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REVIEW ARTICLE

Prevention of Post-operative Crohn's disease recurrence; beyond medications

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Abstract

Historically up to 80% of Crohn's disease patients required at least one surgical resection in their lifetime. Current 'treat to target' management and a burgeoning availability and variety of agents beyond anti-tumour necrosis factor alpha drugs aim to delay and/or reduce the rates of surgery in Crohn's disease. However, surgery continues to be necessary for many. Even more difficult for patients is the need for repeated surgery with the impact this has on their daily life as well as the increasing risk of stoma and nutritional deficiencies with each operation. Despite the use of biologics, immunomodulators and antibiotics post-operative recurrence is common leading to re-operation in about a third of patients at 10 years from the first operation. Therefore, new approaches are required. Predicting which patients will develop recurrence using genetic and microbiome markers is one approach. Choosing surgical techniques that reduce recurrence rates is another and finally dietary approaches to manipulate the microbiome to reduce recurrence are another potential avenue. We review the literature on postoperative recurrence rates as well as the evidence for these alternative approaches. The aim is to be able to reduce recurrence rates whilst accurately predicting which patients will have disease recurrence with the ultimate goal of a more personalised preventive approach.

Keywords: Crohn's disease; postoperative recurrence; genetics; gut microbiome

Introduction

Crohn's disease (CD) is a chronic inflammatory gastrointestinal disease, first described as regional ileitis in 1932 and surgical resection was the only available treatment at that time.[1] The current goals of treatment are induction and maintenance of remission, steroid-free mucosal healing, to improve quality of life and reduce the risk of hospitalisation and surgery.[2] Despite the array and availability of medical treatments for Crohn's disease continues to increase at a pace; however, many patients' disease does not respond to the medication. Indications for surgery include penetrating/ fistulising disease and obstructive disease without significant active inflammation.[3] Increasingly surgery is also being offered as first-line treatment in isolated non-stricturing terminal ileum disease (affecting <40cm).[4]

A large retrospective cohort study from Sweden reported the incidence of primary surgery in Crohn's patients within 5 years of diagnosis as 54.8% (1990-1995), consistently declining to 17.3% (2009-2014), p <0.001. However, re-operation rates remained static.[5]

The rates of postoperative recurrence (POR) vary in the literature according to how this is defined i.e. endoscopic, clinical or surgical recurrence. Endoscopic recurrence is commonly defined according to the Rutgeerts score and is predictive of symptomatic recurrence.[6] This is the most used indicator of recurrence with reported endoscopic recurrence rates of 30% to 90% within a year of primary resection.[7–9] The definition of clinical recurrence varies in studies e.g. need for treatment escalation, increase in Crohn's disease activity index (CDAI) or recurrence of symptoms. Postoperative clinical recurrence is reported as 10% to 38% at 1 year, and 33% to 44% at 5 to 10 years respectively.[9,10] Surgical recurrence i.e. the need for repeat surgery is the most objective definition.[11] These different definitions lead to great heterogeneity in post-operative recurrence rates quoted.

A 2021 meta-analysis (studies mainly included patients from Europe and Canada) estimated the cumulative risk of re-operation in patients with CD diagnosed after 2000 was 14.8% (95% Confidence Interval (CI) 11.0-19.7) and 25% (95% CI 11.9-49.6) after 5 and 10 years respectively. [12] These post-operative surgical recurrence rates are reassuringly lower when compared to a 2014 metanalysis of studies conducted after the 1980s (10-year reoperation rate of 33.6%, 95% CI 31.2-35.4%) and pre-1980s (44.6%, 95% CI 37.7-52.7%).[13]

