Prevention of postsurgical recurrence in Crohn's disease: is it possible?

Preprečevanje pooperativne ponovitve Crohnove bolezni: ali je to mogoče?

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Izvleček

Crohnovo bolezen (CD) odkrijejo pri približno 20 % bolnikov pred 18. letom starosti. Fenotip bolezni je bolj zapleten, kot če se CD pojavi v odrasli dobi, in zahteva bolj agresivno zdravljenje – tudi kirurško. Delež kirurških posegov pri CD v pediatriji se giblje med 10 in 72 %. Indikacije za kirurško zdravljenje vključujejo neodzivnost bolezni na medikamentozno zdravljene (predvsem ob zaostanku v rasti) in zapleten potek. Kirurgija je ključnega pomena, saj omogoča otrokom, da do pozne pubertete nadoknadijo zaostanek v rasti in telesni višini. Vendar pa kirurški poseg ne omogoča ozdravitve in pooperativni relaps (POR) je skoraj neizogiben. Kljub skromnim podatkom v pediatriji pa poročajo o klinični ponovitvi bolezni v 50–94 % in ponovni operaciji v 18–54 % primerov, odvisno od časa spremljanja. POR igra torej odločilno vlogo pri obvladovanju CD. Za zmanjševanje POR se uporabljajo številne strategije, a le nekatere od teh so učinkovite in še te ne v vseh primerih. Zato trenutno še ne obstaja standard zdravljenja za pooperativno obvladovanje CD. Objavljene raziskave pri odraslih, sistematični pregledi in meta-analize so potrdili učinkovitost tiopurinov, nitroimidazolnih antibiotikov in anti-TNFα, med tem ko se budesonid, probiotiki in inerlevkin-10 niso izkazali kot učinkoviti. Mesalazin, čeprav varen, ne pomaga veliko in se njegova uporaba razen v nekaj izbranih primerih ne priporoča. Ker pri otrocih niso izvajali randomiziranih kontroliranih preskušanj, je treba ekstrapolirati podatke iz študij pri odraslih, enteralna prehrana pa lahko igra pomembno vlogo. Pri preprečevanju ponovitve bolezni je treba upoštevati dejavnike tveganja, kako jo ocenjevati, katera zdravila uporabiti glede na dejavnike tveganja in stroškovno učinkovitost, na podlagi dejanskih dokazov.

Abstract

Crohn's disease (CD) is diagnosed in about 20 % of patients before the age of 18 years. Its phenotype is more complicated than in adult-onset CD and requires more aggressive therapy, including surgery. Surgery rates in pediatric CD range between 10 and 72 %. Indications for surgery include medically refractory disease (especially with growth failure) and complicated behaviour. Surgery is crucial, allowing children to catch up in growth and height before late puberty. However, surgery is not curative and post-operative recurrence (POR) is almost inevitable. Even if pediatric data are scarce, clinical recurrence has been reported in 50–94 % and re-operation in 18–54 % of cases, depending on the follow-up time. Thus, prevention of POR has a decisive role in managing CD. Several strategies have been used to decrease POR, with only some being efficacious and not in all cases. Therefore, currently, no standard of care for the management of postoperative CD does exist. The published studies in adults, systematic reviews and meta-analyses have shown efficacy for thiopurines, nitroimidazole antibiotics and anti-TNFα agents, while budesonide, probiotics and interleukin-10 were not effective. Although safe, mesalazine is of little benefit and not recommended, except in few selected patients. Since no randomized-controlled trial has been performed in children, data have to be extrapolated from adults and enteral nutrition may play an important role. In the prevention of recurrence, it is imperative to consider its risk factors, how it should be assessed, and what medication to use in relation to risk factors and cost-efficacy, based on actual evidence.

Background

Approximately 20 % of patients with Crohn's disease (CD) are diagnosed before the age of 18 years.[1] The disease phenotype is more complicated compared to adult-onset CD[2] and requires more aggressive therapy (more steroids, earlier introduction of immunomodulators and more surgery)[3,4]. Indications for surgery in pediatrics include medically-refractory disease (especially with growth failure)[5] and the existence of

complications (perforation, fistula, abscess, stricture)[6,7]. Early surgery should be considered in the presence of growth failure, since it allows a disease-free interval for normal growth and development.[7] Although the inflammatory behaviour (B1) is predominant, complicated disease has also been described in children. At the onset, the penetrating disease (B3) frequency varies between 4[3] and 18 %[8], while the stricturing behaviour (B2) accounts for 4.4[2] to 25 %[3] of CD cases. By the end of the follow-up period, B3 behaviour has been seen in 7[9] to 35 %[10] and B2–in 13[2] to 44 %[3] of patients. Many of these children will require surgery.[11] Even if surgical resections induce remission, they are not curative. Disease recurrence and necessity of a re-operation following a primary resection for CD are common.[12] This review provides an insight into the risk factors for POR, possibilities of monitoring of POR and therapeutic options to prevent it.

