POST OPERATIVE RECURRENCE CROHNS DISEASE

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Introduction

- Surgery in CD is rarely curative, and most patients experience post-operative CD recurrence
- Postoperative recurrence rates vary depending on the modality and definition of assessing recurrence
- Need for careful assessment to ensure the symptoms are not due to other malabsorptive or motility issues post-operatively
- Clinical recurrence rates after resection surgery have been reported from 36% to 86% at 10 years of follow-up

- Various scoring systems exist for monitoring endoscopic CD recurrence, and endoscopic recurrence rates after resection surgery
- Post-operative CD recurrence typically presents on a continuum from histologic findings to endoscopic findings to clinical presentation
- Early endoscopic monitoring and prophylactic pharmacological therapy are key tenets of the post-operative management of patients with CD

Bernell O et al. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. Br J Surg 2000;87:1697–701
Olaison G et al. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. Gut 1992;33:331–5.

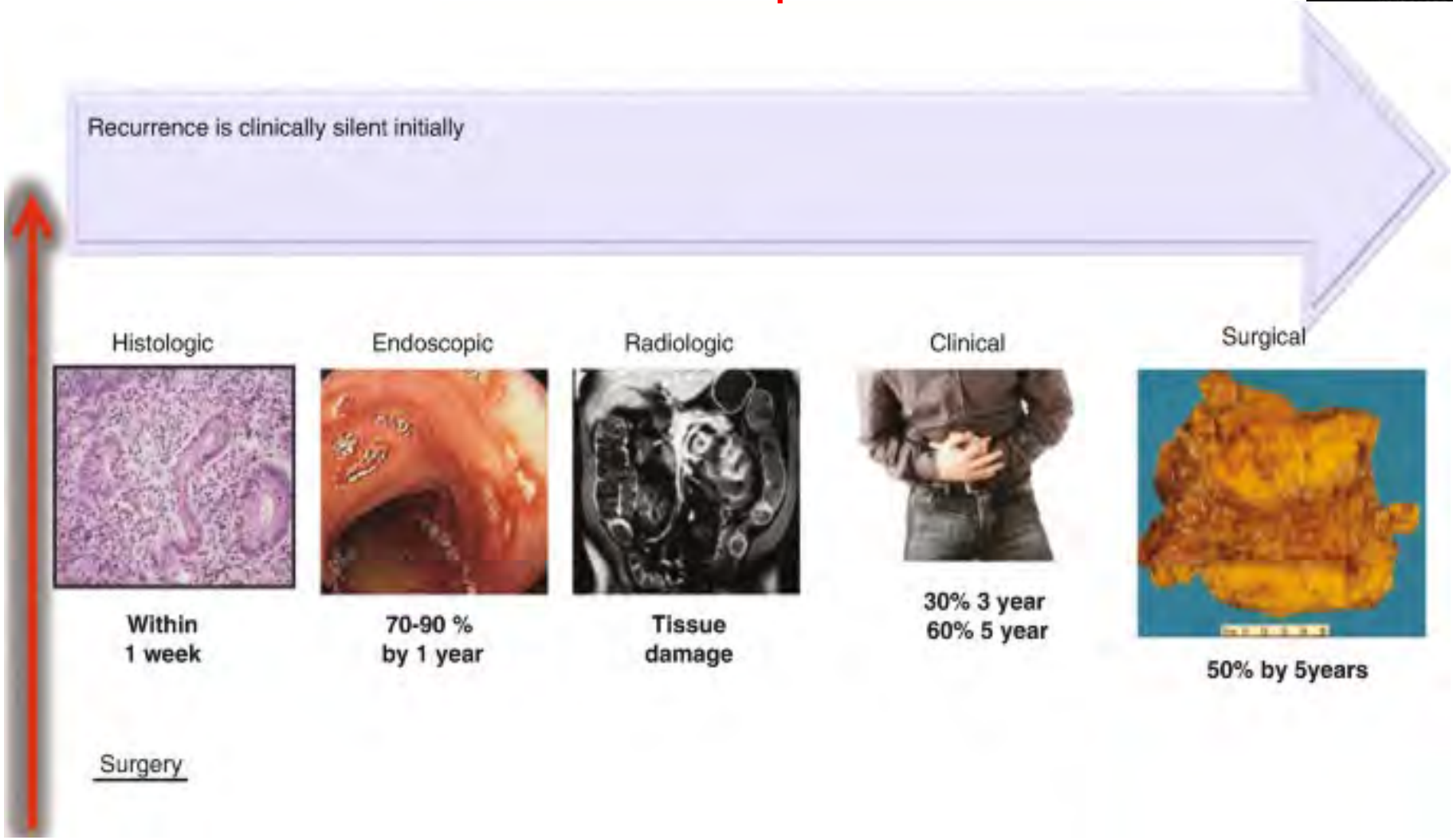
INDICATIONS FOR SURGERY

- Intractable GI hemorrhage
- Fibrotic strictures with obstructive symptoms
- Intestinal Perforation
- Toxic megacolon
- Medically intractable fistulae- intrabdominal and perianal
- Malignancy
- Treatment-related complications, including intra-abdominal abscesses

- The primary surgical procedure is ileo-caecal/ileo-colonic resection(ICR)