Treatments and strategies to prevent POR are limited in their efficacy. There is always a balance to be struck between the under and over-treatment of patients. Current guidelines recommend treatment in patients who have a higher risk of disease recurrence.[14] Smoking is the most significant predictor of postoperative disease recurrence (odds ratio, OR:2.65; 95% CI 1.42-4.97).[15] Other factors that increase the risk of disease recurrence include previous resection, penetrating disease behaviour, associated perianal disease and extensive small bowel (> 50 cm).[16,17] In addition to these, the histological risk factors for POR have been identified, such as the presence of granulomata and myenteric plexitis in the resection margin.[18,19] The current British

Society of Gastroenterology (BSG) guidelines recommend post-operative prophylactic thiopurines or anti-tumour necrosis factor alpha drugs (anti-TNFα) in the presence of one or more of the above risk factors.[14] In a double-blind placebo-controlled randomised control trial (RCT), thiopurines reduced the clinical recurrence rates in smokers by 13% compared to 46% in the placebo group but not in other groups.[20] As endoscopic recurrence can predict clinical recurrence, a strategy of performing colonoscopy at 6 months post-operatively and commencing treatment accordingly is recommended.[14] In one prospective RCT from New Zealand and Australia patients were treated according to risk factors and then if patients had endoscopic recurrence at six months (Rutgeerts i2), their treatment was escalated i.e. initiation or escalation of thiopurine, anti-TNFα alone or both. Recurrence rates in the treatment group versus (vs.) control group were as follows: endoscopic recurrence (49% vs. 67%) and clinical recurrence (27% vs. 40%) respectively.[21]

A 2021 metanalysis of 24 studies looking at the use of anti-TNF agents (infliximab and adalimumab) for the prevention of POR in Crohn's disease reported the effectiveness with reduced rates of endoscopic POR of 21.72% at 1 year, 84.21% at 5 years and surgical POR of 3.76% at 1 year, 17.49% at 5 years.[22] Despite this National Institute for Health and Care Excellence (NICE) evidence review recommends against offering biologics to maintain remission after complete macroscopic resection based on limited clinical evidence and lack of cost effectiveness.[23]

There are a number of prospective studies in progress looking at the best strategies for low-risk patients and those with i2 recurrence at six months to avoid overtreatment (SOPRANO-CD NCT05169593 and POMEROL NCT05072782). A recent ECCO scientific workshop acknowledged the gaps in predictive markers of POR, post-surgical ilecolonoscopy guided medical treatment as an area needing further research.[24]

This narrative review will look at other emerging areas of interest in the prevention of POR.

These include surgical techniques, dietary manipulation and the microbiome as well as individual risk profiling using genetic and immunological profiling.

Methods:

We conducted a comprehensive literature search with the following MeSH terms and free text words: "Crohn's disease", "post-operative", "recurrence", "Exclusive Enteral Nutrition", "enteral nutrition", "Kono-S anastomosis", "side-to-side anastomosis", end to end anastomosis", "mesenteric excision", "microbiome", microbiota", "microflora", "genetics", genome", "mutation".

Effectiveness of surgical techniques in preventing postoperative recurrence of Crohn's disease

Current guidelines recommend stapled side-to-side anastomoses given lower rates of postoperative complications and assume that wider diameter results in lower clinical and

surgical recurrences.[25] This is backed up by 2014 and 2018 meta-analyses reporting the superiority of side-to-side stapled anastomosis over hand-sewn anastomosis in terms of fewer clinical, and surgical recurrences and complications. [26,27]

There are a number of pathophysiological mechanisms which currently form the basis of novel surgical techniques aiming to prevent postoperative recurrence.[28] It is postulated that faecal and colonic content reflux into the upstream small intestine may increase the risk of POR.[29] With this knowledge there is a growing interest in implementing techniques to protect the neo-terminal ileum from colo-ileal reflux to reduce and ideally prevent the POR. Bakkevold et al. tested the effect of ileocolic nipple valve anastomosis preventing the reflux of colonic contents in a single centre non-randomised study of 59 patients showed low 5 yearly cumulative clinical and surgical recurrence of 24% and 16% respectively.[30]The same protective effect of the anti-reflux valve was also demonstrated in small series of 6 patients followed up over 7 years.[31]