What are the frequency and the outcome of surgery in CD?

Approximately 75 % of adults with CD will require surgery over their lifetime, despite optimized medical therapy.[13,14] In a systematic review of 3505 CD children, the reported surgery rates ranged between 10 and 72 %[11] and included partial/total colectomy, small bowel resection, excision of fissure or of fistula.[3] Published resection rates have been reported between 20 and 30 % in 10 years[12] and many patients have a second surgery.[3] Regardless of the high relapse rate, improvements in growth occur in almost all CD children after surgical resection.[7,11,15-18] In Canada, the mean height velocity of patients with growth potential increased significantly from 2.4 cm/year preoperatively to 8.1 cm/year in the first postoperative year.[17] Seventeen French children without recurrence had a mean weight gain of 2.1 kg and a height gain of 3.36 cm.[7] Growth and nutrition improved by 6 and 12 months after surgery, with a significant increase in weight z-score and height z-score, in UK.[18] There was a significant improvement in z-scores for height after surgery also in American children.[19] Catch-up in height and weight was better in French patients who underwent surgery within 3 years after CD diagnosis than those operated later.[20] Also, surgery allows an improvement in the quality of life.[15,16] A very recent report[12] showed that 96 % of Finnish children were completely or moderately satisfied with the outcome of the surgery. Therefore, surgery should not be considered a failure of treatment, rather a necessary intervention to improve the patient's quality of life and correct disease complications.[12,13]

How often does the post-operative recurrence occur?

Postoperative recurrence (POR) of CD is considered virtually inevitable. Without the intimate mechanisms to be yet revealed, POR is probably triggered by interactions between genetics, intestinal content, luminal and mucosal-adherent bacteria and the gut-associated lymphoid tissue.[21] An argument supporting this hypothesis came from patients who underwent ileostomy and diversion of the fecal stream. They did not develop POR, unless bowel continuity was achieved.[22] The indications for subsequent surgeries tend to be similar to those of the first operation, and recurrence occurs usually at the anastomosis site, especially its proximal side.[22-24]

In adults without further treatment, POR may occur as early as 7 days after surgery (assessed by histology).[21] Data from endoscopic follow-up of patients after resection of ileo-caecal disease have shown that, in the absence of treatment, POR rate is around 65–90 % within 12 months[23,24] and 80–100 % within 3 years from the operation.[5] A total of 30 % of patients manifest clinical recurrence (CR) at 3 years, 50 % at 5 years, 60 % at 10 years[14] and 72 % at 20 years[25]. Surgical recurrence (SR) rates are 11–32 % at 5 years, 20–44 % at 10 years and 46–55 % at 20 years.[25]

An interesting recent review focused on the recurrence rate, by separately analyzing adult-randomized controlled trials (RCTs), studies from referral centres and population-based studies.[26] In RCTs, CR occurred by 1 year in 10–38 % of patients, whereas endoscopic recurrence (ER) was reported in 35–85 % of patients. In referral centres, 48–93 % of the patients had endoscopic lesions (Rutgeerts' score ≥ 1) in the neoterminal ileum within 1 year after surgery, whereas 20–37 % had symptoms suggestive of CR. Three years after surgery, the ER increased to 85–100 % and CR occurred in 34–86 % of patients. In

population-based studies, approximately half of patients experienced CR at 10 years.[26]

Data in pediatrics are relatively scarce. In France, CR was reported in 50 % of cases after 2 years.[7] In Finland, ER requiring medical or surgical treatment occurred in 94 % (median 1.8 years after primary resection, range 0.2–12.7).[12] In UK, CR appeared in 55 % of cases within 2.5 years after surgery.[18] In US, CR was 17 % at 1 yr, 38 % at 3 yr and 60 % at 5 yr.[19] In a very recent study in France, recurrence was defined as the need of immunosuppressants or biologicals postoperatively and the risk of recurrence was 18 % at 2 years, 34 % at 5 years and 47 % at 10 years.[20] Re-operation rates in children vary between 18 % (median follow-up of 2.5 years)[18], 27 % (median follow-up of 13 months)[27] and 54 % (by 10 years)[12]. The median time from first surgery to re-resection was two years (range 0–16) and the median period without re-resection was seven years.[12] Recently, the probability of re-operation was estimated at 8, 17 and 29 % (at 2, 5 and 10 years, respectively).[20]

Early recurrence of symptoms is particularly undesirable in teenagers, as prolonged disease activity can lead to significant morbidity and permanent stunting (education, socialization and particularly growth).

How to assess the recurrence?