- Disease frequently recurs at the anastomosis and in the neoterminal ileum proximal to it

The natural course of Postoperative Crohn's disease



D'Haens GR et al 1998

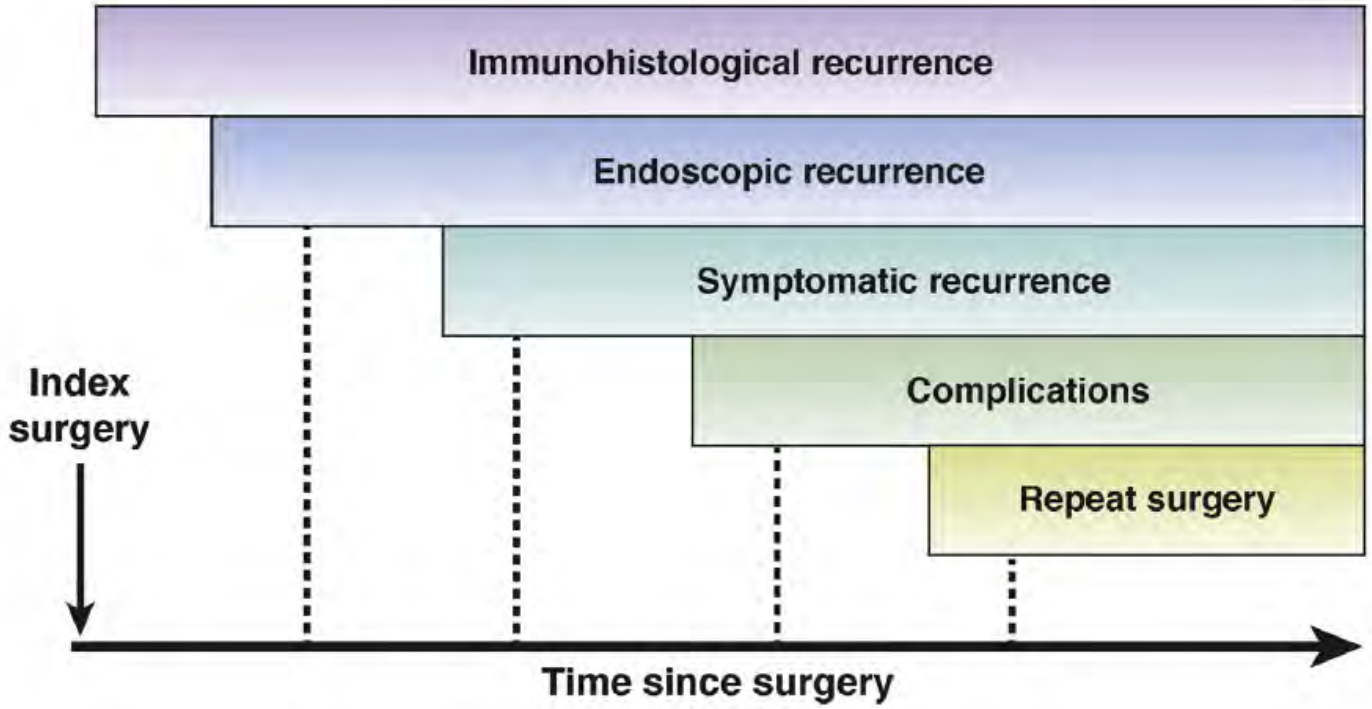


Figure 1. Sequential evolution of immunohistologic changes, endoscopic anastomotic ulcerations, clinical symptoms, and complications such as stricture, perforation, abscess, and further surgery after initial intestinal resection and anastomosis and no preventive therapy. The choice of the follow-up period to study an endpoint will affect the timing of the efficacy endpoint of an intervention after initial surgery. The pace of evolution varies depending on patient characteristics and other yet undefined factors. A 76-week outcome readout may be appropriate for endoscopic recurrence, but not necessarily clinical recurrence.

Gosh S. 2016. http://dx.doi.org/10.1053/j.gastro.2016.04.033

PATHOPHYSIOLOGY

- Microbiome – Sokol et al,
- The mesentery – POCER trial
- Immune system- REMIND Study
- Genetic factors : **NOD2/CARD15**, BATCH2. CARD8 and TNFSF15