The Kono-S anastomosis technique has been the subject of interest and ongoing RCTs as initial results are promising for the prevention of POR. Kono et al. reported the results of this handsewn antimesenteric functional end-to-end anastomosis in 2011.[32] In their index study, Kono-S anastomosis was performed in 69 Crohn's disease patients (2003-2009) and results were compared with conventional anastomosis in a historical cohort of 73 patients (1993-2003). Anastomotic surgical recurrence at 5 years in the Kono-S group was zero compared to 15% in a conventional cohort (p<0.0013). This data has been reproduced by a number of case series and retrospective comparative cohort studies.[33–36] More recently the first RCT from Italy randomised 36 ileocolic Crohn's disease patients in the Kono group and 43 in the conventional group. This RCT showed reduced endoscopic recurrence at 6 months in the Kono group 22.6% vs. 62.8% conventional group (p <0.001, OR 5.91), reduced clinical recurrence after 12 months (8% Kono vs 18% conventional, p=0.2) and 24 months (18% KonoS vs 30.2% conventional group, p: 0.04, OR 3.47).[37] A randomised controlled UK study (MEErKAT) is currently recruiting. (Table 1)

Mesenteric hypertrophy and fat wrapping is a frequent observation in Crohn's disease surgery. It has been postulated that the mesentery is the primary driver of inflammation and post-operative recurrence in Crohn's disease and mesenteric abnormalities have been detected before any apparent mucosal abnormalities.[38,39] The mesentery may exert this effect through a variety of mechanisms ranging from mesenteric fat-driven pro-inflammatory cytokines production and mesenteric lymph nodes harbouring recurrence-driving memory T cells and abnormal B lymphocyte aggregates.[38,40,41] A review by Coffey et al. elaborated on pathological mesenteric contribution to topographic distribution of Crohn's disease and mucosal pattern and showed a correlation between the mesenteric inflammatory index and Crohn's disease

activity index (CDAI) and mucosal inflammation. [39] Mesenteric excision is used in colon cancer surgery but not performed in Crohn's disease surgery due to concerns of bleeding risk from a thickened inflamed mesentery. Coffey et al reported results of ileocecal resection with extensive mesenteric excision in 34 CD patients compared to a historical cohort of 30 CD patients with a mesentery preserving approach.[42] Extensive mesenteric resection led to a statistically significant reduction in surgical recurrence rates of 2.9% vs 40% p= 0.003.[42] Although the results are striking there are many limitations to this study. The two groups were operated on during two very different periods with different lengths of follow-up and were not matched as regards Montreal's classification of Crohn's disease.[43] There was inflammation at the mucosal margins in 79% of the control group and only 16% of the mesenteric resection group and this is a recognised risk factor for disease recurrence.[43]

Kono-S anastomosis techniques and extensive mesenteric excision approaches are currently not recommended. However, the definitive answers to the effectiveness of these promising techniques await the outcomes from the number of large multicentre RCTs currently underway (Table 1)

Table 1: Research on EEN & new surgical techniques (in progress)