In various studies, POR has been assessed by clinical, serological, endoscopic, histological, radiological and surgical parameters. According to the evidence-based ECCO Consensus, the gold standard method for diagnosing the recurrence is ileocolonoscopy, defining the presence and severity of morphologic recurrence and predicting the clinical course (by the Rutgeerts's score).[5,24] POR starts with aphthous ulcerations in the neoterminal ileum and at the anastomosis, with progression to larger ulcers and eventually stricture and fistula.[23] In Rutgeerts's score, lesions i0 and i1 imply endoscopic remission and 80–85 % will remain asymptomatic on no medications for 3 years after the ileocolonic resection. Lesions i2–i4 imply ER of CD. Of patients with severe ER, a score of i3 (diffuse aphthous ileitis) or i4 (diffuse inflammation with already larger ulcers, nodules and/or narrowing), only 10 % are likely to remain asymptomatic for 3 years following their resection.[24,28] Patients with i2- i4 have a 3-year CR rate of 15–20, 40 and 90 %, respectively.[28] Endoscopic evidence > i2 should prompt initiation or escalation of medical therapy, regardless of patient symptoms.[13,29] Ileocolonoscopy may be considered 6–9 months after the surgery[22,30], in order to start treatment escalation if ER is noted. One question still remains: how often should we perform ileocolonoscopy?

However, in a very recent study, there was no clinical benefit from colonoscopy or increased drug therapy within 1 year after operation. Of 70 patients with and 66 without postoperative colonoscopy, CR occurred in 49 % and 48 %, respectively, and further surgery was required in 9 % and 5 %, respectively (NS). Eighty-nine per cent of colonoscoped patients had a decision based on the colonoscopy findings: of these, 24 % had a step-up of drug therapy and 76 % had no step-up. In colonoscoped patients, CR occurred in 60 % with, and 49 % without step-up, while SR appeared in 13 % with, and 9 % without step-up (NS).[31]

As stated by the ECCO Consensus, trans--abdominal ultrasound (especially small intestine contrast ultrasonography–SICUS),[32] magnetic resonance enterography, small bowel capsule endoscopy (VCE) are less invasive diagnostic methods, emerging as alternative tools in identifying POR.[5,13] In a very recent series, the sensitivity, specificity and accuracy of SICUS in detecting POR, compared with ileocolonoscopy, were 98 %, 100 % and 98.3 %, respectively, including severe recurrences.[33] In an earlier study, SICUS, compared with ileocolonoscopy, provided excellent sensitivity in detecting POR in 92.5 %, with only 20 % specificity and an overall accuracy of 87.5 %.[34] Although results from using VCE have been promising, the risk of retained capsule is higher than the risk of complication from ileocolonoscopy.[13] More recently, a VCE scoring index for small bowel disease recurrence has been developed, categorizing the abnormalities into: villous oedema, ulcers and stenosis.[35] A study that compared VCE, SICUS and ileocolonoscopy in the detection of POR after one year found comparable results.[36]

The detection of fecal lactoferrin and calprotectin levels also seems promising, these being non-invasive tests that can help to identify disease recurrence; however, more studies are needed.[37]

CR lags far behind endoscopic/histological recurrence[13] and most patients have clinically silent disease, despite endoscopic evident inflammation. Clinical and serological markers should not be used to assess POR.

What are the risk factors associated with early post-operative recurrence?

Most of the data have been reported in adult studies, excellent reviews being recently published.[26,38] Risk factors could be divided into three groups: patient-related, disease-related and surgery-related.[13] Of all risk factors, the strongest supportive data for POR exists for tobacco smoking and penetrating disease.

Tobacco smoking is also the only modifiable and the only patient-related risk factor for POR. Smoking has been found to increase ER, CR and SR.[39] A meta-analysis of 16 studies that included 2962 patients reported that smokers had a 2-fold increased risk for CR and a 2.5-fold increased risk for SR within 10 years.[40] Studies have shown a dose effect in tobacco smoking with worse relapse rates among heavy smokers (more than 15 cigarettes/day), compared with those smoking less.[25] Female smokers were found to have a higher risk for recurrence than males.[41] Prior surgery is also a high-risk factor.[5] A recent study has shown that an interval of less than 5 years between the first and the second operations is a significant risk factor for a third operation.[42] Multi-site CD has a 2.5-fold increase in surgical relapse rate when compared to single-site disease.[43] To date, there is no single surgery-specific risk factor that has been firmly associated with POR.[13] Although laparoscopic resection seems to have short-term advantage, long-term follow-up did not show any benefit in terms of postoperative CR, ER and SR. Nevertheless, especially in young patients, laparoscopic resection has a cosmetic benefit.[38]

Risk factors for early POR have not been widely studied in children. *Table 1* presents a synthesis of risk factors in determining early POR, based on the available adult and pediatric literature.