PATHOPHYSIOLOGY

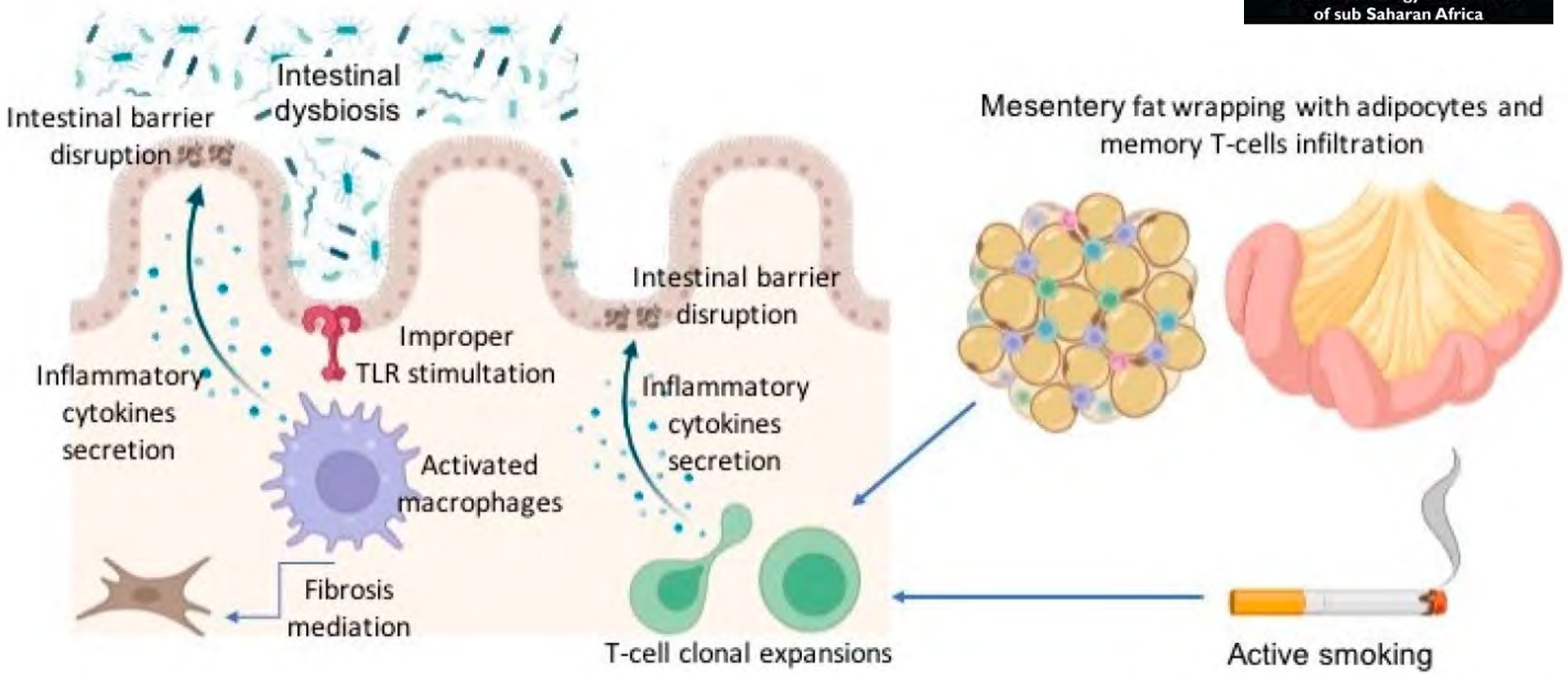


Figure 1. Overview of the main pathophysiological mechanisms behind post-operative recurrence.

Spertino M et al. Management of Post-Operative Crohn's Disease:Knowns and Unknowns. J. Clin. Med.**2024**, 13, 2300

Clinical Recurrence

- Typical symptoms: Diarrhoea, abdominal pains
- Consider other differential diagnoses eg, IBS, Bile acid malabsorption
- A subgroup of patients develops stenosis and will need endoscopic dilatation and/or a second surgery

RISK FACTORS OF RECURRENCE

- **LOWER RISK**
- Non-smoker
- Older patients (>50 years at diagnosis)
- First surgery for CD
- Short segment CD (i.e. <10 to 20 cm)
- Long-standing history of CD (>10 years)

- **MODERATE/HIGHER RISK**
- Active Smoking
- Prior surgical history for CD (≥2)
- Penetrating/fistulizing disease
- Residual luminal disease
- Younger age (< 30 years at diagnosis)
- Shorter disease duration prior to surgery
- Positive resection margins
- Progression to surgery despite Tx with an immunomodulator or biologic agent

No validated clinical score that predicts recurrence

Other predictors of early postoperative CD recurrence

- **Genetics**: NOD2/CARD15
- **Serology**: ASCA, OmpC, CBir1
- **Microbiome**:

  -Increase in E. Coli, Bacteroides, and Fusobacteria

  - low abundance of Faecalibacterium prausinitzii in both resected and postoperative ileal mucosa
- **Histology**:

  -Transmural lesions at the ileal (and possibly colonic) margins

  -Myenteric and submucosal plexitis

  -Granulomas in the resection specimen

Other predictors of early postoperative CD recurrence

- **Operative intervention:**

-Surgical approach(laparoscopic vs laparotomy)

