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REVIEW

Predictors of recurrence of Crohn's disease after ileocolectomy: A review

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Abstract

Recurrence after ileocolectomy for Crohn's disease (CD) is common and occurs in up to 80% of patients. Such recurrence can result in repeated surgical interventions, an increased need for medical treatment and, frequently, an impaired quality of life. The aim of this overview is to provide a summary of the factors associated with disease recurrence after ileocolectomy for CD. Recurrence can be measured clinically or endoscopically using established scoring systems. Radiology and serologic tests can also be used, oftentimes in conjunction with endoscopy and/or clinical findings. Many patient and operative factors as well as pharmacologic treatments have been studied as potential predictors of recurrence. Of these, only smoking and immunomodulatory or biologic medical treatment have repeatedly been shown to effect recurrence. Genetic predictors have been studied and suggested but further evaluation in larger cohorts is necessary. This paper highlights validated, reproducible scoring systems for recurrence and the key findings of studies including patient demographics, operative techniques, various pharmacological treatments and histological findings as predictors of recurrence post ileocolectomy in CD.

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Key words: Crohn's disease; Ileocolectomy; Recurrence; Surgical genetics; Inflammatory bowel disease

Core tip: Disease recurrence after ileocolectomy for Crohn's disease is common. Studies have been very heterogenous in defining recurrence as it can be clinical, endoscopic, radiologic or serologic. Of the potential predictive factors studied, smoking has been consistently demonstrated to increase the risk of recurrence. While immunomodulator and biologic medical treatment have been shown to increase the time between surgery and recurrence and may decrease overall risk. Genetic predictors have been suggested but further evaluation in large groups is needed. Several other demographic and operative factors have been studied. However, none have been consistently shown to affect recurrence risk.

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INTRODUCTION

Crohn's disease (CD) is a chronic immune mediated disease of the gut that was first described as "regional ileitis" by Crohn, Ginzburg and Oppenheimer in a case series presented at American Medical Association annual meeting in 1932[1]. CD is characterized by inflammation, abscesses, fistulization and stricturing that can affect any part of the gastrointestinal tract. However, the most common distribution is the ileocolic region, the location where the small

Table 1 Types of postoperative recurrence and evaluation type

Type of recurrence	Evaluation method
Clinical	Questionnaire, CDAI, Harvey-Bradshaw Index, IBDQ
Endoscopic	Rutgeerts score, Crohn's disease endoscopic index of severity
Radiographic	CT or MR enterography, barium enema small bowel follow through
Serological	Measurement of CRP and ESR
Surgical	Requirement for repeat surgery

CDAI: Crohn's disease activity score; IBDQ: Inflammatory Bowel Disease Questionnaire; CT: Computed tomography; MR: Magnetic resonance; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2 Factors in the Crohn's disease activity score

General well-being
Number of stools/d
Abdominal pain
Weight loss
Presence of arthralgia, fistuli, fever and/or ocular, dermatological or anal manifestations
The need for anti-diarrheal medication
Abdominal mass
Hematocrit

Based on patient symptoms during the 7 d prior to taking the survey.

Table 3 Factors in the Rutgeerts endoscopic recurrence score for postoperative recurrence of Crohn's disease in the distal ileum

Endoscopic appearance	Score
No aphthous ulcers	0
< 5 aphthous ulcers	1
> 5 aphthous ulcers with normal mucosa between the ulcers	2
Diffuse aphthous ulcers throughout the ileum with intervening inflamed mucosa	3
Large ulcers with diffuse inflammation, nodules or narrowing of the ileum	4

bowel and colon meet. Approximately 55% of all CD patients have an ileocolic disease distribution, followed by colonic and small bowel distributions in approximately 20%-30% and 15%-20% and of patients respectively[2].

Although not curative, surgery is commonly required for the sequelae CD (*e.g.*, abscess, fistula, perforation, bleeding and failure of medical treatment). Up to 80% of CD patients require at least one surgical intervention in their lifetime. The most common resection is the ileocolectomy. Recurrence at the site of the anastomosis is common and challenging[3,4]. Multiple resections due to recurrent disease can lead to short gut syndrome, malabsorption and malnutrition with significant morbidity, decreased quality of life and increased hospital and outpatient costs[5]. This review highlights the patient and disease related factors that are associated with an increased risk of disease recurrence after ileocolectomy in its many forms including clinical, endoscopic and radiologic recurrence.

Defining recurrence

Recurrence can be defined in several different ways using a multitude of modalities. Such inconsistency in regard to what constitutes recurrence in conjunction with heterogeneity among patient populations and prophylactic measures against recurrence given leads to a large variance in recurrence rates between studies (Table 1)[6]. Clinical and endoscopic recurrence are most commonly reported.

Clinical recurrence is loosely defined as an increase in patients' symptoms including diarrhea, weight loss and abdominal pain. For the most appropriate investigation and reporting of clinical recurrence, established validated quality of life questionnaires such as the Inflammatory Bowel Disease Questionnaire[7] or scoring systems such as the Crohn's disease activity score (CDAI) or Harvey-Bradshaw Index should be used[8]. The CDAI can be clinician or self-administered and contains subjective questions (on general well-being and symptoms such as abdominal pain) as well as objective measures (such as hematocrit, numbers of stools per day, weight loss, the presence of arthralgia, fistuli, fever, an abdominal mass and/or ocular, dermatological or anal manifestations) (Table 2)[9,10]. Endoscopic recurrence uses colonoscopy or ileoscopy as appropriate to determine the presence of recurrence, which is most commonly found at the site of the anastomosis. The Rutgeerts visual grading system evaluates the presence and number of aphthous ulcers and the intervening mucosa in the perianastomotic region and is the most commonly used internationally recognized endoscopic grading system for post ileocolectomy recurrence (Table 3)[11,12]. Radiographic recurrence is less commonly studied and is often utilized as an adjunct to clinical or endoscopic recurrence. CT or MR enterography, small bowel follow through and/or barium enema are the modalities currently employed[13]. Serological recurrence is defined by the elevation of serum inflammatory markers such as C reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Although more novel interleukin markers have been studied, none are in clinical use to date. Surgical recurrence is determined by the requirement for repeat ileocolectomy and is often indicative of more severe disease. Oftentimes, these different classifications of recurrence are studied in conjunction with each other.