Anatomical location as a risk factor has been reported differently in pediatrics. In a Canadian study, ileocolonic diffuse inflammation was associated with significant earlier recurrence (50 % at 1 year) than predominantly small bowel disease (50 % recurrence at 5 years).[17] The same site was a risk factor for recurrence in a British study.[18] Other locations favouring POR have been reported as: upper gastrointestinal involvement in France,[7,20] perianal disease in France[7] and colonic disease in the USA.[19] Patients with colonic CD had a significantly shorter POR-free interval (median 1.2 yr) than those with ileocecal (median 4.4 yr) or diffuse disease (median 3.0 yr).[19]

Failure of medical therapy, independent of disease location, as the sole indication for surgery was also associated with a significantly earlier relapse than when surgery was performed for an intestinal complication (abscess or obstruction) in the Canadian study.[17] Failure of medical treatment as the only indication for surgery has also been reported as a risk factor in the USA and

Table 1: Risk factors for early post-operative recurrence in Crohn's disease

Adult-definite factors	Adult-possible factors (controversial)	Adult-no contributing factors	Pediatric risk factors
Smoking[5] Prior intestinal surgery[5,42] Penetrating disease[5] Perianal location[5,26] Extensive small bowel resection (> 50 cm)[5] Progress to surgery despite immunomodulators[44]	Early age at initial surgery (< 20 y[45,46], < 30 y[44], < 40 y[47]) Short duration of disease to first surgery[48] Ileocolonic disease[48] Use of corticosteroids <3months prior to surgery[48] Multi-site disease[43] Anastomosis site[25] Presence of granuloma[26] Myenteric plexitis[26] NOD2 mutation[26] Increased TGFβ[26] Low level of IL-10- mRNA[26]	Gender Surgical procedure (laparoscopy vs. laparotomy)[38] Type of anastomosis[38] Resection margins[49] Family history of IBD[26] C-reactive protein level[26]	Age at diagnosis < 14 y[20] Longer duration until surgery[17,20] Ileocolonic CD[7,17,18] Colonic CD[19] Upper gastrointestinal involvment[20] Failure of medical therapy[17-19] Pre-operative use of 6MP[19] Stenosing disease[20] Perforating disease[20]

NOD2 - nucleotide-binding oligomerization domain-containing protein 2; TGFβ - transforming growth-factor β; IL – interleukin; mRNA – messenger ribonucleic acid; IBD – inflammatory bowel disease; 6MP – 6 – mercaptopurine; y - year

UK.[18,19] Presence of a severe active disease at the time of surgery and preoperative use of 6-mercaptopurine were independently associated with higher POR rates.[19]

Contrary to adult data, preoperative longer duration of symptomatic disease has been found as a risk factor in children. CR in Canadian children was 50 % by 4 years (when preoperative duration of disease was 1–4 years) and 50 % by 3 years (when disease had been present for > 4 years before the operation), which was significantly higher than in those undergoing resection within one year of the onset of symptoms, with a CR of 30 % by 8 years.[17] The very recent French data support the same idea: the risk for recurrence is 2.5 times lower, when the resection is performed during the first three years after the diagnosis.[20]

What is the optimal approach in order to prevent the post-operative recurrence?

a. What are the types of interventions?

There is a paucity of trials evaluating long-term follow-up and prevention of POR in CD. There are no formal guidelines for the prevention of POR in adult CD, except the ECCO recommendations[5]. Moreover, no RCT has been performed in pediatrics and decisions have to be extrapolated from adult studies.

I. 5ASA (5-amino-salicylates)

Sulfasalazine (SASP) and especially mesalazine[50-56] have been used in most studies, probably given their safety profile. Various systematic reviews and meta-analyses have included some of these studies.

In a 2009-Cochrane review of 5 RCTs,[51,52,54-56] mesalazine was associated with a significantly reduced risk of CR (RR 0.76; 95 % CI 0.62 to 0.94, number needed to treat–NNT = 12) and of severe ER (i > 3) (RR 0.50; 95 % CI 0.29 to 0.84, NNT = 8) when compared to placebo. When compared to thiopurines, mesalamine was associated with a higher risk of any ER (RR 1.45, 95 % CI 1.03 to 2.06), but a lower risk of serious adverse events (RR 0.51; 95 % CI 0.30 to 0.89).[57]

A more recent (2011) Cochrane review[58] included studies on both SASP and mesalazine[51-55] (with 1 included study different from the previous Cochrane review). Analyzed together, 5ASA were significantly more effective than placebo for the prevention of CR or ER (OR 0.68; 95 % CI 0.52 to 0.90). No statistically significant difference was found between 5ASA and thiopurines for preventing relapses (OR 1.08 95 % CI, 0.63 to 1.85), but there have been only 2 studies and insufficient evidence to allow any conclusions.[58]

A systematic review and meta-analysis (2011) showed that SASP was of no benefit in preventing relapse in 448 patients[59]. Mesalazine was more effective in 834 patients than placebo or no therapy[50-55]. The NNT for mesalazine (of 10) was better than in the 2009-Cochrane review, but the authors included another positive study from 1994[50]. The NNT with all 5ASA to prevent CR in one patient was 13.[59]

The 2012 meta-analysis[38] concluded that mesalamine was more effective in preventing CR than placebo[51,52,54,55], but did not show overall difference in preventing ER[50,51,54-56].