-Blood transfusion requirement

-Excision margin length

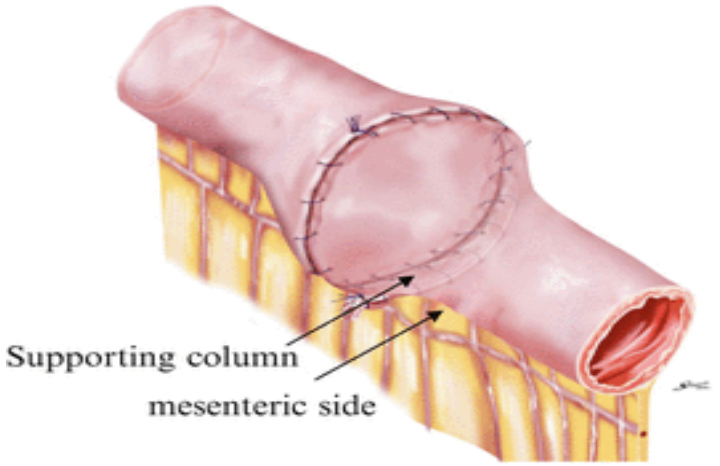
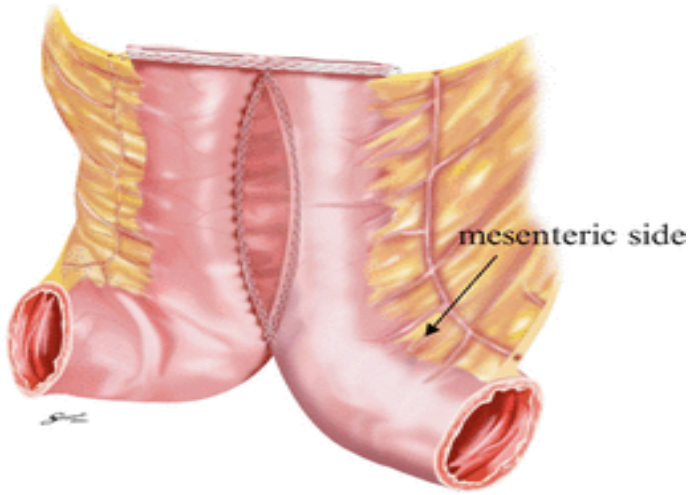
-Perioperative complication

-Anastomotic orientation, technique

- Mesenteric excision extent
- Strictureplasty

Kono-S anastomosis

- Recently there has been growing interest in extending the mesenteric resection and in the Kono-S anastomosis
- A hybrid manual and stapled anastomosis based on the concept of mesenteric exclusion

Kono-S anastomosis	Functional end-to-end
	
Supporting column can prevent distortion	Nothing can prevent distortion
Stapling site is covered by anastomotic site	Adhesion to stapling sites
Easy to access like a end-to-end	Difficult to access by enteroscope

Kono, T., Fichera, A. (2015). Recurrent CD: Surgical Prophylaxis—Kono-S Anastomosis. In: Fichera, A., Krane, M. (eds) Crohn's Disease. Springer, Cham. https://doi.org/10.1007/978-3-319-14181-7_17

Kono-S anastomosis

- Two meta-analyses confirmed the effectiveness of Kono-S in preventing POR when compared to other types of anastomoses
- A Kono-S anastomosis may reduce both endoscopic and clinical POR according to one RCT and two meta-analyses.

Inflammatory Bowel Diseases, 2024, **30**, 1877–1887
https://doi.org/10.1093/ibd/izad252
Advance access publication 1 November 2023
Review Article - Clinical

Rates of Endoscopic Recurrence In Postoperative Crohn's Disease Based on Anastomotic Techniques: A Systematic Review And Meta-Analysis

Olga Maria Nardone, MD, PhD,[*,†] Giulio Calabrese, MD,[‡] Brigida Barberio, MD, PhD,[§] Mariano Cesare Giglio, MD, PhD,[‡] Fabiana Castiglione, MD,[‡] Gaetano Luglio, MD, PhD,[¶] Edoardo Savarino, MD, PhD,[§] Subrata Ghosh, MD, PhD,[‖] and Marietta Iacucci, MD, PhD[†,‖]

Results: Seventeen studies, with 2087 patients who underwent ileocolic resection for CD were included. Among these patients, 369 (17,7%) Kono-S anastomoses were performed, while 1690 (81,0%) were conventional ileocolic anastomosis. Endoscopic postoperative recurrence at ≥6 months showed a pooled incidence of 37.2% (95% CI, 27.7-47.2) with significant heterogeneity among the studies ($P < .0001$). In detail, patients receiving a Kono-S anastomosis had a pooled incidence of ePOR of 24.7% (95% CI, 6.8%-49.4%), while patients receiving a conventional anastomosis had an ePOR of 42.6% (95% CI, 32.2%-53.4%).

Conclusions: Kono-S ileocolic anastomosis was more likely to decrease the risk of ePOR at ≥6 months compared with conventional anastomosis. Our findings highlight the need to implement the use of Kono-S anastomosis, particularly for difficult to treat patients. However, results from larger randomized controlled trials are needed to confirm these data.

Immediate postoperative complications

- In a retrospective multicentre study, Carvello *et al*. found that the occurrence of postoperative complications is an independent risk factor for endoscopic POR after primary ICR for CD

HISTOLOGICAL RISK FACTORS

- **Microscopic resection margins**: Histological inflammation at the resection margins is significantly associated with an increased risk of endoscopic POR after an ICR for CD
- **Plexitis:** In 2006, in a cohort of 59 CD patients, Ferrante *et al.* showed that the presence of myenteric plexitis in proximal margins of ICR specimens was predictive of early endoscopic POR
- **Granulomas and enlarged lymph nodes:** A meta-analysis found a significantly higher rate of clinical and surgical POR in CD patients with granulomas in the ICR specimens.