Endoscopic, radiographic and serologic recurrence rates are in actuality higher than reported as frequently, only clinically symptomatic patients are investigated. Additionally, there is limited concordance between the different types of recurrence in the individual patient. For example, Bordieianou *et al*[14] compared endoscopic, symptomatic and surgical recurrence rates in approximately 200 ileocolectomy patients and found that while 31.2% of their cohort had documented endoscopic recurrence, only 23.1% had symptomatic and 11% had surgical recurrence. This disparity was also demonstrated

Table 4 Overall recurrence rates by post ileocolectomy follow up and type of recurrence

Time post ileocolectomy	Type of recurrence	% of ileocolectomy Patients	Ref.
1 yr	Clinical	0%-44%	McLeod *et al*[61], Walters *et al*[10], Aratari *et al*[27], Bordeianou *et al*[14], Sorrentino *et al*[28], Pascua *et al*[53]
	Endoscopic	0%-84%	Bordeianou *et al*[14], Walters *et al*[10], McLeod *et al*[15,61], Regueiro *et al*[16,82], Rutgeerts *et al*[11], Pascua *et al*[53], Domènech *et al*[80], Sorrentino *et al*[28], Meresse *et al*[40], Lasson *et al*[89]
	Surgical	4%-25%	Aratari *et al*[27], Iesalnieks *et al*[57]
5 yr	Clinical	32%	Aratari *et al*[27]
	Endoscopic	55%-77%	Bordeianou *et al*[14], McLeod *et al*[15], Yamaoto *et al*[42]
	Symptomatic	50%	Bordeianou *et al*[14]
	Surgical	4%-25%	Bordeianou *et al*[14], Aratari *et al*[27], Riss *et al*[56], Yamamoto *et al*[42]
10 yr	Clinical	52%	Aratari *et al*[27]
	Endoscopic	74%	Malireddy *et al*[17], Bordeianou *et al*[14]
	Surgical	12%-57%	Stocchi *et al*[18], Aratari *et al*[27], Riss *et al*[56], Iesalnieks *et al*[57]

in McLeod *et al*[15] 1997 study which included a variety of CD resections, of which 60% were ileocolectomies. Interestingly, 21% of patients with severe symptoms had minimal endoscopic or radiologic evidence of recurrence. Conversely, 28% of the asymptomatic patients studied had endoscopic or radiologic evidence of severe recurrence. Similarly, Regueiro's study of 24 CD patients 1 year post ileocolectomy demonstrated a poor correlation between CDAI scores, serum CRP or ESR and endoscopy findings[16]. Only 87% of patients with endoscopic or radiologic recurrence had symptoms in Malireddy's study[17].

Endoscopic recurrence generally occurs earlier than other types of recurrence with an overall mean time from surgery to endoscopic recurrence ranging from 6 mo to 4 years[14,17]. Mean time to symptomatic recurrence is approximately 5 years[14]. Mean time to repeat surgery has the longest duration, approximately 7 (range of 5-11) years[9]. Overall, rates of approximately 30% for endoscopic, 23% for symptomatic or clinical and 11%-50% for surgical recurrence are documented in the literature[3,14,18]. However, it is more clinically relevant to evaluate recurrence by time period, according to time since ileocolectomy. Overall recurrence rates by time period are shown in Table 4. The multiple factors affecting recurrence are discussed below.

Table 5 Effect of smoking on postoperative recurrence

Association	Number and type of patients	Ref.
Recurrent clinical symptoms (OR = 2.96) Shorter duration to clinical relapse (104 wk shorter) Recurrent clinical symptoms (worse CDAI scores) Increased rates of endoscopic recurrence Increased likelihood of requiring surgery	59 patients post colonic resection for CD (not only ileocolectomies) 182 post colonic resection for CD (not only ileocolectomies)	Kane *et al*[22] Cottone *et al*[23]
Smoking at the time of the 1st ileocolectomy conferred a 2.1 fold increased likelihood of requiring another operation	176 post ileocolectomy patients with at least 1 recurrence	Unkart *et al*[21]
OR of 2.2 for clinical recurrence Increased risk of surgical recurrence particularly at 10 years (OR = 2.6)	Meta-analysis of 16 studies, 2962 patients	Reese *et al*[24]
Smokers had a lower 5 and 10-yr recurrence free likelihood (65 and 45% *vs* 81 and 64% in nonsmokers) Recurrence free rates were lower in those that smoked > 15 cigarettes per day	141 ileocolectomy patients	Yamamoto and Keighley[26]
Patients that quit smoking are less likely to require redo ileocolectomy	266	Ryan *et al*[25]
No association with recurrence	89 lap ileocolectomy patients	Malireddy *et al*[17]
No association with clinical or surgical recurrence	83	Aratari[27]
No association with clinical or endoscopic recurrence	43 resections (30 = Ileocolectomies)	Sorrentino[28]

CD: Crohn's disease; CDAI: Crohn's disease activity score.

PATIENT FACTORS

Demographics

Although gender, age at diagnosis, age at surgery and disease duration have been studied as potential predictors of post-operative recurrence, no correlation has been consistently demonstrated[14,17,19,20].

A positive family history of IBD was demonstrated to confer a 2.2 fold increased likelihood of requiring a second ileocolectomy in Unkart's study of 176 post ileocolectomy patients with at least one surgical recurrence. However, this result has not been replicated in the literature[21].