Identifier	Location	Study Design	Title	Size	Intervention	Primary Outcome	Recruitment Status
NCT041 60325	Jinling Hospital Nanjing China	RCT	The Effect of Exclusive Enteral Nutrition Combined with Azathioprine in Maintaining Remission of Patients with Crohn's Disease After Surgery	54	Patients are randomized to two groups: Postoperative 3 months of EEN +Azathioprine Post operative normal diet +Azathioprine	Postoperative Endoscopic recurrence at 1 year	Recruiting
NCT052 14430	Jinling Hospital Nanjing China	RCT	Exclusive Enteral Nutrition for Remission of Crohn's Disease After Surgery	198	Patients are randomized to two groups 3months of EEN after surgery and 1months of EEN after surgery	Postoperative endoscopic recurrence (>i2b Rutgeert's score) at 1 year	Recruiting
NIHR133 657	Multicent-re UK (40 NHS hospitals)	RCT	Optimisation before Crohn's surgery using Exclusive enteral Nutrition (OCEaN)	618	Patients will randomised to 6 weeks EEN before surgery vs usual diet	6 weeks postoperative: 1. Assessing the impact of Crohn's disease on life quality (Patient reported Crohn's Life Impact Questionnaire) 2. Post-operative complications (Comprehensive Complication Index, CCI)	Recruitmen t from April 2023
NCT032 56240	Multicentre: US, Belgium, Finland, Italy, GermanySp ain	RCT	Prospective Randomized Study of the Kono-S Anastomosis Versus the Side to Side Functional End Anastomosis in Prevention of Post operative Recurrence of Crohn's Disease	88	Patients are randomized in two Groups: Group 1: Kono-S anastomosis Group 2: side-to-side functional end anastomosis.	Postoperative Endoscopic remission with Rutgeert's score at 12 and 18 months	Recruiting
NIHR131 988	Multicentre UK, 12 NHS Hospitals	RCT	MEErKAT MEsenteric Excision and Kono-s Anastomosis Trial	308	Patients are randomised to one of four groups: (1) Kono-S + radical mesenteric resection; (2) Kono-S + close mesenteric resection; (3) Standard anastomosis + radical mesenteric resection; (4) Standard anastomosis + close mesenteric resection	Postoperative endoscopic recurrence after 12 months and at 3 years (Rutgeert's score >/=i2).	Recruiting
NCT037 69922	General Hospital of Eastern Theater Command Nanjing, Jiangsu, China	RCT	The MESOCOLIC Trial: Mesenteric Excision Surgery or Conservative Limited Resection in Crohn's Disease	116	Patient are randomised to Extensive mesenteric excision (mesentery resected 1cm from the root of ileocolic artery & vein) vs Limited Mesenteric excision (close mesenteric excision 3cm from the border of bowel)	Accumulated 5-year postoperative surgical recurrence	Recruiting
NCT046 23476	Policlinico Tor Vergata Roma, RM, Italy	Prospective pilot study	PAtophysiological, Nodal-based Approach for Crohn's Disease Excision: A PILOT Study	12	Patient with ileocolic Crohn's diseas requiring 1st surgery Excision of lymph nodes draining the disease bowel and latero-lateral anastomosis to be carried out	Post operative Endoscopic recurrence at 6 & 12 months (Rutgeerts Score >1)	Recruiting

Can dietary manipulation reduce post-operative recurrence rates?

Epidemiological studies provide extensive, although inconsistent data on dietary risk factors for IBD development.[44] The diet with the best therapeutic evidence is Exclusive Enteral Nutrition (EEN). EEN is a term used for a complete liquid diet, with the exclusion of routine dietary components for a defined period of time, and is a therapeutic strategy for the induction of remission in active Crohn's disease.[45] Elemental forms of EEN have poor palatability, however polymeric (whole protein) and semi-elemental (peptide) formulas are better tolerated and the Cochrane review demonstrates no statistically significant difference in terms of efficacy between these formulations.[46] Most frequently used forms of EEN are polymeric feeds such as Fortisip™, Ensure™, or Modulen™.[47] In adults, RCTs on EEN to induce remission are lacking, however, a Cochrane review showed EEN was effective but inferior to steroids; most likely due to poor compliance with EEN.[46]

