12 [52% vs 58%, p = ns]			
Immunomodulators						
Methotrexate	**No data**			**No data**		
Thiopurines	**Effective**			**Effective**		
	Meta-analysis, 4 studies, n = 433 [Peyrin-Biroulet *et al.*, 2009][59]	Thiopurines vs placebo/mesalazine/metronidazole	Reduced clinical POR [mean difference 8%, 95% CI: 1–15%, p = 0.021]	RCT, n = 78 with endoscopic POR [Reinisch *et al.*, 2010][90]	Mesalazine vs azathioprine	No difference in treatment failure [11% vs 22%, p = 0.19] at year 1, but clinical POR less often with azathioprine; endoscopic improvement more frequent with azathioprine [34.4% vs 63.3%, p = 0.023]
	Meta-analysis, 3 studies, n = 293 [Peyrin-Biroulet *et al.*, 2009][59]	Thiopurines vs placebo/mesalazine/metronidazole	Reduced endoscopic POR [mean difference 15%, 95% CI 1.8–29%, p = 0.026]	RCT, n = 46 with endoscopic POR [Orlando *et al.*, 2020][91]	Mesalazine vs azathioprine	No difference in treatment failure [21% vs 14%, p = 0.702] at year 1, but clinical POR less often with azathioprine; endoscopic improvement more frequent with azathioprine [8.3% vs 36.4%, p = 0.035]
	Meta-analysis, 3 studies, n = 408 [Gjuladin-Hellon *et al.*, 2019][47]	Thiopurines vs placebo	Reduced clinical [51% vs 64%, RR 0.79, 95% CI 0.67–0.92] POR after 12–36 months			
	Meta-analysis, 2 studies, n = 321 [Gjuladin-Hellon *et al.*, 2019][47]	Thiopurines vs placebo	No reduction in endoscopic [67% vs 75%, RR 0.85, 95% CI 0.64–1.13] POR after 12–36 months			
Anti-TNF	**Effective**			**Effective**		
	RCT, n = 297 [Reguiero *et al.*, 2016][56]	Infliximab vs placebo	No difference in clinical [12.9% vs 20%, p = 0.097] POR, but clear reduction of endoscopic [30.6% vs 60%, p < 0.002] POR at week 76	Meta-analysis, 2 studies, n = 50 patients with endoscopic POR [Carla-Moreau *et al.*, 2015][48]	Infliximab vs control arms [azathioprine or mesalazine]	Infliximab more effective in treating endoscopic POR [OR 16.64; 95% CI 2.51–110.27]
				Retrospective cohort, n = 179 patients with endoscopic POR [Cañete *et al.*, 2020][99]	Observational, mean follow-up 51 months [both infliximab, n = 83, and adalimumab, n = 96]	Endoscopic improvement in 61%, including 42% achieving endoscopic remission; better outcomes with concomitant use of thiopurines and with infliximab [vs adalimumab]; no impact of pre-operative anti-TNF exposure
Ustekinumab	**Uncertain**			**Uncertain**		
	Retrospective cohort, n = 63 [Buisson *et al.*, 2021][60]	Observational, ustekinumab [n = 32] vs azathioprine [n = 31]	Reduced endoscopic [28% vs 54.5%, p = 0.029] POR at month 6	Retrospective case-series, n = 15 with clinical and endoscopic POR [Tursi *et al.*, 2021][100]	Observational	Clinical remission in 12/15 at a median time of 6 months; endoscopic remission in all 11 patients with colonoscopy during follow-up

Table 1. Continued

	Prevention of POR			Treatment of POR		
	Retrospective cohort, *n* = 40 [Manosa *et al.*, 2022][63]	Observational, median follow-up 17 months	Clinical POR in 32% at month 12, and endoscopic POR in 42% within 18 months			
	Retrospective cohort, *n* = 297 [Yanai *et al.*, 2022][62]	Observational, ustekinumab [*n* = 34] and vedolizumab [*n* = 39] vs anti-TNF [*n* = 224]	Endoscopic POR in overall population was 41.8% at year 1, with no differences between ustekinumab and anti-TNF [OR 1.86, 95% CI 0.79–4.38]			
Vedolizumab	**Uncertain**			**Uncertain**		
	Retrospective cohort, *n* = 80 [Yamada *et al.*, 2018][61]	Observational, vedolizumab [*n* = 22] vs anti-TNF [*n* = 58]	Endoscopic remission at month 6–12 less frequent compared to anti-TNF [25% vs 66%, *p* = 0.01]	Retrospective cohort, *n* = 58 with endoscopic POR [Macaluso *et al.*, 2022][102]	Observational, mean follow-up 25 months	Endoscopic improvement in 48% after a mean of 16 months; clinical failure in 19% after 1 year; new resection needed in 12%
	Retrospective cohort, *n* = 25 [Manosa *et al.*, 2022][63]	Observational, median follow-up 26 months	Clinical POR in 30% at month 12, and endoscopic POR in 40% within 18 months			
	Retrospective cohort, *n* = 297 [Yanai *et al.*, 2022][62]	Observational, ustekinumab [*n* = 34] and vedolizumab [*n* = 39] vs anti-TNF [*n* = 224]	Endoscopic POR in overall population was 41.8% at year 1, with no differences between vedolizumab and anti-TNF [OR 0.55, 95% CI 0.25–1.19]			