The most studied and most recognized risk factor for post-operative recurrence is smoking (Table 5). Several studies evaluating smoking as a predictor of recurrence do not exclusively study ileocolectomies. One such study by Kane *et al*[22] followed 59 CD patients post colonic resection. Sixty-nine percent of smokers *vs* 23% of nonsmokers had recurrence documented using a clinical symptom activity score. Odds ratio for recurrence was 2.96 in the smoking cohort and a strikingly shorter dura-

tion to clinical relapse was seen in smokers (130 *vs* 234 wk in nonsmokers). Cottone *et al*[23] similarly followed 182 surgical CD resection patients for 6 years and demonstrated that both smoking and greater disease extent were associated with worse clinical (CDAI) scores and increased risk of endoscopic recurrence. Although several variable were studied, the only significant predictor of surgical recurrence was smoking. Meta-analysis of 16 studies published between 1966-2007 inclusive of 2962 patients undergoing resection for CD demonstrated an OR of 2.2 for clinical postoperative recurrence in smokers and an increased risk of surgical recurrence particularly at 10 years (OR = 2.6, 55.5% *vs* 32.1% in nonsmokers)[24]. However, again, this analysis was not limited to patients who had undergone ileocolectomies only.

Studies that focus solely on ileocolectomy recurrence include Unkart *et al*[21] study which demonstrated that smoking at the time of the 1st ileocolectomy confers a 2.1 fold increased likelihood of requiring another operation. http://www.ncbi.nlm.nih.gov/pubmed?term=Unkart%20JT%5BAuthor%5D&cauthor=true&cauthor_uid=18536967 Repeat ileocolectomy rates of 59%-69% in smokers have been noted by Cullen *et al*[3] and Ryan *et al*[25]. Another study evaluated the relationship between the number of cigarettes smoked daily and recurrence in 141 ileocolectomy patients. Smokers had lower 5 and 10 year recurrence free likelihoods (65% and 45 % *vs* 81% and 64% in non-smokers). Recurrence free rates were lower in those that smoked > 15 cigarettes per day[26]. Although the majority of studies have shown an increased risk for reoperation, Maliredy, Aratari and Sorrentino did not see such an association in their studies which included approximately 195 patients combined[17,27,28].

Genetics

Since the advent of genome wide associations studies, several studies inclusive of large cohorts of both IBD patients and healthy individuals have been performed thus creating a pool of IBD-associated genes and single nucleotide polymorphisms (SNPs). To date, over 300 SNPs and 150 genetic loci have been associated with IBD[29]. With these IBD-associated genes established, a shift towards using these markers to further characterize disease behavior, including postoperative recurrence in CD, has begun[30]. Several "surgical genetics" studies have identified markers of the need for resection in their CD cohorts including mutations within the NOD2, TNFSF15 and C13ORF31 genes[31]. However, fewer studies have focused on determining a marker of recurrence.

NOD2 (nucleotide-binding oligomerization domain-containing protein 2), also known as CARD15 (caspase recruitment domain-containing protein 15), was the first gene to be associated with IBD in 2001[32]. Located on chromosome 16, the gene is expressed in several different cell types key to the pathogenesis of CD such as dendritic cells, monocytes, intestinal epithelial cells and Paneth cells. Its protein product is involved in the recognition a dipeptide found in the bacterial cell wall[33]. NOD2 has been previously associated with ileal[34] and stricturing CD[35].

An early German study evaluated the NOD2 genotypes of 51 post ileocolectomy patients. Fourteen patients required a repeat ileocolectomy. Of the 14, 12 harbored at least 1 NOD2 mutation[36]. This association may be specific to patients of German and other not yet determined ethnicities, as this increased incidence of NOD2 mutations in patients with recurrent disease was not replicated in an Italian multi-center study of 253CD patients, 42% of whom had ileocolic disease. In this study, no relation between NOD2 genotype, age at diagnosis or smoking status and recurrence was found[37]. Similarly, in a recent meta-analysis of 6 studies inclusive of 1003 patients with CD NOD2 genotype was not associated with surgical recurrence. Overall, 39% of patients with a NOD2 mutation required further resection *vs* 30.5% of patients without a mutation (P = 0.06). However, the included studies were very heterogenous, which may have affected results[38].

Another study of only ileocolectomy patients demonstrated the presence of a mutation in the autophagy associated IRGM (Immunity-related GTPase family, M) gene to be significantly associated with more frequent ileocolectomies and earlier time to reoperation in 66 CD patients. Ileocolectomy was performed every 6.8 +/- 1.3 years on average in patients with the at risk genotype for SNP rs4958847 *vs* once every 11.4 years in patients with the wild type genotype[39].

Meresse *et al*[40] studied G microsatellite genotype with the anti-inflammatory gene, IL10 in 36 post ileocolectomy patients. Although genotype affected IL-10 production, no association was seen with endoscopic recurrence.

Nutritional status

Poor nutritional status has been consistently associated with poor outcomes in CD surgery[41]. Thus postoperative enteral feeding has been studied as a potential way to reduce the risk of complications and recurrence. Often, such studies are technically difficult to perform, particularly after patients are discharged from the hospital, and mid-study patient exclusion due to noncompliance is common. In one such Japanese study of 40 post ileocolectomy patients followed for 5 years, 20 received nighttime continuous nasogastric feeding with an elemental diet and a low fat diet during the day. The other 20 did not receive the nighttime feed and had an unrestricted diet. No postoperative steroid, immunosuppressants or biologics treatment was given to either cohort. Thirty percent of the nighttime feeding group *vs* 70% of the controls had endoscopic recurrence at 1 year. Twelve months after surgery, 10% of the night feed and 45% of the control group required biologics during the follow up. Rates for surgical recurrence were 5% and 25% in the 2 groups but this was not statistically significant[42].