ECCO review of perioperative dietary therapy reports EEN as a promising preoperative optimisation strategy for reducing complications and improving nutritional status in Crohn's disease patients.[48] There is emerging evidence on the effectiveness of EEN in reducing endoscopic POR. Wang et al. compared the effectiveness of 4 weeks of preoperative EEN given to a group of 41 patients undergoing bowel resection for ileal and ileocaecal Crohn's disease to a non-EEN group of 39 patients. The researchers defined the post-operative endoscopic recurrence as Rutgeerts score ≥ i2 and clinical recurrence as CDAI ≥ 150 or at least an increase of 70. They demonstrated the reduced endoscopic POR in EEN vs non-EEN groups; 7.1% vs 25.6% (at 6 months *p* 0.03), 21.4% vs 33.3% (at 12 months *p* 0.23), 31% vs 43.6% (at 18 months *p* 0.24), 47.6% vs 56.4% (at 24 months *p* 0.43). Clinical recurrence was similar at 2 years (*p* >0.05).[49] Another study using similar definitions of endoscopic and clinical POR, also supports these findings and reported significantly fewer 6 months endoscopic POR in the patient group who received 4 months of preoperative EEN compared to the control cohort (11.4% vs 28.4%, *p* 0.044). Again, this difference was not demonstrated for clinical recurrence between the two groups at 12 months.[50] The same study evaluated the factors associated with early endoscopic recurrence and found preoperative EEN as an independent factor reducing this risk OR: 0.32 (CI 0.113 - 0.949, *p* 0.040).[50]

There is also an interest in partial enteral nutrition (PEN) where a proportion of a patient's diet is liquid formula feed providing 30% to 50% of the caloric requirement. A prospective nonrandomised parallel controlled trial by Yamamoto et al. investigated the outcomes of clinical POR (CDAI ≥ 150) and endoscopic POR (Rutgeerts ≥ i2) in PEN cases (20 patients) compared to controls (20 patients) at 1 year following the ileal and ileocolic resection for Crohn's disease. PEN cohort was commenced on a combination of nocturnal elemental diet via nasogastric route at one to two weeks postoperatively plus a

low-fat diet during day time and continued this for one year. The clinical and endoscopic recurrence rates at one year in PEN group were reassuringly low, clinical; 5% PEN vs 35% controls (*p* 0.048), endoscopic 30% PEN vs 70% controls (*p* 0.027).[51]A further extension of the same study showed that 30% of PEN group developed clinical recurrence (CDAI ≥200) compared to 60% in the control group over the last 4 years of study and cumulative recurrence rate requiring infliximab (*p* 0.02) and reoperation (*p*=0.08) were lower in PEN group.[52]

The first large UK multicentre RCT aiming to recruit 618 patients from 40 UK-wide hospitals will start recruitment in April 2023 and will provide valuable information on the role of EEN compared to normal diet in the preoperative optimisation of Crohn's disease. Although not one of the primary outcomes, post-operative endoscopic and clinical recurrence will be measured at one year. There are a number of ongoing international RCTs aiming to establish the effectiveness of EEN (Table 1)

The protective and therapeutic role of specific diets such as the Mediterranean diet[53], empirical diet inflammatory pattern scoring[54], and exclusion diets[55] have been explored in general, but not in the context of reducing or preventing the disease recurrence following resection in Crohn's disease.

It is postulated that the therapeutic effect of EEN is mediated by altering the gut microbiome.[44,56,57] EEN causes a broad reduction in bacterial diversity, changes community-level metabolic functions, and may increase microbial dysbiosis initially followed by recolonization with favourable microbiota promoting remission.[57] It is possible that the beneficial effect of EEN in the postoperative period is due to a favourable alteration of the microbiome establishing a healthier symbiotic profile. Assessment of gut microbiota profile alteration in the context of pre or post-operative EEN may improve our understanding of the pathogenesis of POR in Crohn's disease and microbial therapeutic targets.