Note: endoscopic improvement is defined as a reduction of the Rutgeerts score of 1 point or more.
Abbreviations: CI: confidence interval, CFU: colony-forming units, ns: non-significant, POR: postoperative recurrence, RCT: randomized controlled trial, RR: relative risk, TNF: tumour necrosis factor.

the two groups at 3 months [budesonide 31% vs placebo 35%] and 12 months [52% vs 58%]. Ewe et al. conducted a multicentre, randomized, double-blind, placebo-controlled trial, evaluating the effectiveness of budesonide 3 mg daily in preventing POR.[40] The recurrence rate after 1 year [endoscopic and/or clinical] was 57% in the budesonide group and 70% in the placebo group without a statistically significant difference. Data on the role of prednisone are lacking.

2.4. Immunomodulators

The efficacy of thiopurines [azathioprine, mercaptopurine] to prevent POR has been assessed in several RCTs.[27,28,42–45] D'Haens *et al.* compared metronidazole 250 mg/8 h alone or combined with azathioprine [2–2.5 mg/kg/day], observing significantly lower rates of endoscopic POR at 1 year with a combination of azathioprine and metronidazole [43.7% vs 69.0%; $p = 0.004$].[27] Mañosa *et al.* carried out an RCT in which the efficacy of azathioprine in monotherapy [2.5 mg/kg/day] was compared to azathioprine plus metronidazole [20 mg/kg/day].[28] Although they observed numerical lower rates of endoscopic POR at 6 and 12 months in the combination group [28% vs 44% and 36% vs 56%, respectively], these differences were not statistically significant. In the largest double-blinded placebo-controlled RCT to date [$n = 240$], 13% of patients treated with mercaptopurine vs 23% of patients treated with placebo had a clinical POR after 3 years, but the difference was not statistically significant.[46]

The most recent Cochrane meta-analysis concluded that thiopurines are more effective than placebo in preventing clinical POR after 12–36 months of follow-up [51% vs 64%, RR 0.79, 95% CI 0.67–0.92].[47] A significant difference between thiopurines and placebo in endoscopic POR could, however, not be observed. Other meta-analyses also included mesalazine and anti-TNF as controls.[37,48–50] Whereas the reduction in clinical POR was not consistently significant, azathioprine does seem to prevent endoscopic POR more often compared with mesalazine, but less often compared with anti-TNF [see below].

Of note, the role of thioguanine and methotrexate in the prevention of POR has not been evaluated.

2.5. Anti-tumour necrosis factor therapy

A few prospective studies and a small open-label RCT suggested a potential role for anti-TNF in preventing POR.[51–55] PREVENT, a large double-blind, placebo-controlled trial evaluating postoperative infliximab in 297 patients with CD, failed to demonstrate a statistically significant reduction in clinical POR at 76 weeks (a ≥70-point increase from baseline with a total Crohn's Disease Activity Index [CDAI] score ≥200), yet showed a clear reduction in endoscopic POR [30.6% vs 60.0%, $p < 0.001$].[56] Importantly, none of the patients received a classical intravenous induction with infliximab [all started immediately with infliximab 5 mg/kg every 8 weeks] and observed clinical relapse rates were quite low, although patients were enrolled based on the presence of at least one risk factor for recurrence.

For adalimumab, no placebo-controlled RCTs have been performed to date. Savarino *et al.* performed a small three-arm RCT comparing postoperative use of adalimumab [160/80/40 mg every other week, $n = 16$] against azathioprine [2 mg/kg/day, $n = 17$] and mesalazine [3 g/day, $n = 18$] in preventing endoscopic and clinical POR with a 2-year follow-up.[45] The rate of endoscopic POR was significantly lower in patients treated with adalimumab [6.3%] compared with azathioprine (64.7%; odds ratio [OR] = 0.036 [95% CI 0.004–0.347]) and mesalazine (83.3%; OR = 0.013 [95% CI 0.001–0.143]). There was a significantly lower proportion of patients in clinical POR [Hanauer rating scale ≥2] in the adalimumab group [12.5%] compared with azathioprine (64.7%; OR = 0.078 [95% CI 0.013–0.464]) and mesalazine (50%; OR = 0.143 [95% CI 0.025–0.819]). Finally, quality of life was better in the adalimumab group than in the azathioprine (OR = 0.028 [95% CI 0.004–0.196]) and mesalazine (OR = 0.015 [95% CI 0.002–0.134]) groups. In the POCER study, endoscopic POR occurred in 33/73 [45%] thiopurine-treated patients vs 6/28 [21%] adalimumab-treated patients [intention-to-treat; $p = 0.028$].[57] However, this study was not designed to compare the outcome of different medical therapies. In a further RCT comparing adalimumab and thiopurines for the prevention of POR, 84 patients were randomly assigned to receive postoperative therapy with either adalimumab 160/80/40 mg every other week or azathioprine 2.5 mg/kg/day, both associated with a 3-month course of metronidazole.[30] In both intention-to-treat and per-protocol analyses, no differences in the rate of endoscopic POR [defined by a Rutgeerts score ≥i2b] or severe endoscopic POR were observed between the two study groups.