Much attention has been given to the gut microbi-

ome and how it interacts with the disease process in CD[43]. However, few studied have centered on altering the gut microbiome to maintain remission in patients who have undergone resection. A meta-analysis of 10 controlled clinical trials evaluating disease recurrence, demonstrated that probiotics were not associated with either endoscopic or surgical remission. In this meta-analysis patients who had undergone surgery or medical treatment prior to the administration of probiotics were not considered separately[44]. Another systematic review of 24 manuscripts evaluating endoscopic recurrence demonstrated that enteric diets were associated with 61% reduction in endoscopic scores. However, again postoperative patients and patients in medical remission were not considered separately[45]. One multicenter randomized study by Van Gossum *et al*[46] focused only on post ileocolectomy patients and the effect of administration of the probiotic LAl *vs* placebo on early (12 wk) post ileocolectomy recurrence in 49 patients. Patients were stratified according to smoking status. There was no difference in endoscopic or clinical recurrence scores seen between the 2 groups. Twenty one percent of the placebo *vs* 15% of the probiotic group had recurrence scores indicative of severe recurrence but this difference was not statistically significantly different.

DISEASE BEHAVIOR

Penetrating vs non-penetrating

Disease behavior is difficult to use as a predictor of endoscopic recurrence due to the varying course of CD typically seen within the individual patient. The Montreal classification of inflammatory *vs* stricturing *vs* penetrating (fistulizing/abscessing) disease is commonly used to classify CD according to its behavior[47]; however, behavior often changes from inflammatory to stricturing or penetrating over time[48-50]. Also, at any time point a patient may have more than 1 type of disease behavior, (*i.e.*, a stricture and a fistula) presenting challenges with classification. Additionally, penetrating disease that is initially responsive to a particular medical treatment may lose responsiveness with repeated doses and thus transform from a penetrating to inflammatory to penetrating phenotype when responsiveness ceases[51].

Nonetheless, several studies have attempted to correlate disease behavior with risk of post-operative recurrence. In multiple studies, including 2 large Italian multicenter studies, disease behavior was not shown to affect the risk of disease recurrence clinically, surgically or endoscopically[14,20,27,52]. Although not a primary end point of the study, a meta-analysis of 12 randomized controlled trials that evaluated medical therapies after CD resections (not exclusively ileocolectomies) from 1966 to 2005, demonstrated that fistulizing disease was significantly associated with endoscopic but not clinical recurrence in patients who had been given placebo treatment[53].

Granulomatous disease

Granulomas, or histologic areas of macrophage fusion, are a hallmark of CD but need not be present for a definitive diagnosis[54]. An association between granulomas and disease severity has been suggested but not proven[55]; however, an association between the presence of granulomas in the ileocolic resection specimen and recurrence has been consistently demonstrated. In an observational study by Malireddy *et al*[17] recurrence rates in 89 patients who had undergone laparoscopic ileocolectomy from April 1994-August 2006 (with a median follow up of 3.5 years) were evaluated. A 61% endoscopic, radiologic or pathologic recurrence rate was noted. The median time for recurrence was 13.1 mo (range, 1.3 mo to 8.7 years). Several potential prognosticators for recurrence including postoperative biologic and other medical treatment were also studied. The only significant predictor of recurrence found on multivariate analysis was the presence of granulomas in the initial resection specimen. An earlier Irish study of 139 patients who underwent ileocolectomy between 1980 and 2000 evaluated the presence of symptoms, endoscopic recurrence and radiological recurrence. Again, the presence of granulomas in the specimen was significantly associated with clinical and surgical recurrence[3]. In a similar early study of 114 ileocolectomy patients, 66% with granulomas *vs* 48% without experienced an endoscopic recurrence within the first year after an ileocolectomy[11]. In 1997, Anseline *et al*[20] evaluated 130 CD patients undergoing a variety of resections. After multivariate analysis, the presence of granulomas was significantly associated with recurrence.

INDEX ILEOCOLECTOMY DETAILS

Urgent vs elective resection

Several groups have hypothesized that if a patient's first ileocolectomy is performed under emergency circumstances, this likely reflects more severe disease and thus may predict an increased likelihood of recurrence. One retrospective multicenter Italian review evaluated clinical recurrence (defined as the need for steroids in conjunction with endoscopic or radiologic findings) and surgical recurrence in 83 CD patients who underwent ileocolectomy for severe disease at the time of diagnosis *vs* 124 who underwent surgery later in their disease for medical refractory disease and/or complications secondary to their disease. Recurrence was evaluated at 1, 5 and 10 years. Clinical recurrence was less frequent in the early surgery group at all-time points. No difference was seen in the need for or timing of repeat surgery between the 2 groups[27]. Another retrospective study of 116 consecutive patients undergoing their first ileocolectomy at a large Austrian referral center between 1997 and 2006 demonstrated that urgent index ileocolectomy increased the risk of repeat surgery approximately 6 fold[56].

Sepsis

Another potential marker of severe disease is perioperative sepsis at the time of index ileocolectomy. However, results are conflicting and further study is warranted. Elevated white cell count was associated with endoscopic

recurrence on univariate analysis in Caprilli *et al*[52] study of 110 ileocolectomy patients. However, an increased risk of recurrence in urgent *vs* elective ileocolectomy patients was not demonstrated. Iesalnieks *et al*[57] studied 282 patients who underwent 331 varied CD resections between 1992-2005. On multivariate analysis, postop intraabdominal septic complications and history of a previous resection were associated with increased surgical recurrence risk at all-time points studied from 1-10 years. At 1 year patients with a history of sepsis had a recurrence rate of 25% *vs* 4% of those without sepsis. At 10 years rates were 57% and 38% respectively.

Laparoscopic vs open approach

As laparoscopic surgery and stapled anastomosis initially gained popularity for use in the CD population in the 1980s, an interest in determining if either technique decreases the risk of recurrence post ileocolectomy led to several studies. One such retrospective review of 113 patients undergoing their index ileocolectomy between 1987-2003 (with a mean follow up of approximately 70 mo) demonstrated a slightly lower, but not significantly different, rate of postoperative medical treatment requirement in laparoscopic *vs* open patients (39% *vs* 54%). Surgical recurrence was seen in 9.5% (6/63) of laparoscopic *vs* 24% (12/50) of open ileocolectomy patients during a mean follow up of 81 mo. Time to recurrence was not affected. Both groups had a median time to recurrence of approximately 60 mo[58]. Similarly, Stocchi *et al*[18] performed a prospective randomized trial in which 77 patients underwent laparoscopic ileocolectomy and 29 underwent an open procedure. Both cohorts had a similar postoperative prophylactic medication regimen and a mean follow up of 10.5 years. Reoperation rates were the same in the 2 groups (approximately 26% in each). Endoscopic and radiologic recurrence rates were similar. Forty-eight percent of laparoscopic patients experienced endoscopic or radiologic recurrence *vs* open patients who demonstrated a 66% endoscopic recurrence and 52% radiologic recurrence rate. The most recent meta-analysis on laparoscopic *vs* open approach included 33 studies and included 2519 patients. No statistical difference was seen in surgical recurrence rates which were 25 per 1000 person years in the laparoscopic group *vs* 34 per 1000 person years in the open group[59].