Microbiome predictive potentials for postoperative recurrence and therapeutic targets

The aetiopathogenesis of Crohn's disease is multifactorial and involves a complex interplay of genetic defects, and environmental factors such as diet resulting in the accumulation of pathobionts; a phenomenon termed dysbiosis.[58] This is followed by larger alteration in bacterial taxa, and overall decreased microbial diversity triggering chronic inflammation.[58] There appears to be a link between gut microbiome dysbiosis and post-operative disease recurrence.[59,60] In a small pilot study using largely early microbiome techniques i.e. pyrosequencing and microarray data De Cruz et al. showed increased biodiversity between the time of surgery and six months postoperatively. Patients with disease recurrence retained microbiota favouring proteolytic fermentation and lactic acid production, including Enterococcus and Villonella species. In contrast, those remaining in remission had a predominance of saccharolytic Bacteroides, Prevotella, Parabacteroides species

and butyrate-producing Firmicutes.[61] Using similar technology Wright et al reported reduced Faecalibacterium (< 0.1%) and detectable Proteus in the postoperative ileal mucosa when corrected for smoking predicted increased risk of post-operative endoscopic recurrence (Rutgeerts ≥ i2) OR: 14 (1.7–110), *p* 0.013 and 13 (1.1–150), *p* 0.039, respectively.[62]

More recent studies using 16S RNA sequencing identified distinct temporal trends in luminal and mucosal microbial profiles between those with POR and remission.[63–65] A large prospective cohort of 121 CD undergoing ileocaecal resection study reported differences in the that the mucosal-associated microbiota between those with recurrence and without. Recolonisation after ileocecal resection in cases with endoscopic POR at 6 months was characterised by increased Fusobacteria of both mucosal and faecal communities compared to patients without endoscopic POR. Lachnopiraceae enrichment and a decrease in Streptococcaceae and Actinomycineae were seen in patients without POR. The mucosa-associated microbiota profile had good discriminative power to predict POR and was to be superior to clinical risk factors.[66] One study found that endoscopic POR was associated with an increased concentration of urinary levoglucosan and some of the urinary metabolites correlated with the mucosal microbial profile of those with endoscopic POR.[67]

There is limited consensus on the use of the predictive potential of faecal or mucosal microbial sequencing due to the cost of this analysis and the heterogeneity found in studies.[68]

The obvious next question given the divergence in microbial patterns in patients with or without POR is whether regulation of gut microbiota can prevent POR. Several trials have investigated the role of antibiotics and probiotics. Rutgeerts et al. reported that 3 months of treatment with metronidazole significantly reduced the incidence of severe endoscopic POR compared to placebo (13% vs. 43%, *p* 0.02).[69] Although metronidazole delayed the clinical POR at 1 year, the effect was not maintained at 2 and 3 years. Moreover, Metronidazole was not tolerated by 30% of patients.[69] Taking ornidazole 1g/day was similarly effective in reducing clinical recurrence at 3 months and 1 year, however not beyond 1 year.[70] Ciprofloxacin did not prove effective in preventing postoperative recurrence.[71] Rifaximin is an appealing option due to its non-absorbable property with a reduced side-effect profile however at present there are no reported trials using Rifaximin alone in the context of post-operative recurrence.[14,71] However Rifaximin for three months followed by VSL#3 for nine months was effective in preventing the severe endoscopic POR when compared to Mesalazine in a study published only in abstract form.[72]

Another approach would be using pro or prebiotics to alter the microbiome and reduce POR. Two RCTs looked at Lactobacillus Johnsonii and both failed to show a decrease in endoscopic POR rates .[73,74] A small prospective study using VSL#3 (100 billion viable bacteria, comprising 4 strains of Lactobacillus, 3 strains of Bifidobacterium,

and 1 strain of Streptococcus Salivarius subspecies Thermophilus) showed a decrease in severe endoscopic POR at 1 year in the subgroup of patients with POR at 90 days and who started treatment immediately post-operatively. The primary outcome was set at 90 days and there was no significant difference found at this time point. [75] A small randomised placebo-controlled trial by Chermesh et al. recruited 30 Crohn's patients in the immediate post-operative period to the treatment arm with Synbiotic 2000 (4 probiotics and 4 prebiotics) or placebo in 2:1.This RCT did not find the difference in clinical and endoscopic POR at 3 and 24 months or at withdrawal.[76]

So overall, the therapeutic benefits of antibiotics and probiotics directed at preventing the POR remain largely inconclusive or negative.