One network meta-analysis was unable to draw conclusions as to which treatment [mesalazine, antibiotics, budesonide, immunomodulators or anti-TNF] was most effective in preventing clinical relapse and endoscopic relapse due to low-certainty evidence in the networks,[58] whereas other meta-analyses showed a benefit of anti-TNF compared to mesalazine and thiopurines.[37,49,50,59] Recently, Beelen *et al.* performed a meta-analysis using individual participant data derived from six original RCTs that compared thiopurines and anti-TNF agents for the prevention of POR in different subpopulations, yielding 645 participants.[50] A superior effect was demonstrated for anti-TNF compared with thiopurines for clinical POR [RR 0.50; 95% CI 0.26–0.96], endoscopic POR [RR 0.52; 95% CI 0.33–0.80] and severe endoscopic POR [RR, 0.41; 95% CI 0.21–0.79]. In Poisson regression analysis, previous exposure to anti-TNF and penetrating disease behaviour were associated with endoscopic POR. The advantage of anti-TNF agents as compared with thiopurines was observed in both low- and high-risk groups, confirming the superiority of anti-TNF at preventing both endoscopic and clinical POR after ICR.

2.6. Ustekinumab and vedolizumab

Data reporting on the efficacy of ustekinumab or vedolizumab in the setting of POR are extremely limited. Buisson *et al.* retrospectively collected data from 63 consecutive patients treated with ustekinumab [$n = 32$] or azathioprine [$n = 31$] after ICR in nine centres.[60] The primary endpoint was endoscopic POR at 6 months. After adjusting according to the propensity score analysis for the main risk factors [smoking, fistulizing phenotype, prior bowel resection, resection length >30 cm and two or more biologics before surgery] and for the use of thiopurines or ustekinumab prior to surgery, the rate of endoscopic POR at 6 months was lower in patients treated with ustekinumab compared to patients treated with azathioprine [28.0% vs 54.5%, $p = 0.029$]. In another retrospective study, Yamada *et al.* compared endoscopic remission rates, defined as a simple endoscopic score for CD [SES-CD] of 0, at 6–12 months after surgery, between 22 patients

receiving vedolizumab and 58 patients receiving anti-TNF.[61] The rate of endoscopic remission in the vedolizumab group was significantly lower as compared to the anti-TNF group [25% vs 66%, $p = 0.01$]. Vedolizumab use was the only factor associated with endoscopic POR in multivariate analysis [OR 5.77, 95% CI 1.71–19.4, $p = 0.005$]. The results were supported by a propensity score-matched analysis demonstrating lower rates of endoscopic remission [25% vs 69%, $p = 0.03$]. In contrast, a large retrospective multicentre European cohort analysis [$n = 297$] showed similar endoscopic POR rates at 1 year in patients on early prophylaxis with anti-TNF, ustekinumab and vedolizumab.[62] Furthermore, the results of a retrospective ENEIDA cohort study in 40 patients treated with ustekinumab and 25 treated with vedolizumab for the prevention of POR showed an endoscopic POR of 40% for vedolizumab and 42% for ustekinumab within 18 months after surgery.[63] These preliminary data support the potential usefulness of both ustekinumab and vedolizumab for the prevention of POR. However, further prospective [preferable randomized] investigation of larger populations is certainly required.

3. Non-Pharmacological Prevention of Postoperative Recurrence

3.1. Smoking discontinuation

The best described environmental factor affecting the outcome of CD, including in the postoperative setting, is tobacco smoking. Undeniably, continued smoking results in a worse disease course as well as in a higher risk of POR after ICR.[64–66] The cumulative rates of clinical and surgical POR are consistently elevated in smokers than in non-smokers, with a marked higher risk of symptomatic relapse in heavy smokers [smoking more than 15 cigarettes per day] than in mild smokers.[67–70] The most recent meta-analysis reported an increased odds of a flare after ICR [OR 1.97; 95% CI 1.36–2.85], and need for second surgery [OR 2.17; 95% CI 1.63–2.89] in smokers compared to non-smokers.[66] Interestingly, rates of postoperative relapse were significantly lower among ex-smokers than among smokers. So, smoking cessation is beneficial at any stage, including in the perioperative setting.[71–73] Unfortunately, there is poor awareness among patients of the benefits of smoking cessation,[74,75] and measures to help patients stop are underused.[76] Nevertheless, when active measures are employed, significant numbers of smoking cessation can be achieved. In the TABACROHN study, 31% of 408 patients did stop initially, with 23% still abstinent after 18 months of follow-up.[77] Without support, the likelihood of long-term abstinence in smokers attempting to stop was quite low, namely 12% after 1 year.[78] Efforts should direct better communication techniques to educate patients on the widespread health risks [including postoperative CD recurrence] of smoking in parallel with assistance to quit smoking by offering counselling and referral to a smoking cessation service.