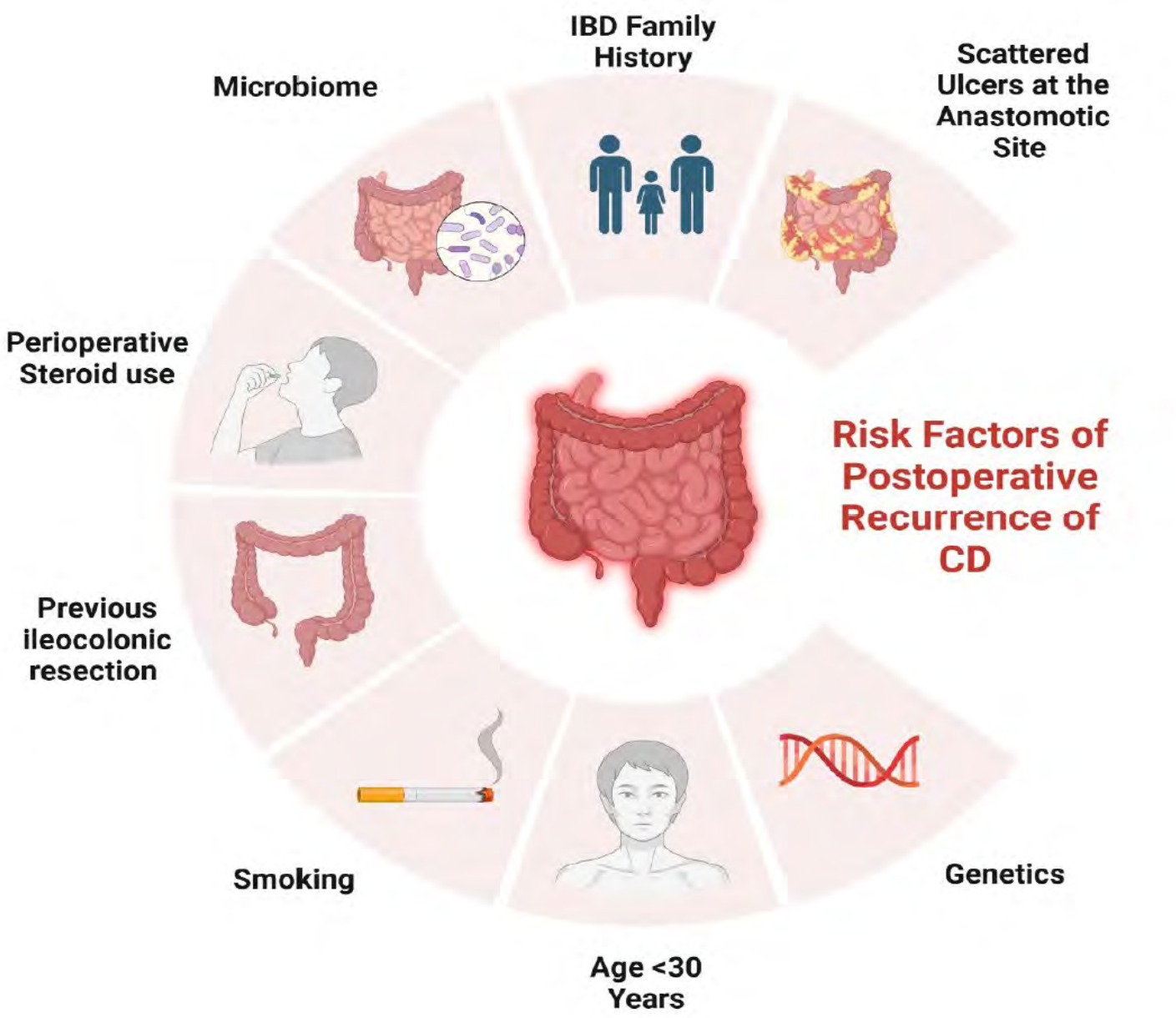


Figure 1. Risk factors of POR in CD.

Aljabri R et al. Optimizing Biologic Therapy for the Prevention of Post-Operative Recurrence in Crohn's Disease: Current Evidence and Future Perspectives. Biomedicines **2025**,13,1232.