Post-operative recurrence-associated Genetic signals

Genetic contribution to the pathogenesis of Crohn's disease was first recognised from familial observations and twin studies.[77] Genome-wide association studies (GWAS) have identified 163 IBD susceptibility loci, of which 30 are specific to Crohn's disease.[78] Among these NOD2 is the most well-established pathological loci and is strongly associated with ileal disease, fistulating stenotic disease behaviour, and the need for surgery.[79] NOD2 mutations alter the regulatory interactions between microbiota and mucosal immunity resulting in increased disease predisposition.[80] NOD2 variations (loci G908R, L1007fs, R720W) not only increase the risk of Crohn's development but also the risk of post-operative surgical recurrence.[81–83] A 2021 metanalysis on postoperative recurrence (defined as surgical recurrence in 67.9% of included studies) reported specific risk alleles at NOD2 as a significant risk factor for POR with OR 1.64 (95% CI 1.18-2.27, *p* 0.003).[84] More specifically, the R720W SNP variant increased the risk of post-surgical recurrence OR 1.59, 95% CI 1.06-2.40, *p* 0.02.[84]

In addition to NOD2, studies over the last decade have investigated a variety of susceptibility loci in relation to the increased risk of POR.[85–88] Gerich et al. reported number of variant IBD loci; LSP1/TNNI2 (HR 1.4, *p* 0.04), PTGER4 (HR1.3, *p* 0.04), DAP (HR 1.4, *p* 0.04) and immune-related genes; FAM49B (HR 3.2, *p* 3x10-6), PELI3 (HR 1.8, *p* 1x10-6), CHL1 (HR 2.6, *p* 4x10-5), STK24 (HR1.7, *p* 9x10-5) bearing significant association to reduced time to post-operative surgical recurrence. [87] A prospectively followed cohort of 191 Crohn's patients with intestinal resection were genotyped for 8 loci relevant to adaptive immunity and identified homozygous risk allele at BACH2 (rs 1847472) increased the risk of post-operative surgical recurrence (HR 1.54;95% CI 1.00-2.36 *P*<0.05).[88] A retrospective study of 137 Crohn's patients with previous one resection, analysed for the time to surgical recurrence, reported CARD 8 (rs 2043211) was independently associated with risk of surgical recurrence (OR 7.56, CI 1.13-50.37), *p* 0.036.[86] In a retrospectively studied cohort of 66

patients with previous ileocolectomy, 20 patients with SNP rs4958847 IRGM (immunity-related GTPase family M, a gene involved in autophagy) had an average of one surgical resection every 6.87+/- 1.33 years compared to the 46 patient without the risk allele for this SNP who averaged one surgery in 11.43+/- 1.21 years p=0.007).[85]

The evidence for loci other than NOD2 generates from single studies lacking the consistency and differences in examined loci, end point of recurrence. A standardised reporting framework on genetic association studies for post operative recurrence as suggested by Dang et al. should be implemented for future research.[84]

Conclusion:

Earlier diagnosis and early 'step down' treatment are strategies that may help reduce the need for first operation in patients with Crohn's disease complications i.e. structuring/fistulating disease. Reducing the risk of post-operative disease recurrence is likely to need a different strategy balancing the risks of overtreatment with the risk of repeated surgery. We need to be able accurately to predict which patients will develop recurrent disease and target treatments appropriately. Clinical and histological data as well as genetic phenotyping and mucosal microbial analysis could be modelled to offer more personalised treatment. High-risk individuals could then be offered dietary, microbial as well as medical therapies to reduce POR. Results of surgical studies are eagerly awaited to help decide if the current approach needs to change to Kono-S with mesenteric resection. Further research is needed to determine whether this model can accurately predict post-operative recurrence and if so which treatments would be most effective in each individual so that repeated surgery is avoided.

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