3.2. Nutrition

Some studies have evaluated the benefit of an elemental diet on POR. One study compared 20 patients who continuously received enteral nutritional therapy, and 20 who had neither nutritional therapy nor food restriction, and found a significantly reduced endoscopic POR 1 year after ICR in the intervention group [30% vs 70%, $p = 0.027$].[79] A small retrospective study found a nominally lower rate of endoscopic POR 1–2 years after ICR in patients who adhered to an elemental diet as compared to patients who did not [14.3% vs 41.2%, $p = 0.078$].[80]

3.3. Complementary alternative medicines

Several probiotics evaluated for the prevention of POR include a multistrain probiotic containing eight different probiotics [*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*],[81] *Lactobacillus johnsonii*,[82] *Lactobacillus rhamnosus* strain GG,[83] and Synbiotic 2000 [a mixture of probiotics and prebiotics].[84] None of these studies found a significant effect. A small prospective, single-blind study suggested lower clinical and endoscopic POR in patients treated with *Tripterygium wilfordii*, a vine used in traditional Chinese medicine.[85] However, in a follow-up study, *Tripterygium wilfordii* was less efficacious than azathioprine in preventing endoscopic POR.[86]

Curcumin, the anti-inflammatory component of the turmeric plant, was no more effective than placebo in preventing POR.[87] More recently, postoperative treatment with a high-dose of vitamin D did not reduce endoscopic or clinical POR compared to placebo.[88]

Finally, different approaches that may impact on quality of life after surgery, such as sport and adapted physical activity, should also be recommended, even though no data are available on their impact on the risk of POR.[89]

4. Medical Treatment of Postoperative Recurrence

Data on the medical treatment of POR are generally scarce and of limited quality. The wide heterogeneity of definitions used for disease recurrence and treatment outcomes further complicates interpretation of the available studies. Most of the current evidence is for biological treatment with anti-TNF [Table 1].

4.1. Antibiotics

There are no data supporting the use of antibiotics in the treatment of POR.

4.2. Mesalazine

Results from two comparative RCTs suggest a potential but limited benefit of mesalazine in the treatment of postoperative CD, but placebo-controlled studies are lacking.[90,91] Reinisch *et al.* compared the efficacy of mesalazine and azathioprine in 78 patients with endoscopic but no clinical POR.[90] Treatment failure, defined as clinical recurrence or study drug discontinuation after 1 year, was overall low and comparable between mesalazine- and azathioprine-treated patients [11% vs 22%; $p = 0.19$]. Similar results were reported by Orlando *et al.* in 46 patients with severe endoscopic CD recurrence, showing no differences in therapeutic failure after 1 year of treatment with either high-dose mesalazine or azathioprine [21% vs 14%; $p = 0.702$].[91] In both studies, therapeutic failure was more often driven by clinical POR in the mesalazine-treated groups, while adverse events were the main reason for therapeutic failure in the azathioprine-treated groups.

Mesalazine-treated patients showed endoscopic improvement less frequently as compared to azathioprine-treated patients [reduction in Rutgeerts scores in 8–34% vs 36–63% after 1 year]. A small case-control study showed no benefit from the addition of mesalazine in patients with subclinical endoscopic POR while already on a thiopurine.[92]

4.3. Corticosteroids

Although oral budesonide and systemic corticosteroids are recommended for the induction of clinical remission in patients with CD,[11] data on their efficacy in the treatment of POR are lacking.

4.4. Immunomodulators

A retrospective case-series including 15 patients was the first to document macroscopic healing of recurrent severe ileitis after treatment with azathioprine.[93] Anecdotal prospective evidence confirmed the potential of azathioprine to improve endoscopic lesions.[94] An underpowered RCT comparing the efficacy of systematic vs endoscopy-driven treatment with azathioprine in postoperative CD demonstrated endoscopic remission at week 102 in 42% of patients who had to initiate azathioprine at week 26 or week 52 because of endoscopic POR [$n = 31$].[95] Two previously mentioned RCTs showed the greater ability of azathioprine compared to mesalazine in preventing clinical symptoms and for reducing the Rutgeerts score in asymptomatic patients with endoscopic POR.[90,91] Higher 6-thioguanine levels were associated with endoscopic improvement in a *post hoc* analysis of one of these trials.[96]

Data on the efficacy of thioguanine and methotrexate in the treatment of POR are lacking.

4.5. Anti-tumour necrosis factor therapy

Evidence from both prospective and retrospective studies supports the use of anti-TNF therapy in the treatment of endoscopic POR. In a meta-analysis including two pilot trials, infliximab was more effective at treating endoscopic POR than the control arms.[48] However, the total patient sample was low [$n = 50$], and the confidence interval remained broad [OR 16.64; 95% CI 2.51–110.27]. No meta-analysis on clinical POR could be performed as only one of the two studies assessed that. Other uncontrolled prospective data exist for both infliximab and adalimumab. Regueiro *et al.* offered open-label infliximab to 13 patients who were initially treated with placebo in an RCT and had developed endoscopic POR at 1 year postoperatively. During follow-up, 58% had an improvement in endoscopic inflammation, but nearly one-half still required additional surgery.[97] In the POCER study, 33 patients in the 'active care' group and originally treated with azathioprine were stepped-up to additional adalimumab due to endoscopic POR at month 6.[29] Endoscopic remission at 18 months was achieved in 13 out of 33 [39%]. In another single-centre prospective study, 9/15 [60%] patients achieved complete [Rutgeerts score i0, $n = 3$] or near-complete [Rutgeerts score i1, $n = 6$] endoscopic remission and 5/9 [56%] achieved clinical remission after 24 months of adalimumab treatment for endoscopic POR.[98]

In the largest retrospective series of anti-TNF [$n = 83$ infliximab, $n = 96$ adalimumab] for the treatment of endoscopic POR, endoscopic improvement [defined as any reduction in the baseline Rutgeerts score] was observed in 61%, including 42% who achieved endoscopic remission.[99] Concomitant use of thiopurines and treatment with infliximab [compared to adalimumab] were associated with endoscopic improvement and endoscopic remission. Interestingly, 53 patients [30%] in this study had already been treated with anti-TNF therapy before surgery, and almost half of them [24/53] even received the same anti-TNF after surgery, particularly infliximab. Nevertheless, exposure to anti-TNF therapy before surgery did not influence the outcome of anti-TNF therapy after surgery.