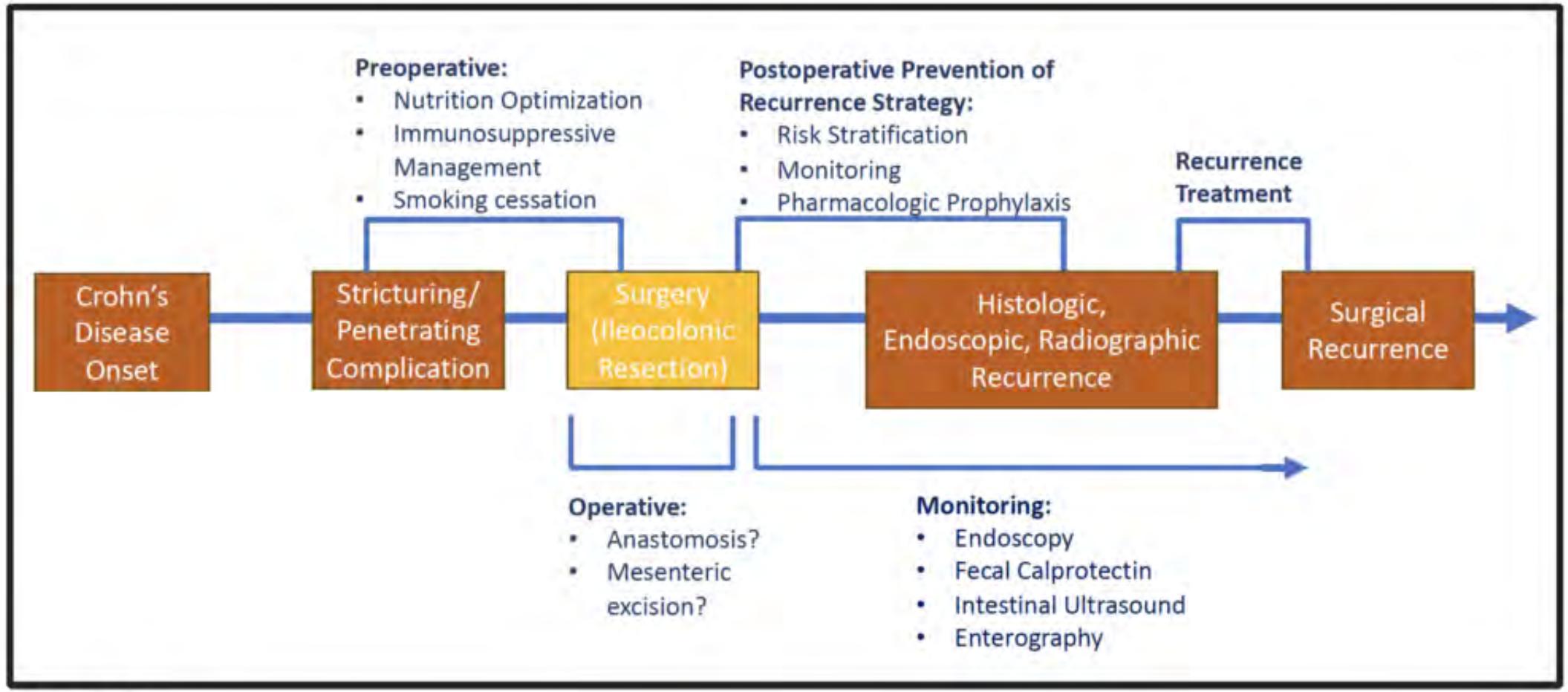


Figure 1.

Reguero M et al. A review on the Practical management of postoperative Crohn's disease. Practical gastro 2024

Monitoring -Endoscopy

- Gold standard for diagnosing POR
- Ileocolonoscopy every 6-12months after surgery-POCER trial
- Rutgeerts' score (RS)- predicts future clinical and surgical risks
- In 1990, Rutgeerts et al. conducted a study demonstrating that the severity of endoscopic lesions observed within one year after surgery at the neoterminal ileum and ileocolonic anastomosis predict the likelihood of clinical activity in the future.
- Video Capsule endoscopy

Table 1. Rutgeerts' score and modified Rutgeerts' score to assess postoperative recurrence in patients with Crohn's disease.

	Score	Endoscopic Findings
Endoscopic Postoperative Remission	i0	no lesions
	i1	≤5 aphthous ulcers
Endoscopic Postoperative Recurrence	i2	>5 aphthous ulcers with normal mucosa in-between or large lesions limited to anastomosis
	i2a (mRS)	lesions limited to the ileocolonic anastomosis (with/without anastomotic stenosis)
	i2b (mRS)	>5 aphthous ulcers or larger lesions with normal mucosa in-between the neoterminal ileum (with/without anastomotic stenosis)
	i3	aphthous ileitis with diffusely inflamed mucosa
	i4	diffuse inflammation with large ulcers, nodules and/or strictures

mRs = modified Rutgeerts' score.

Fasulo E et al. The Management of Postoperative Recurrence in Crohn's Disease. *Journal of Clinical Medicine*. 2024; 13(1):119