Resection margins and type of anastomosis

Stapled anastomosis has now virtually replaced the hand sewn technique in the majority of centers performing ileocolectomies for CD. Two studies, inclusive of 199 and 89 ileocolectomy patients, evaluated resection margins and anastomotic type. In both studies, no difference in clinical recurrence was found between patients whose resection margins were affected by disease *vs* those who had unaffected margins. There was also no difference seen between stapled or hand sewn anastomoses[14,17]. In the only randomized study to date, Fazio *et al*[60] evaluated recurrence in 131 ileocolectomy patients randomized to undergo resections with proximal margins either 2 or 12 cm from the macroscopically diseased tissue followed up for median of 56 mo. The resection specimen was also studied for microscopic signs of disease. Surgical recurrence was found in 25% of patients who had undergone a limited resection *vs* 18% of those who had undergone the more extensive resection ($P > 0.05$). Clinical recurrence was demonstrated in 33% *vs* 29% of those with limited and extended resections respectively. No relation was seen between microscopic CD found at the resection margin and recurrence.

In Bordeianou's study of approximately 200 ileocolectomies, stapled anastomosis although significant on univariate analysis, lost significance on multivariate analysis[14]. End-to-end *vs* side-to-side anastomotic techniques has also been evaluated in 2 randomised trials comparing anastomosis types in 98 and 139 CD patients respectively. Both studies failed to demonstrate a difference in symptomatic or endoscopic recurrence rates between the groups. The first study demonstrated an endoscopic recurrence rate of 42.5% in the end-end *vs* 37.9% in the side-side anastomosis groups and a symptomatic recurrence rate of approximately 22% in both groups[61]. The second study demonstrated that overall, on multivariate analysis, anastomosis type did not affect endoscopic recurrence. However, a 3 fold risk of recurrence was seen in a subgroup of patients with end-end anastomoses who were treated with 5 aminosalicylates (ASAs). This increased risk was not seen in those not treated with ASAs[52]. Meta-analysis of 8 studies published between 1992-2005 inclusive of 661 ileocolectomy patients compared end-to-end anastomosis *vs* other anastomotic configurations (stapled side-to-side, end-to-side or side-to-end, stapled circular end-to-end). No significant difference was found in clinical or surgical recurrence between the different groups[62].

Techniques to potentially minimize risk of recurrence are currently under development. The Kono-S is one such novel technique. This technique utilizes a linear stapler-cutter to transversely divide the tissue for resection. The corners of the 2 stapled lines are sutured together and antimesenteric longitudinal enterotomies are created on both sides. The enterotomies are then closed transversely in two layers resulting in an anti-mesenteric functional end-to-end anastomosis. This technique has shown promise in a small cohort of 18 patients, 43% of whom have undergone follow-up endoscopic surveillance with an average Rutgeert's score of 0.7 (0-3) at a mean of 6.8 mo[63].

MEDICAL TREATMENT TO PREVENT DISEASE RECURRENCE

Key studies on the effect of medical treatment for the prevention of recurrence are highlighted in Table 6. Traditionally, treatment paradigms for CD followed a "bottom up" approach with initial treatment comprised of corticosteroids, antibiotics and/or 5 ASAs. Escalating

Table 6 Key studies on medical treatment for the prevention of postoperative recurrence in post ileocolectomy patients

Interventions Compared	Study Design	Study Numbers (end of follow-up)	Follow-up	Clinical Improvement	Endoscopic Improvement	Other	Ref.
Mesalamine *vs* Placebo	Double Blind, Multicenter	87	12 mo	59% of placebo *vs* 41% of mesalamine had a clinical relapse	Significantly less severe and less frequent lesions in mesalamine group ($P < 0.008$)	Severe endoscopic or radiologic was 24% in mesalamine *vs* 56% of placebo ($P = 0.004$)	Brignola *et al*[68]
Budesonide *vs* placebo	Double-blind, randomized trial	129	12 mo	No difference in CDAI at any time point in the study	Only patients who underwent surgery for increased disease symptoms (not fibrostenotic or fistulizing disease) had a significantly lower endoscopic recurrence rate (32% *vs* 65% of the placebo group)	AT 12 mo the ESR value was 13.3 mm/h in the budesonide group *vs* 20.2 mm/h in the placebo group ($P = 0.017$). Mean CRP values after decreased from 19.0 to 6.2 mg/L in the budesonide group and from 12.7 to 12.2 mg/L in the placebo group ($P = 0.018$)	Hellers *et al*[64]
Mesalamine *vs* placebo	Double-blind, placebo controlled[1,2]	246	48 wk	25% of the mesalamine *vs* 36% of the placebo had a relapse [(per CDAI) $P = 0.06$] On subgroup analysis ileocolonic patients had fewer relapses on mesalamine (21% *vs* 41%) $P = 0.003$		10% *vs* 23% surgical recurrence ($P = 0.13$)	Sutherland *et al*[67]
Mesalamine *vs* placebo	Randomized	163 post-surgical patients[1] 109 were post ileocolectomy	Maximum 72 mo		Endoscopic and radiological recurrence was significantly decreased in the mesalamine group with relative risks of 0.6 ($P = 0.016$)	31% symptomatic recurrence rate (symptoms plus endoscopic and/or radiological confirmation of disease) *vs* 41% in the control group, $P = 0.03$	McLeod *et al*[69]
6 MP, mesalamine or placebo	Multi (5) center, double blind, randomized	131	24 mo	Clinical recurrence was improved by mesalamine or 6 MP. Clinical recurrence rates at 24 mo were 50% for 6 MP, 58% for mesalamine and 77% for placebo ($P = 0.04$)	Only 6 MP, not mesalamine was superior to placebo to prevent endoscopic and radiographic recurrence at 24 mo. Relapse was 43% with 6 MP, 63% with mesalamine, 64% with placebo ($P = 0.03$)	Radiographic recurrence rates were 33% for 6 MP, 46% for mesalamine and 49% for placebo ($P > 0.05$)	Hanauer *et al*[76]
Infliximab *vs* mesalamine (control)	Prospective, multicenter pilot study to determine if giving infliximab after diagnosis of postoperative endoscopic ileocolic CD recurrence at 6 mo can induce endoscopic remission at 54 wk	24 (19 had ileocaecal disease)	54 wk	No clinical recurrence in the infliximab group at 6 mo 18% of mesalamine who had clinical relapse by 9 mo	No endoscopic remission at 54 wk in the mesalamine group *vs* the infliximab group 54% had endoscopic remission at 54 wk ($P = 0.01$)		Sorrentino *et al*[28]
Adalizumab *vs* AZA *vs* mesalamine	Randomized	51	2 yr		The ADA treated patients had the lowest incidence of endoscopic recurrence (6.3% *vs* 64.7% of the AZA group and 83.3% of the mesalamine group)		Savarino *et al*[83]