Even if 5ASA are better than placebo, especially in preventing CR, their potential benefit is modest, with a NNT of approximately 16 to 19 patients to avoid one relapse, which raises issues about the cost-effectiveness of this therapy. The only advantage is that they are safe and well tolerated.[58]

Given all the above data, 5ASA do not seem to play a role in preventing POR, except in low risk patients.[5,38]

II. Thiopurines (Azathioprine–AZA/6 – mercaptopurine – 6MP)

The studies using thiopurines in the prevention of POR are described in *Table 2*.

The 2009 Cochrane review of 5 studies reported that AZA/6MP were associated with a significantly reduced risk of CR [55,60-63] (RR 0.59; 95 % CI 0.38 to 0.92, NNT = 7) and ER[55,62,63] (RR 0.64; 95 % CI 0.44 to 0.92, NNT = 4), when compared to placebo.[57]

A thiopurine-dedicated meta-analysis in preventing POR[65] included only four of the previous studies[55,61-63] (433 patients) and showed that thiopurines were by 8 % more effective than placebo/5ASA in reducing 1-year CR with a NNT of 13 and 2-year CR with a NNT of 8 (by 13 % more effective than controls). AZA was 15 % more effective than controls in preventing ER at 1 year with a NNT of 7. Conversely, they were not more

effective than controls in preventing severe endoscopic recurrence (> i3 or i4). Analyzed versus placebo, thiopurines were more effective at 1 year, for the prevention of CR (with 13 %, NNT = 7) and ER (with 23 %, NNT = 4). The rate of adverse events leading to drug withdrawal was significantly higher in thiopurine-treated patients than in control arms (17 vs. 10 %, respectively, p = 0.021).[65]

The meta-analysis published in 2012[38] included only 3 of the previous studies[55,61,63] and added 1 RCT from 2010[64]. The authors concluded that thiopurines were more effective than placebo in preventing CR (P = 0.018) and ER (P = 0.015). However, overall analysis showed no significant difference in preventing CR at one-year follow-up, comparing AZA/6-MP to placebo or mesalamine (mean difference 3.8 %, 95 % CI 3.6–11.1 %). At 2-year follow-up, the only two available studies showed that thiopurines were significantly more effective than placebo or mesalamine in preventing CR (mean difference 13.1 %, 95 % CI 2.3–23.9 %). ER rate at one year showed a significant difference for AZA/6MP compared to placebo (mean difference 19.7 %, 95 % CI 8.4–31.0 %).[38]

Given all these data, we may conclude that thiopurines are moderately effective in preventing POR, globally better than 5ASA, even if they have important side effects.[5,57]

III. Nitroimidazole antibiotics

Two studies have been published, studying Metronidazole for 3 months[66] and Ornidazole for 1 year[67] versus placebo. The Cochrane review concluded that nitroimidazoles reduced the risk of CR (RR 0.23; 95 % CI 0.09 to 0.57, NNT = 4) and ER (RR 0.44; 95 % CI 0.26 to 0.74, NNT = 4) compared to placebo. However, they were associated with higher risk of serious adverse events (RR 2.39, 95 % CI 1.5 to 3.7).[57]

Moreover, the meta-analysis from 2012 showed that at 3-month follow-up, ER was significantly reduced in an overall analysis (mean difference 23.7 %, CI 95 % 6.4–41.4 %). At 1 year, there was still a significant difference in ER rate with 53.6 % in the Ornidazole group, compared to 78.8 % in the placebo group. However, a high percentage of dropouts due to side effects was observed. At 3-year follow-up, there was no significant difference anymore.[38]

Table 2: Thiopurine-controlled studies in the prevention of postoperative recurrence in Crohn's disease