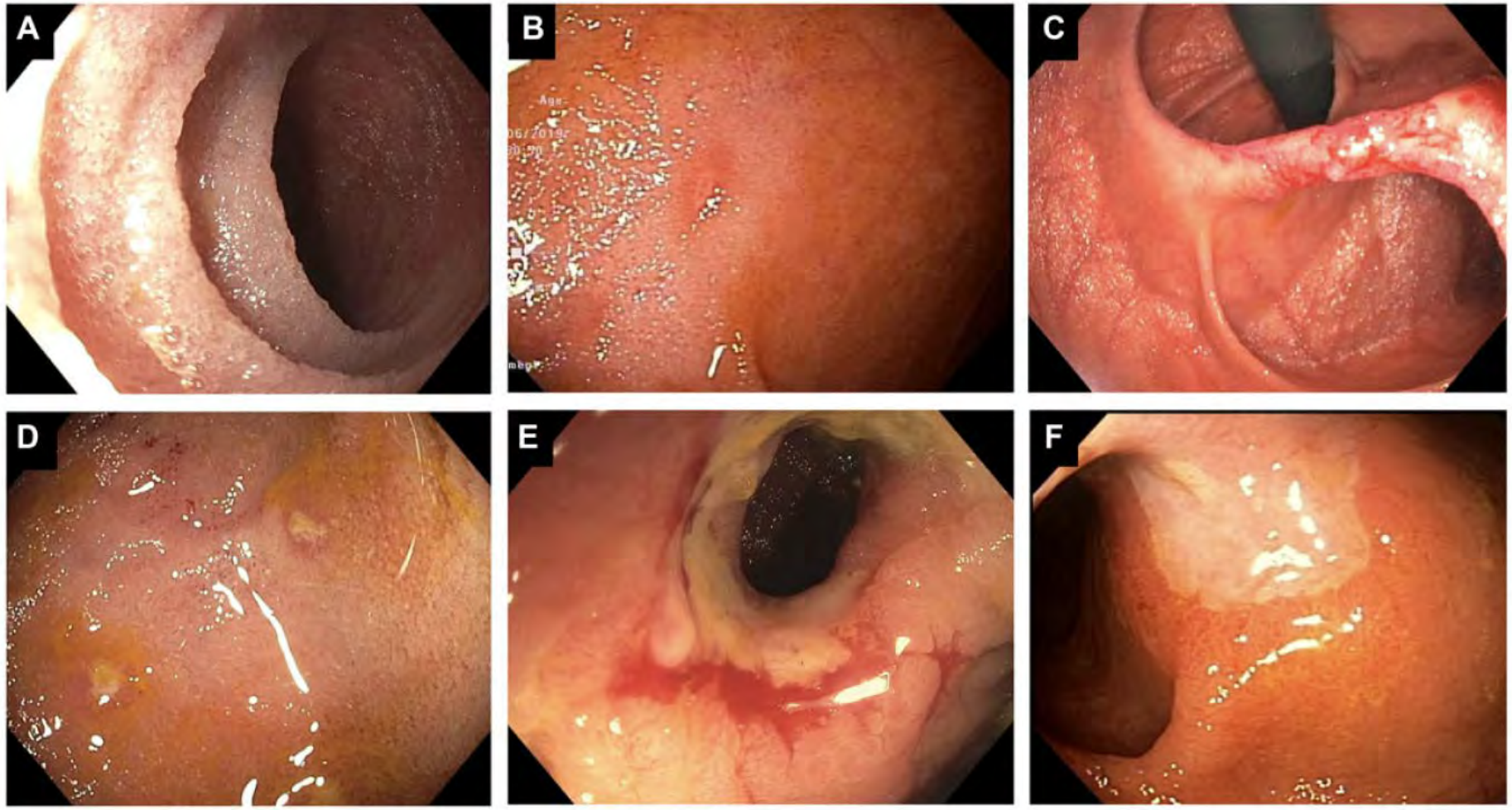


Figure 1. Lesions in the neo-terminal ileum associated with Rutgeerts ratings i0 to i3. (A) normal i0; (B) i1 lesion; (C) i2A lesion; (D) i2B lesion with erosion; (E) i3 stricturing lesion; (F) i3 large ulcer. Figures reprinted with permission of Bo Shen, MD.

Lee KE et al. Post-operative prevention and monitoring of Crohn's disease recurrence. Gastroenterol Rep (Oxf). 2022 Nov 16;10:goac070

- The endoscopic follow-up of patients without recurrence after the first endoscopic assessment is less clear
- Guidelines from the Global Interventional Inflammatory Bowel Disease Group for the endoscopic evaluation of surgically altered bowel in IBD recommends a subsequent ileocolonoscopy for disease monitoring and that dysplasia surveillance should be performed every 1–3 years at the discretion of the treating physician

Video Capsule Endoscopy

- Sensitivity and specificity for POR – 50-79% and 94-100% respectively
- Typically performed 6-12 months after surgery
- Can detect proximal bowel lesions missed by colonoscopy
- Risk of capsule retention due to postoperative strictures

Monitoring –Cross-sectional imaging

- **Intestinal Ultrasound:**

-Increased BWT(>3mm), bowel dilation(>25mm) or stricture(<10mm)

- useful after small bowel resection with an anastomosis that is beyond the accessibility of the endoscope.

-Diagnostic accuracy might improve with different ultrasonographic contrast methods, including small intestine contrast ultrasound (SICUS) and contrast-enhanced ultrasonography (CEUS), which have been compared to “simple” IUS

- **CT or Magnetic resonance enterography (MRE):**

-Non-invasive -the MONITOR index

-Anastomotic recurrence vs fibrostenosis at the anastomotic site (comb sign, stratification)

Monitoring -Biomarkers

- **Fecal Calprotectin(FC)**

-it allows for the differentiation of active and inactive disease, prediction of possible relapses, and the monitoring of response to treatment

- ECCO workshop recommendation is to begin measuring FC levels three months after surgery and eventually anticipate endoscopic assessment according to its levels and trend in the follow-up –**POPCUR randomized trial**
- A meta-analysis published in 2018 assessed the yield of FC for predicting endoscopic recurrence. Most of the studies were prospective and defined recurrence as RS > i2.
- The best diagnostic accuracy was obtained for an FC value of 150 g/g, with a pooled sensitivity of 70% (95% CI 59–81%) and specificity of 69% (95% CI 61–77%)
- A study by Boschetti et al. with 86 patients and examinations performed after a mean interval of 8.2 +/- 0.5 months found that a cut-off point of 100 g/g was the most effective in distinguishing between endoscopic remission and recurrence, with a sensitivity of 95%, specificity of 54%, positive and NPVs, as well as overall accuracies of 69%, 93%, and 77%, respectively

Monitoring -Biomarkers

- **Serum Biomarkers:**
- The low disease burden in early recurrence and the inconsistent elevation of CRP levels make CRP measurement insensitive to detecting early disease recurrence
- **Endoscopic healing index (EHI),** a blood test that measures 13 serum proteins that allow for the adequate identification of patients with endoscopic remission

Emerging Biomarkers

- Oncostatin M(OSM),
- Serum IL-23 levels
- Gut-specific transcriptomic signatures.