Infliximab *vs* placebo	Randomized	24	1 yr	Clinical remission was higher in the IFX group (80% *vs* 54%) but $P = 0.38$)	Endoscopic and histologic recurrence was significantly lower at 1 yr in the patients treated with infliximab (1 of 11; 9.1% and) *vs* placebo (11 of 13 patients; 84.6%). $P = 0.0006$	Lower histologic recurrence in the IFX group (3 of 11/27% *vs* 11 of 13/85% of placebo) $P = 0.01$	Regueiro *et al*[82]
Metronidazole +AZA or placebo	62	Randomized	12 mo	Endoscopic recurrence was observed in 14 of 32 (43.7%) patients in the AZA group and in 20 of 29 (69.0%) patients in the placebo group at 12 mo post-surgery ($P = 0.048$. At 1 yr 21% of the AZA group were lesion free *vs* 3% of the placebo ($P = 0.04$)			D'Haens *et al*[77]
Metronidazole *vs* placebo	Double-blind controlled	51	3 yr	Clinical recurrence rates at 1 yr were 4% in the metronidazole *vs* 25% of placebo) NSD $P = 0.04$. Reductions at 2 yr (26% *vs* 43%) and 3 yr (30% *vs* 50%) both NSD	At 12 wk, 21 of 28 patients (75%) in the placebo group had recurrent lesions in the neoterminal ileum *vs* 12 of 23 patients (52%) in the metronidazole group ($P = 0.09$)		Rutgeerts *et al*[65]
Immunosuppressants (AZA/6 MP or MTX) *vs* control (5 ASAs or no treatment)		26 patients undergoing their 2nd ileocolectomy	3 yr (range 17-178 mo)	Clinical recurrence was lower in the immmunosuppressant group *vs* the control group (3/12, 25% *vs* 6/10, 60%; $P < 0.05$) No difference in time to recurrence was seen (approximately 27 mo in both groups)		The control group required a 3rd resection more commonly. (7/12, 58% *vs* 2/14, 17% $P < 0.02$)	Alves *et al*[79]
AZA therapy commenced immediatiely post resection	Prospective, observational	56 consecutive patients 15 or 27% had ileocolectomies	Mean 12-84 mo	No clinical recurrence at 12 mo recurrence	70% had endoscopic recurrence at 12 mo. The cumulative probability of endoscopic recurrence was 82% at 5 yr		Domènech[90]

[1]Study included non ileocolectomy patients in addition to ileocolectomy patients; [2]Study included medically treated patients in addition to ileocolectomy patients. AZA: Azathioprine; 6 MP: 6 mercaptopurine; ASAs: Aminosalicylates.

treatment in the form of immunomodulators or biologics either replaced this treatment or was added to it as the disease flared or progressed. Steroids and antibiotics are rarely given as monotherapy to prevent relapse in CD currently. Thus, studies that focus on their efficacy are commonly from the 1980s and 1990s. One such double-blind, randomized trial performed in 13 European centers followed 63 patients given budesonide and 66 patients given placebo post ileocolectomy. At 1 year, no difference in endoscopic recurrence was seen between the 2 groups. However, a significantly lower endoscopic recurrence rate was seen in a subgroup of patients treated with budesonide, namely those who had undergone surgery for increased disease symptoms rather than obstruction or fistulization (32% *vs* 65% of the placebo group)[64].

Studies on antibiotic monotherapy have been limited to metronidazole. In a double-blind controlled trial evaluating the use of metronidazole as monotherapy post ileal resection in 51 patients, recurrent lesions were

seen in 75% of the placebo group *vs* 52% of the metronidazole group at 12 wk ($P = 0.09$). At 1 year, clinical recurrence rates were much lower in the metronidazole group (4% *vs* 25%); however significance was lost at 2 years (26% *vs* 43%)[65].