Author year	Type of trial, duration	Population (n)	Medication	Effect (%)	Comments
Nos 2000[60]	Prospec-tive, 2 years	39	AZA 50 mg/d vs 5ASA 3 g/d	Morphologic recurrence*: 64 vs. 69 Serological recurrence: 45 vs. 44 CR: 36 vs. 37	At 2 years, only 11 AZA-cases vs. 16 completed the study Low-dose AZA
Hanauer 2004[55]	RCT, 2 years	131	6MP 50 mg/d vs. 5ASA 3 g/d vs. placebo	ER: 43 vs. 63 vs. 64 CR: 50 vs. 58 vs. 77 (6MP vs. placebo: p = 0.045)	Significant for ER High drop-out rate (31 % of all cases)
Ardizzone 2004[61]	OL, 2 years	142	AZA 2 mg/kg vs. 5ASA 3 g/d	ER: 17 vs 28 (NS) SR: 6 vs 10 (NS)	AZA favourable in cases with previous resection (OR 4.83)
Herfarth 2006[62]	RCT, DB, 1 year	79	AZA 2–2.5 mg/kg/d vs. 5ASA 4 g/d	CR or severe ER: 17 vs 37 (NS)	Adverse drug events (33 % AZA vs. 11 % 5ASA, NS)
D'Haens 2008[63]	RCT, 1 year	81 (high risk for POR)	AZA 100–150 mg/d, 1 year + MTZ 3 months vs. MTZ	ER: 58 vs 78 (p = 0.035) Significant ER: 43.7 vs 69 (p = 0.048)	Possible advantage of adding MTZ for 3 months
Reinisch 2010[64]	RCT, DB, 21 centres in Europe, 1 year	78 (moderate / severe ER, no CR)	AZA 2.0–2.5 mg/kg/d vs 5ASA 4 g/d	Treatment failure: 22 vs. 10.8 (NS) Significant endoscopic ≥ 1 point reduction in RS between baseline and 1 year: 63.3 vs. 34.4 (p = 0.023) CR: 0 vs 10.8 (p = 0.031)	Significant more adverse reactions with AZA (22 % vs 0 % 5ASA)

AZA – azathioprine; 6MP – 6-mercaptopurine; 5ASA – 5-amino-salicylates; d – day; CR – clinical recurrence; ER – endoscopic recurrence; SR – surgical recurrence; RCT–randomized controlled trial; DB – double blind; OL- open-label; NS – not-significant; MTZ – metronidazole; RS – Rutgeerts score; POR – post-operative recurrence; OR – odds ratio
** Morphologic recurrence: endoscopic recurrence > 1 (RS) or radiological or ultrasonographic recurrence*

Nitroimidazole antibiotics are moderately effective in preventing POR; however, they are poorly tolerated when taken on a daily basis.[38] According to the ECCO Consensus, imidazole antibiotics alone are less effective than thiopurines in the prevention of POR.[5]

IV. Enteral nutrition

One group from Japan published their 5-year experience with elemental formula infusion during nighttime plus a low-fat diet during daytime, compared to patients with normal food, in adults after resection for ileal or ileocolic CD, without medication such as steroids, purines or biologics. Recurrence requiring Infliximab (IFX) therapy and reoperation occurred in 10 % and 5 % in the first group, compared to 45 % and 25 % in the second group, repectively.[68] Their earlier study showed that 1 year after operation, ER and CR were observed in 30 % and 5 % in the enteral nutrition (EN) group compared to 70 % and 35 % in controls, respectively, demonstrating the benefit of the supplementary EN.[69]

In children with CD, exclusive EN for 6–8 weeks is considered the first-line therapy in inducing remission.[5,70] Studies have shown that partial EN could be continued after the first 8 weeks of exclusive EN, significantly increasing the rate of maintaining the remission and also improving growth and nutritional status (especially when associated to other therapies).[71] Thus, partial EN could be considered in children for the prevention of POR, particularly in those with growth impairment.

V. Other non-biological therapies

Neither budesonide[57], nor probiotics or synbiotics[57,72] are efficacious for the prevention of POR.[38]

VI. Anti-TNFα agents

The meta-analyses and systematic reviews presented above have shown that despite the use of 5ASA, nitroimidazoles and thiopurines, 1-year ER rate is approximately 45 %, and many of the patients experience CR and require surgery.[44] Given the good results with antiTNFα agents in inducing and maintaining remission in CD, they have been used also in the prevention of POR. Only a few studies using IFX and Adalimumab (ADA) have been performed *(Table 3),* showing excellent results in preventing severe histological recurrence, as well as ER and CR.[38] In all these studies, antiTNFα agents were administered within 4 weeks of surgery. Only one was placebo-controlled[74] and the number of patients in these studies was generally small. There were no significant adverse events *(Table 3).*

An international, multicenter RCT, double-blinded study, called PREVENT, is underway. Patients with ileocolonic resection at increased risk of recurrence are included, receiving IFX or placebo every 8 weeks through week 200 in order to prevent POR. The primary endpoints will be CR or ER at 76 weeks(cit. in 38).

There have been also 3 published studies (none placebo-controlled) showing efficacy of IFX in treating ER (Rutgeerts score ≥ 2), being able to induce mucosal healing *(Table 4).*

The results of these studies recommend the use of the antiTNFα agents in the prevention of POR. However, they should be reserved only for high-risk patients or after diagnosing ER.