4.6. Ustekinumab

The efficacy of ustekinumab in patients with active postoperative CD [Harvey–Bradshaw index of ≥5 or higher, and Rutgeerts score ≥i2] was reported in a case series from Italy, with clinical remission achieved in 12 out of 15 patients at a median time of 6 months, and endoscopic remission achieved in all patients with colonoscopy during follow-up.[100] In a retrospective single-centre study comparing patients treated for endoscopic POR with ustekinumab [$n = 48$] or anti-TNF [$n = 57$], the therapeutic efficacy of ustekinumab was shown to be lower than anti-TNF therapy for several remission outcomes: clinical remission (40% vs 61% [$p = 0.08$]), endoscopic/biochemical remission (42% vs 72% [$p = 0.01$] endoscopic, i.e. SES-CD < 3, Rutgeerts score ≤i2a, or absence of ulcers, or biochemical, i.e. faecal calprotectin <150 mg/g or C-reactive protein [CRP] < 1 mg/dL), and deep remission [15% vs 44% [$p = 0.008$]).[101] The exact definition of 'postoperative CD recurrence' used by the authors, however, remains unclear, because the data were only available in an abstract.

4.7. Vedolizumab

Macaluso *et al.* included 58 patients initiating vedolizumab because of endoscopic POR. Endoscopic success, defined as a reduction of at least one point in the Rutgeerts score, was seen in 48% of patients after a mean of 15 months. Clinical failure was reported in 19% of patients at 1 year, and in 33% of patients at the end of follow-up. A new ICR was required in seven patients [12%].[102]

5. Non-Pharmacological Treatment of Postoperative Recurrence

In an RCT comparing early [immediate postoperative] vs late [at 90 days post-ICR] introduction of a multistrain probiotic containing eight different probiotics, there was no reduction in inflammatory cytokines at day 365 compared to day 90 in the group with late introduction.[81] This indirect evidence points against a potential benefit of probiotics in the treatment of postoperative CD recurrence.

The use of exclusive enteral nutrition or specific diets to treat postoperative CD recurrence has not been examined.

6. Endoscopic Interventions for Postoperative Crohn's Disease

Although several articles discuss endoscopic interventions for postoperative CD, most are case-series with a few cohort or case-control studies. Currently, there are no RCTs on this topic. Most of current research focuses on endoscopic balloon dilation [EBD] for symptomatic strictures [mostly at the anastomotic line or ileal inlet], and are embedded in current guidelines.[10,11,18,103] Newer and adjunct techniques such

as needle knife stricturotomy [NKS], stents in isolation or alongside EBD, and endoscopic injections with steroids, anti-TNF or mesenchymal stem cells are insufficiently studied and should therefore not be promoted.

6.1. Endoscopic balloon dilation

ECCO guidelines support both EBD and surgery [strictureplasties and redo ICR] as suitable treatment options for short [<5 cm] symptomatic CD strictures at an ileocolonic anastomosis or the neo-terminal ileum.[10,104] EBD outcomes for postoperative sub-group of CD strictures were analysed in two recent systematic reviews and meta-analyses. The first analysed 1089 patients with 2664 dilations reporting an overall technical [passage of the endoscope through the stricture] and symptomatic response rate [resolution of obstructive symptoms] of 84% and 58% respectively, with a post-dilation surgical rate of 32%.[105] No differences were observed between anastomotic strictures and *de novo* strictures in the ten studies where they were compared [RR 1.1, CI 0.96–1.2]. Similarly, complication and perforation rates of 22% and 5% were not significantly different to *de novo* strictures [15% and 9%]. The more recent review identified six out of 56 studies that restricted outcome to anastomotic strictures in which the effectiveness of EBD for anastomotic strictures was similar to *de novo* strictures.[106] Of note, a few studies report higher complication rates for larger balloon diameters and deep ulceration at the anastomosis.[107]

In two EBD studies focusing on asymptomatic postoperative CD, no difference in clinical outcomes was observed.[108,109] However, EBD allowed assessment of endoscopic POR severity in 20 out of 43 patients, resulting in escalation of medical therapy, suggesting a role in guiding treatment decisions.[108]

6.2. Needle knife stricturotomy

The effects of NKS using an electrocautery needle knife as adjunctive treatment are reported in two studies on anastomotic CD strictures. One compared NKS with EBD,[110] and another NKS with ICR.[111] In 21 NKS-treated patients compared with 164 EBD-treated patients, the respective rates for technical success were 100% and 90%, for post-intervention stricture surgery 9.5% and 34%, for post-procedural perforation rates 0% and 9%, and for bleeding 1% and 0%, respectively.[110] However, a shorter follow-up period in the NKS cohort [10 months vs 4 years] leads to uncertainty about both risks and benefits.