The commonly used aminosalicylate based drugs, including mesalamine, generally have low side effect profiles and have been shown by meta-analysis to prevent relapse in inactive CD[66]. However, results from studies evaluating their long term efficacy in the prevention of post ileocolectomy recurrence are not impressive, particularly in regard to clinical recurrence. One large double blind, placebo controlled study by Sutherland *et al*[67] compared clinical recurrence as defined by CDAI scores in medical and surgical CD patients (who had undergone a variety of resections) treated with either mesalamine or placebo. At 48 wk, 25% of the mesalamine *vs* 36% of the placebo had a clinical recurrence. However, disease recurrence was only 10 d later in the mesalamine treated patients. Interestingly, ileocolonic patients had fewer relapses on mesalamine (21% *vs* 41% given placebo) on subgroup analysis. In another double-blind, multicenter clinical trial published in 1995, 87 patients were treated with mesalamine or placebo within 1 mo after undergoing ileocolectomy. At 12 mo, 41% of the 17 patients who relapsed clinically had been given mesalamine. Using endoscopic and radiological evaluation with scoring systems, the mesalamine group had significantly less frequent and less severe lesions and milder disease. Disease was classified as "severe" in 24% of the mesalamine treated patients *vs* 56% of those given placebo[68]. In another study published the same year, 163 post resection patients (of whom 109 had undergone ileocolectomy) were randomized to receive either mesalamine twice a day or placebo. During a maximum follow up of 72 mo, 31% of those given mesalamine experienced a symptomatic recurrence defined as symptoms plus endoscopic and/or radiological confirmation of disease *vs* 41% in the control group[69].

A new paradigm of a "top down" approach to the treatment of CD in which surgery and early institution of immunomodulatory and/or biologic drug therapy has been suggested by large trials such as the SONIC trial. This approach has demonstrated improved mucosal healing, a reduction in steroid use, longer remission times and faster clinical response than the traditional bottom up approach[70,71]. Additionally, multidrug therapy has been proven to increase drug serum levels, address multiple disease mechanisms and potentially reduce the production of anti-drug antibodies[70,72,73]. The immunomodulatory drugs azathioprine (AZA) and 6 mercaptopurine (6 MP) are two drugs commonly used in the top down approach. Used on their own or in conjunction with other IBD medications, these drugs have a high success rate in treating flares, reducing the steroid requirement and increasing remission rates in medically treated disease and[74,75] have been suggested to be effective at reducing recurrence and increasing duration from surgery to recurrence. In a 5 center, double blind study inclusive of 131 post ileocolectomy patients randomized to receive 6 MP, mesalamine or placebo, only 6 MP was superior to placebo for the prevention of endoscopic and radiographic recurrence at the study endpoint of 24 mo. Clinical recurrence rates were improved by mesalamine or 6 MP administration with recurrence rates of 50% for 6 MP, 58% for mesalamine and 77% for placebo at 24 mo demonstrated. Endoscopic and radiologic recurrence rates were 43% and 33% for 6 MP, 63% and 46% for mesalamine and 64% and 49% for placebo[76].

The utility of immunomodulatory drugs has been studied in subgroups of patients who are at increased risk for recurrence. D'Haens *et al*[77] studied 62 patients who were aged < 30, had a history of multiple ileocolectomies and/or had penetrating disease. Post ileocolectomy, all patients were given metronidazole for 3 mo with either azathioprine or placebo for 12 mo. At 12 mo, a significant difference in endoscopic recurrence was observed with 43.7% of patients in the AZA group experiencing recurrence *vs* 69.0% of those in the placebo group. Endoscopically, 21% of the AZA group were lesion free *vs* 3% of the placebo ($P = 0.04$). Mañosa *et al*[78] virtually reversed this study and administered AZA to 50 ileocolectomy patients postoperatively. At 3 mo, patients were randomized to receive either metronidazole or placebo. At 12 mo, endoscopic recurrence was seen in 36% of the metronidazole and 56% of the placebo group. However, this difference was not significant, suggesting that AZA on its own may be sufficient. In another high risk group, those undergoing their 2nd ileocolectomy for anastomotic recurrence, immunosuppressant drugs were shown to decrease clinical and surgical recurrence. Twenty-six patients were randomized to receive an immunosuppressant drug (6 MP, AZA, Methotrexate, $n = 14$) or a control treatment (5 ASAs, $n = 5$ or no treatment, $n = 7$). Clinical recurrence rates were lower in the immunosuppressant treated group *vs* the control group (3/12, 25% *vs* 6/10, 60%; $P < 0.05$). No difference in time to recurrence was demonstrated between the groups (approximately 27 mo in both groups). The control group required a 3rd resection more commonly (7/12, 58% *vs* 2/14, 17%, $P < 0.02$)[79]. Other evidence suggests that AZA/6 MP treatment may delay but not prevent recurrence. Fifty-six consecutive patients commenced on AZA treatment immediately after resection were studied in Domènech *et al*[80] observational study. Fifteen (27%) had ileocolectomies. Seventy percent of the cohort had endoscopic recurrence at 12 mo. However, no clinical recurrence was observed. At approximately 3 years' follow up, 30% of patients maintained endoscopic remission. At 5 years, the cumulative probability of endoscopic remission dropped to 18%. Due such evidence, the American Gastrological Association has recommended that as 6 MPs likely reduce the risk of clinical and endoscopic recurrence, they should be used in those at "high risk" for recurrence or 'in whom postoperative recurrence would have deleterious effects[81].

The anti-tumor necrosis factor (TNF) drugs, including infliximab and adalimumab are among the newest IBD drugs and have rapidly gained popularity over the past 10 years. A role for these drugs in the prolongation of postoperative remission has been suggested by preliminary studies. In one such study, significantly lower 1 year postoperative endoscopic and histologic recurrence rates were demonstrated in patients who had undergone ileal resection who were treated with infliximab. 9.1% (1 of 11) of these patients had endoscopic recurrence *vs* 27% (3 of 11) that were given placebo. Clinical remission rates were also higher in the infliximab group (80% *vs* 54% of the placebo group) but this difference wasn't significant[82]. One prospective, multicenter but also small Italian study, aimed to determine if the administration of infliximab after diagnosis of postoperative endoscopic recurrence of ileocolic CD can induce endoscopic remission at 54 wk. Mesalamine was used as the control. In the mesalamine group (n = 11), no endoscopic remission was seen at 54 wk. Two patients had clinical recurrences at 8 and 9 mo. In the infliximab group (n = 23), 54% had endoscopic remission at 54 wk. None had clinical recurrence[28].