In children, only one study using IFX focused on the post-operative results. One-third of the patients treated postoperatively with IFX for active disease underwent re-resections despite the therapy. The authors found no significant difference in the number of relapses or re-resections between patients who underwent surgery before the era of antiTNFα agents or after it.[12]

b. What therapy should be chosen according to risk factors and when is the optimal timing to start?

Patients should be stratified according to the risk of POR, however no consensus has been obtained yet. Decisions should be individual-based, taking into consideration the indication for surgery, pre-surgical therapy, risks for recurrence and the benefit-risk ratio of the preventive intervention.

Regueiro et al. developed an algorithm based on risk factors, however it has not been validated and it concerns only adults.[13,44,48] In the *low-risk group*, they included patients with long-standing CD (> 10 years), non-smokers, with first surgery and short stricture (< 10 cm).[13] No medication would be recommended, only an ileocolonoscopy 6–12 months postoperatively. If the patient has ER of i1 or i2, then treatment with an immunomodulator is recommended. A recurrence of i3 or i4 will probably require

another surgery, however an anti-TNF agent would be recommended. In their experience, recurrence in these low-risk patients is rare (only 10 %) and postoperative ER > i2 is very unlikely. *Moderate-risk group* included patients with less than 10 years of CD, long stricture or inflammatory CD (> 10 cm). The authors suggest thiopurines immediately, with or without a 3-month course of Metronidazole. An ileocolonoscopy is performed at 6–12 months and if there is no recurrence, the immunomodulator is continued. For those patients with > i2 recurrence, escalation to an anti-TNFα agent is recommended.[13] *The high-risk group* included patients with penetrating CD, prior surgery for CD, those who continued to smoke and/or have failed immunomodulators. These patients should be placed on prophylactic anti-TNFα therapy postoperatively. At 6–12 months after surgery, patients should have an ileocolonoscopy and if there is no POR, then their anti-TNFα therapy is continued. If there is ER, their anti-TNFα should be optimized (checking anti-TNF antibodies and serum trough levels) or changed to another anti--TNF and, if not previously taken, should have an immunomodulator added.[13]

Table 3: Anti-TNFα therapy started within 4 weeks after surgery in Crohn's disease

Author, year	Type of trial, duration	Population (n)	Medication	Effect (%)	Comments
Sorrentino 2007[73]	NR, 2 years	23	IFX* + MT × 10 mg/d vs. 5ASA 2.4 g/d	ER or CR: 0 vs. 75	ER: RS ≥ 2
Regueiro 2009[74]	RCT, DB, 1 year	24	IFX* vs. placebo	HR: 27.3 vs. 84.6 ER: 9 vs. 84.6 CR: 20 vs. 46.2 (NS)	ER: RS ≥ 2 No difference in adverse events[75]
Yoshida 2012[76]	R, OL, 3 years	31	IFX* vs placebo	ER at 1 year: 21 vs. 81 CR at 1 year: 0 vs. 31.2 CR at 3 years: 6.7 vs. 43.7	Serological remission also significantly higher with IFX; no adverse events
Sakuraba 2012[77]	OL, 2 years	10 (multiple surgeries for penetrating CD)	IFX*	ER / radiological recurrence: 60 CR: 40	18.2 % adverse effects
Fernandez Blanco 2010[78]	OL, 1 year	20	ADA**	Moderately active HR: 35 ER: 10 CR: 0	-
De Cruz 2011[79]	Case series, 6 months	11 (high-risk for POR, thiopurine-intolerant)	ADA**	ER: 9	-
Papa-michael 2012[80]	OL, 2 years	23 (high risk for POR, 8 after surgery vs. 15 with ER at 6 months, despite IFX, AZA or 5ASA)	ADA**	Group I: ER – 25, CR: 12.5 Group II: Complete or near complete mucosal healing – 60, Clinical remission: 56	No serious adverse events
Savarino 2012[81]	Case series, ~ 3 years	6 (surgery for fibrotic stricture)	ADA**	0 recurrence	Clinical, radiological, endoscopic/ histological criteria
Aguas 2012[82]	Observational, 1 year	29 (high-risk for POR, 51.7 % failed IFX)	ADA**	MR***: 36.8 ER: 20.7 CR: 13.7	1 patient with adverse events

R – randomized; NR – not-randomized; RCT–randomized controlled trial; DB – double blind; OL – open-label; RS – Rutgeerts score; AZA – azathioprine; 5ASA – 5-amino-salicylates; IFX – infliximab; ADA – adalimumab; MTX – methotrexate; NS – not-significant; CR – clinical recurrence; ER – endoscopic recurrence; HR – histological recurrence; POR – post-operative recurrence; CD – Crohn's disease
** IFX: 5 mg/kg–weeks 0, 2, 6, and then every 8 weeks;*
*** ADA: 160/80 mg at weeks 0 and 2 and then 40 mg every other week*
**** Morphological recurrence–magnetic resonance (MR) score ≥ MR1*

Another striking issue concerns the timing of starting the medication – whether to treat postoperatively or delay therapy until diagnosing ER. According to the ECCO Consensus, prophylaxis is best started within two weeks of surgery, although an early start has not been proven superior to later treatment[5] (except IFX)[74]. The duration of prophylaxis should be at least 2 years.[5]

c. What is the best option considering cost/effectiveness?