6.3. Stenting

Self-expandable stents have been described in relatively small studies.[112–114] One RCT compared EBD with stenting, wherein 80% in the EBD group were free of a new therapeutic intervention at 1 year compared with 51% in the stent group (OR 3.9 [95% CI 1.4–10.6]; $p = 0{\cdot}0061$), suggesting superiority of EBD.[114] A systematic review reported technical and clinical success rates of 96% and 73%, respectively, for 76% of 99 patients following a stent for postoperative anastomotic strictures.[115] Complications developed in 36% of patients, with symptomatic and asymptomatic stent migration in 24% of cases. In 15% of patients, surgery was mandatory because of either immediate stent-related complications or a stent failure, while 56% of patients remained symptom-free without any additional intervention over a mean follow-up period of 11–49 months. Fewer patients were free of therapeutic interventions at 1 year after placement of fully covered self-expandable stents compared with EBD [51% vs 80%] with similar safety outcomes. Stent migration remains the key limiting factor. Biodegradable stents [polydioxanone monofilament] were disappointing in resolving this problem, but newer lumen-apposing stents show promising results.[116]

6.4. Endoscopic injectables

The benefits of intralesional injection of corticosteroids and anti-TNF after EBD for anastomotic CD strictures are unclear.[117–121] Anti-inflammatory and anti-fibrotic properties of mesenchymal stem cell shown in animal models failed to show improvement in a small phase I–II open-label pilot trial.[122]

7. Surgical Interventions for Postoperative Recurrence

Surgical recurrence has often been defined as the need of a reintervention after previous primary surgery. Surgical indications for disease recurrence follow similar criteria as primary surgery and include medically refractory disease and complications due to strictures, fistula and abscesses. The site of the index surgery [e.g. the ileocolonic anastomosis] is the commonest site for surgical recurrence, although up to 30% of recurrences occur separate from it. Interestingly, fewer recurrences were reported at strictureplasty sites when compared to resection sites.[123,124] The risk for reoperation after ICR ranges from 9% to 70% of patients with CD within 10 years of their initial surgery.[6,8,125–127]

7.1. Minimally invasive approach

A laparoscopic approach has been reported as a feasible and safe option for redo surgery. No differences were found in terms of morbidity and conversion rate in a retrospective study comparing laparoscopic surgery for surgical POR within an historical cohort of patients undergoing primary resection. However, a longer operative time was registered for patients undergoing surgery for POR.[128] The well-known benefits of laparoscopy, including low postoperative morbidity, shorter hospital stays and rapid gastrointestinal recovery, were confirmed also for recurrent disease in a retrospective case control series.[129] Conversion was mainly related to intra-abdominal adhesions. Another recent retrospective case control study confirmed that a laparoscopic approach is feasible and safe for the majority of repeat ICRs when performed at a high-volume centre.[130]

In addition, a retrospective study has demonstrated that redo surgery can have similar outcomes [conversion rates, need for an ostomy, overall complications, reoperation rates] compared to original primary resections.[131] As a result, it has been suggested that a history of prior ICR, whether performed open or laparoscopically, should not be considered a contraindication to a laparoscopic approach.[132] Repeated surgery for complicated CD was associated with an increased rate of minor but not major complications.[133] Similarly, another retrospective study has confirmed that repeated surgery for recurrent CD in patients undergoing three or more ICRs was not associated with an increased risk of severe postoperative morbidity.[134]

Small cohort retrospective studies have suggested that repeated resections might be associated with an increased risk of short bowel syndrome [SBS].[135,136] However, there

is insufficient evidence to consider repeated resections as a proxy of SBS. In fact, it has been shown that either single massive resection or repeated limited resections [often due to postoperative complications leading to early redo surgery] can lead to SBS. On the other hand, it seems that SBS occurring after repeated resections might present a better nutritional prognosis as compared to massive resection more probably related to an enhanced intestinal adaptation.[137]

8. Postoperative Strategy

In the landmark study by Rutgeerts *et al.*, 61% of 89 patients developed endoscopic POR at 1 year and 74% at 3 years after surgery.[20] Despite the development of this endoscopic score for assessment of end-to-end ileocolic anastomosis, its use has continued after the change of surgical procedures to side-to-side anastomosis [and the more recently developed Kono-S anastomosis]. A more detailed endoscopic assessment of the anastomosis has been proposed recently, although this proposal requires clinical validation and several research questions remain unanswered [Table 2].[138] When the Rutgeerts score is used for the definition of endoscopic POR, these figures have not changed in recent years, as observed in the most recent placebo-controlled trial for POR prevention in which 81% of 142 included patients developed endoscopic POR as early as 6 months after surgery.[88] However, it is also certain that, among patients showing endoscopic POR, only a small proportion developed severe endoscopic POR with an ensuing high risk for clinical POR. The figures for severe endoscopic POR [Rutgeerts score of i3–i4] in the above-mentioned studies were 15% at 6 months[88] and 44% at 12 months.[20] Consequently, three different strategies have been proposed, as follows.