Infliximab is the most commonly used and studied anti-TNF drug. However, a recent randomized control trial evaluated the efficacy of adalimumab for the prevention of post ileocolectomy recurrence[83]. Fifty-one patients were randomized to receive adalizumab, AZA or mesalamine postoperatively. At 2 years, the adalizumab treated patients had the lowest incidence of endoscopic recurrence (6.3% *vs* 64.7% of the AZA group and 83.3% of the mesalamine group). Similarly clinical recurrence was lower in the adalizumab treated patients (12.5% *vs* 65% in both the AZA and mesalamine groups).

The timing of postoperative treatment has sparked a great interest due to the side effects of many IBD medications. The use of a "tailored treatment approach" to determine the effect of the timing of drug commencement on symptomatic recurrence after ileocolectomy was studied by Bordeianou *et al*[14]. In their cohort of 199 ileocolectomy patients, 35% were given immediate post ileocolectomy prophylaxis in the form of antibiotics, 5 ASAs, immunomodulators (6 MP/AZA) and/or anti-TNFs. Sixteen percent were commenced on a drug regimen at the time of endoscopic recurrence and 49% percent did not receive any treatment. Symptomatic recurrence occurred in 29% of those treated immediately postoperatively *vs* 44% of those who were treated after recurrence. After multivariate analysis, the significant difference between the 2 groups was lost and the only remaining significant prognostic factor recurrence was Charlson Comorbidity Index[84]. Malireddy *et al*[17] studied pre *vs* postoperative administration of anti-TNFs and immunomodulators in 89 laparoscopic ileocolectomies. Timing of treatment did not affect recurrence rates. Postoperative medical treatment lengthened the time to recurrence with a median time to recurrence of 25 mo demonstrated in the group given pharmacoprophylaxis *vs* 16 mo in the control group. However, this difference was not statistically significant.

SERUM MARKERS

Serum markers such as CRP and ESR are relatively noninvasive to obtain and have been demonstrated to reflect disease activity. Thus such markers may be potential prognosticators for post ileocolectomy recurrence. ESR and CRP were studied in a randomized controlled multicenter Italian trial of 98 patients undergoing their first ileocolectomy. When evaluating endoscopic recurrence at 6, 12, 24, and 36 mo post operatively, ESR and CRP were not correlated with endoscopic recurrence[52].

Pro and anti-inflammatory cytokines are not measured in clinical practice. However, they offer the potential to be used as markers of disease activity and, possibly, disease recurrence. Yamamoto *et al*[85] evaluated levels of the proinflammatory cytokines IL-6 (interleukin 6), IL1B and TNFα in blood, ileal biopsies and rectal biopsies at enrollment and 1 year after ileocolectomy in 36 patients. On univariate analysis, the 16 patients who experienced a clinical relapse (determined by CDAI scores) demonstrated significantly higher IL1B, IL-6 and TNFα levels in their ileal mucosa compared to the 20 patients who did not experience clinical relapse. There was no association with these markers in either the blood or rectal mucosa and relapse demonstrated. On multivariate analysis, IL-6 remained as an independent predictor of clinical relapse. IL-6 has also been demonstrated to be increased in the serum of CD patients with previously quiescent CD experiencing a disease flare[86]. IL10 is a well-known anti-inflammatory cytokine. Meresse *et al*[40] studied IL-10 levels and endoscopic recurrence in 36 patients 3 mo post ileocolectomy. Recurrence rate was 53%. Patients with recurrence had significantly lower IL-10 production. When ileal mRNA expression levels were compared with the patients' individual genotypes, varying IL10 production based on IL-10. G microsatellite genotype was seen. However, there was no correlation between genotype and endoscopic recurrence.

Faecal calprotectin (FC) and lactoferrin have been widely studied as noninvasive markers of gut inflammation. Recently, several groups have attempted to correlate levels of these markers with risk of postoperative recurrence in CD. Lamb *et al*[87] were among the first to study a potential correlation. In their cohort of 13 post-surgical CD patients followed for 1 year (3 of whom had ileocolic disease) and a separate cohort of 104 patients who gave a single stool sample at a median of 24 mo postoperatively (28 of whom had ileocolic disease) both FC and lactoferrin correlated with clinical symptoms as evaluated by Harvey Bradshaw Index. Both markers were found to be more accurate at predicting clinical recurrence than CRP, platelet count and endoscopic appearance. Patients with Harvey Bradshaw scores indicative of severe disease activity (n = 28) had FC and lactoferrin levels of 661 μg/g and 116.6 μg/g *vs* 70.2 μg/g

and 5.9 μg/g in those with clinically inactive disease (n = 43) (P < 0.001). Although levels of both markers were slightly higher in those with endoscopic recurrence, this difference was not statistically significantly different between the groups. Subsequently, FC levels of 29 ileocolectomy patients were studied by Lobatón *et al*[88] Levels correlated more closely with clinical recurrence than CRP, white cell count and platelet count. Endoscopic recurrence scores also correlated with levels. Lasson *et al*[89] in a study published in Jan 2014, evaluated FC levels in 30 ileocolectomy patients in specimens collected monthly postoperatively for 1 year. Fifty-eight percent had endoscopic remission at one year. FC levels fluctuated over time and were mainly affected by diarrhea. Although median calprotectin levels were not significantly different between patients in remission and patients with recurrence, the majority of patients with high values had recurrence. This may have been influenced by diarrhea at the time of sampling.

CONCLUSION

Crohn's disease cannot be cured. Surgical resection offers an opportunity for "resetting" the disease into a state of temporary remission. It is known that after surgical resection recurrence rates range from 20 to over 60 percent. Identifying modifiable risk factors for postoperative disease recurrence can assist the clinician in implementing more aggressive prophylactic treatment to prevent recurrence and to sustain remission. The application of an optimal strategy for preventing postoperative recurrence is a multidisciplinary task that includes the gastroenterologist and the colorectal surgeon, as well as all the supporting staff that can ensure preoperative optimization, detailed and timely surgical intervention and early implementation of appropriate treatment to keep the patient in remission.

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