Two very recent papers reviewed the literature and addressed this interesting issue. The first one compared five strategies–no treatment, AZA, nitroimidazoles, upfront IFX, and tailored IFX (initiation of IFX in patients with severe ER at 6 months). The base-case 1-year CR rate was 24 % with a reduction in recurrence of 41 %, 77 %, and 99 % for AZA, nitroimidazoles, and IFX, respectively. Antibiotics were the most cost-effective option for preventing POR, but they have been associated with high rates of intolerance. Upfront IFX is the most efficacious strategy but is not cost-effective even in high-risk patients. Reserving IFX use for high-risk patients with early ER is more cost-effective than upfront use in all patients.[86] The other group compared four strategies–no prophylaxis, mesalamine, thiopurines and IFX. Compared to no-prophylactic treatment, AZA/6-MP had the most favourable incremental cost-effectiveness ratio (ICER) in the prevention of CR up to 1 year. At 5 years, mesalamine had the most favourable ICER in this model.[87]

In conclusion

In conclusion, there is a lot of uncertainty regarding the prevention of POR and pediatric data are scarce. Ileocolonoscopy is considered the gold-standard in determining the recurrence. However, magnetic resonance enterography, SICUS, VCE and fecal markers may become good acceptable tools, as they are less or non-invasive. No total agreement exists with regards to defining the risk factors for POR. The optimal strategies are still unknown and none of them is ideal; however, prevention of POR is possible. Thiopurines and nitroimidazolic antibiotics are able to reduce postoperative CR and ER. IFX and ADA are also able to prevent ER and histological recurrence[38], but more studies are required. IFX also appears promising in ER treatment (inducing mucosal healing). Even if 5ASA are of little benefit, they seem to be cost-effective at 5 years. In children, supplementary EN should have an important role. The decision on the most appropriate treatment and the time for its introduction remains individualized and depends on local practices. Studies focusing on genetics, immunology, gut microbiota, diet and their interactions will provide more insights into this burning issue.

Table 4: Infliximab in the treatment of endoscopic recurrence of Crohn's disease

Author, year	Type of trial, duration	Population (n)	Medication	Effect (%)	Comments
Yamamoto 2009[83]	OL, 6 months	26 with ER at 6 months (after 6 months of 5ASA) (8 IFX, 8 AZA, 8 5ASA)	IFX 5 mg/kg/8 weeks vs. AZA 50 mg/d vs. 5ASA 3 g/d	Endoscopic improvement: 75 vs. 38 vs. 0 CR: 0 vs. 38 vs. 70 Complete mucosal healing: 38 vs. 13 vs. 0	Mucosal IL-1β, IL-6, TNFα levels: significant ↓ with IFX, no significant change with AZA and significant ↑ with 5ASA
Sorrentino 2010[84]	Case series, 1 year	10 with ER, 4 months after stopping IFX (IFX previously given, 5 mg/kg/8 weeks, 3 years with no ER)	IFX 3 mg/kg/8 weeks	Endoscopic remission: 100	40 % reduction from the standard dose is effective Fecal calprotectine levels–correlated with endoscopic scores
Sorrentino 2012[85]	OL, multicenter 54 weeks	24 with ER at 6 months (13 vs 11)	IFX 5 mg/kg/8 weeks vs. 5ASA 2.4 g/d	Endoscopic remission: 54 vs. 0 Clinical remission: 100 vs. 82	IFX: 69 % with improvement in the endoscopic score

OL – open-label; AZA – azathioprine; 5ASA – 5-amino-salicylates; IFX – infliximab; CR – clinical recurrence; ER – endoscopic recurrence; IL – interleukin; TNFα–tumour necrosis factor α; d – day; ↑–increase; ↓–decrease

List of abbreviations

ADA ..... adalimumab
5ASA 5-amino-salicylates
AZA ..... azathioprine
CD ..... Crohn's disease
CR ..... clinical recurrence
EN ..... enteral nutrition
ER ..... endoscopic recurrence
IFX ..... infliximab
6MP ..... 6- mercaptopurine
NNT ..... number needed to treat
NS ..... not significant
POR ..... post-operative recurrence
RCTs ..... randomized controlled trials
SASP ..... sulfasalazine
SICUS .... small intestine contrast ultrasonography
SR ..... surgical recurrence
TNFα ..... tumour necrosis factor α
VCE ..... videocapsule endoscopy

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