8.1. Systematic medical prophylaxis

This strategy is based on the fact that up to 70–80% will develop early [within 18 months] endoscopic lesions and that this is clearly associated with an increased risk for symptomatic relapse. This strategy consists of starting an effective drug therapy early after surgery to prevent endoscopic POR and is supported by the reduction in endoscopic POR rates obtained in RCTs with thiopurines and anti-TNF agents.[139] As a supportive argument, most of these patients previously developed CD-related complications, which poses a risk for a further course of complicated disease. Conversely, up to 20–30% of patients who will not develop endoscopic POR without any therapy would be overtreated, and 40–50% of patients who will only develop intermediate lesions [Rutgeerts i1–i2] carry a low risk of mid- and long-term clinical and surgical POR. In these patients, the risk of drug-related side effects might overcome their potential preventive benefits. Due to the occurrence of adverse events, the use of imidazole in the postoperative setting is not generally recommended.

Table 2. Unanswered research questions

UNANSWERED RESEARCH QUESTIONS
• What is the natural evolution of i1 lesions vs i2a lesions vs i2b lesions?
• What is the natural evolution of ulcerative lesions limited to the anastomotic line, the ileal blind loop, the ileal body or the ileal inlet?
• Are biological therapies more efficacious than thiopurines in the prevention and/or treatment of postoperative endoscopic recurrence?
• What is the role of non-anti-TNF biological therapies and small molecules in the prevention and/or treatment of postoperative endoscopic recurrence?
• What is the most optimal postoperative strategy [systematic medical prophylaxis, endoscopy-driven therapy or a risk-stratification strategy]?
• Which risk factors should be used to better identify patients at high risk of POR needing immediate medical prophylaxis?
• How many risk factors are needed to define a patient at high risk of POR?
• Is there a role for specific diets to prevent and/or to treat POR?
• Which endoscopic intervention can decrease the risk of repeat bowel obstructions due to a stenosis of the ileocolonic anastomosis?

8.2. Endoscopy-driven therapy

To avoid overtreatment and taking advantage of the 'deep' remission induced by a curative resection, this strategy proposes an early endoscopic monitoring [after 6–12 months] and treatment with thiopurines or anti-TNF agents in the case of severe lesions. In fact, mucosal recurrent lesions can resolve or improve with thiopurines and anti-TNF agents.[90,99] However, there remains a proportion of patients who will not improve and may develop clinical and surgical POR. Ferrante *et al.* performed an RCT in which CD patients were randomized to systematic prevention with azathioprine or endoscopy-driven treatment [with endoscopic assessments at 6 and 12 months and beginning thiopurines in the case of ≥i2 lesions].[95] No differences were observed in the endoscopic POR assessed 18 months after surgery, although the study was statistically underpowered to achieve robust conclusions. Recently, the results of a multicentre, European, retrospective, real-life study comparing systematic prevention and endoscopy-driven strategy including 336 patients suggested a significantly higher endoscopic POR rate among patients following the endoscopy-driven strategy in the adjusted logistic regression analysis.[140] In a similar study including 376 consecutive CD patients from three different Dutch sites, endoscopy-driven therapy was associated with more endoscopic POR within the first year compared to systematic prophylactic therapy, but not with an increased risk of clinical POR within 3 years.[141] The authors favoured an endoscopy-driven approach in order to avoid potential overtreatment of a significant number of patients.

Of note, postoperative endoscopic assessment can eventually be replaced by intestinal ultrasound and faecal calprotectin.[142]

8.3. Risk-stratification strategy

To avoid over- and undertreatment, this strategy proposes the use of those parameters that have been repeatedly identified as risk factors for POR [active smoker, prior resections, penetrating pattern and perianal disease] to stratify patients among high or low risk and using systematic prevention only in high-risk patients. Recently, the REMIND study found that the more risk factors, the higher the risk of endoscopic POR.[143] A prospective Dutch cohort study of 213 patients after ICR showed that clinical risk stratification is adequate to predict endoscopic recurrence [Rutgeerts' score ≥i2b] at 6 months, whereas the additional predictive value of histology is limited.[144] In the POCER study, patients with any risk factor received thiopurines [or adalimumab in the

case of intolerance] whereas those with no risk factors were prescribed a 3-month course of metronidazole. At the final endoscopic assessment [18 months], the rates of endoscopic POR [48% vs 56%] and severe endoscopic POR rates [17% vs 12%] were quite similar in the low- and high-risk groups.[57] Recently, a Dutch retrospective study challenged the proposed criteria for high risk of POR in current European, British and American guidelines as none of these risk factors was significantly associated with endoscopic POR.[145] No studies assessing the usefulness of microbiological data among the risk factors has yet been performed.

9. Discussion

Despite several medical therapies that prevent and/or reverse endoscopic and clinical POR, reliable markers to guide an optimal strategy for the postoperative setting are lacking. Both ECCO and AGA guidelines suggest immediate prophylaxis therapy in the majority of patients.[13,19] In spite of that, such an approach will undoubtedly lead to overtreatment with unnecessary exposure to side effects. Furthermore, when patients request treatment discontinuation years after ICR with systematic postoperative prophylaxis, clinicians face a gap in evidence-based advice. However, the ongoing SOPRANO-CD study in patients with CD undergoing an ICR with ileocolonic anastomosis will specifically address this evidence gap by randomization to systematic prophylaxis with biological therapy or an endoscopy-guided approach [NCT05169593]. A similar but underpowered trial with azathioprine showed comparable outcomes for the endoscopy-driven approach as for immediate postoperative prophylaxis.[95]

Based on the currently available data, we propose a postoperative strategy to guide clinical practice [Figure 1]. A strong emphasis on smoking cessation for all patients after ICR should include specific active measures to make it successful.[78] In general, postoperative therapy should be based on an intensive shared decision-making process. Patients with [recently] active perianal fistulizing disease, concomitant immune-mediated inflammatory diseases [IMIDs] such as spondyloarthropathy, extra-intestinal manifestations [EIMs] or prior involvement of the colon merit continuation [or introduction] of efficacious immunosuppressive or biological therapy. Next, active smoking, penetrating disease as an indication for the index ICR, and/or previous ICRs may qualify for immediate prophylactic therapy by a multidisciplinary team.[15] In all other situations, the benefit of continuation [or introduction] of immunosuppressive or biological therapy is less clear, but should also be discussed with and possibly offered to the patient. Although both thiopurines and biologicals have been shown to be efficacious, anti-TNF agents appear superior to thiopurines in the most recent meta-analysis.[50] Finally, a first postoperative endoscopy should be performed after 6 months for all ICR patients for timely initiation or optimization of prophylactic therapy based on the endoscopic findings. At this stage it is unclear if i1 and i2a lesions have a different natural outcome compared to i2b lesions, and if all these lesions require treatment optimization [Table 2]. Further research will examine differential treatment of patients with i2a or i2b endoscopic POR [POMEROL, NCT05072782].

In conclusion, despite important progress in the field of POR since the pivotal papers by Paul Rutgeerts, the prevailing gap in accurate predictors of POR disempowers

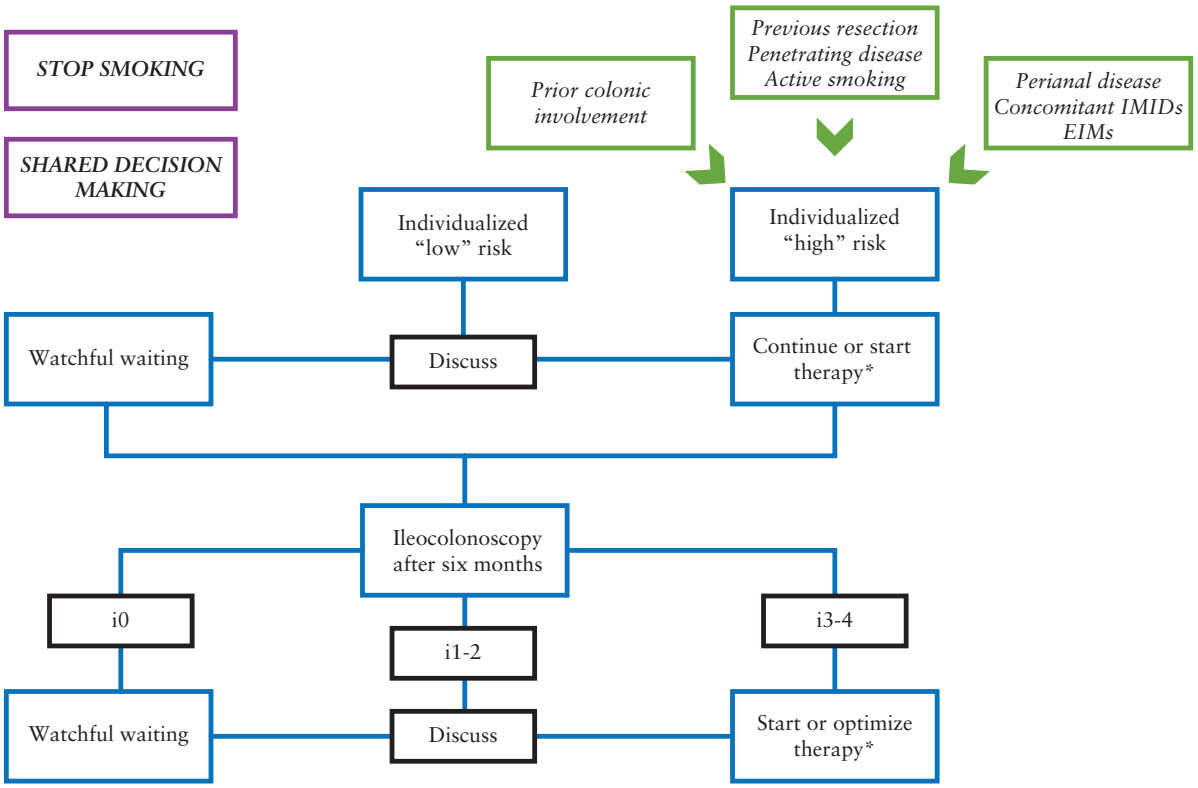

Figure 1. Proposed postoperative strategy in patients with Crohn's disease undergoing an ileocolonic resection
EIM: extra-intestinal manifestation; IMID: immune-mediated inflammatory disorder.

clinicians from choosing between systematic prophylaxis, risk stratification strategy and an endoscopy-driven approach. Further prospective studies are warranted on the identification of better markers of postoperative recurrence as well as a direct comparison between postoperative strategies.

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