PROPHYLAXIS

- The ECCO guidelines recommend starting it in patients with risk factors for recurrence.
- AGA guidelines recommend starting early generalized prophylaxis
- Prophylactic therapy should begin soon after surgery to limit the development of endoscopic postoperative lesions

Prophylaxis -Antibiotics

- Reduce the risk of endoscopic and clinical recurrence by approximately 50%
- Nitroimidazole antibiotics

  -Metronidazole 20mg/kg/day

  -Ornidazole 500mg bd– higher withdrawal rates due to AEs

  -Use is usually limited to 3-12 months, and the disease usually recurs within a couple of years after antibiotics are stopped
- Ciprofloxacin showed no significant difference in the rate of endoscopic POR compared to placebo(65% vs. 69%,$p < 0.805$)
- Rifaximin- no studies in postop setting

Prophylaxis -Mesalazine

- Several studies have used different doses of mesalazine to prevent clinical POR.

Prophylaxis -Corticosteroids

- Budesonide – RCTs by Hellers et al and Ewe et al- No significant difference between budesonide and placebo

Hellers et al. (1999) [95]	Budesonide 6 mg/d vs. placebo	RCT	129 patients	35 (17–81)	62/67	nR = 28%	Endoscopic POR 3 months (52% vs. 31%, p = NA); Endoscopic POR 12 months (58% vs. 52%, p = NA)	Ineffective
Ewe et al. (1999) [96]	Budesonide 3 mg/3 d vs. placebo	RCT	62 patients	34 (23–47)	37/46	nR = 62%	Clinical and/or endoscopic POR 1 year 1 (57% vs. 70%)	Ineffective

Prophylaxis - Immunomodulators

- –

Gjuladin-Hellon et al. (2019) [102]	Thiopurines vs. placebo	Meta-analysis 3 studies	408 patients	NA	NA	NA	Reduction endoscopic POR 12–36 months (67% vs. 75%, RR 0.85, 95% CI 0.64–1.13); Reduction clinical POR 12–36 months (51% vs. 64%, RR 0.79, 95% CI 0.67–0.92)	Effective
Peyrin-Biroulet et al. (2009) [101]	Thiopurines vs. placebo/ metronidazole/ 5-ASA	Meta-analysis 4 studies	433 patients	NA	NA	NA	Reduction endoscopic POR (mean difference 15%, 95% CI 1.8–29%, $p = 0.026$); Reduction clinical POR (mean difference 8%, 95% CI: 1–15%, $p = 0.021$)	Effective

Anti-TNF Therapy

- Based on clinical trials, anti-TNF therapy compared with placebo resulted in 49% and 76% relative reductions in clinical and endoscopic recurrence at 18months, respectively
- Adalimumab (ADL) was also effective in the postoperative setting in the POCER study
- Can start anti-TNF therapy within 4 weeks of ileocolonic resection and primary anastomosis

De Cruz P et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet 2015;385:1406–1417.

PREVENT TRIAL

Gastroenterology 2016;150:1568–1578

Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection

Miguel Regueiro,[1] Brian G. Feagan,[2] Bin Zou,[3] Jewel Johanns,[3] Marion A. Blank,[4] Marc Chevrier,[3] Scott Plevy,[3] John Popp,[4] Freddy J. Cornillie,[5] Milan Lukas,[6] Silvio Danese,[7] Paolo Gionchetti,[8] Stephen B. Hanauer,[9] Walter Reinisch,[10,11] William J. Sandborn,[12] Dario Sorrentino,[13,14] and Paul Rutgeerts,[15] for the PREVENT Study Group

- 297 pts at 104 sites worldwide
- All study patients had undergone ileocolonic resection within 45 days before randomisation
- Infliximab(5mg/kg) or placebo Q8W for 200wks
- At week 76, endoscopic recurrence was 30.6% in the infliximab group compared to 60.0% in the placebo group

Crohn's disease management after intestinal resection: a randomised trial-POCER Trial (De Cruz et al. Lancet 2015)

- Was designed to assess the endoscopic recurrence (Rutgeerts score i2-i4) at 18 months after surgery.
- 174 patients were included, and were stratified into low or high risk of recurrence, and a basal treatment was initiated according to the risk.
- Patients were randomized in two arms: Active care (a colonoscopy was performed at 6 months after surgery and treatment was intensified in case of endoscopic recurrence) and a standard care (no colonoscopy was performed until the end of the study)

Crohn's disease management after intestinal resection: a randomised trial-POCER Trial (De Cruz et al. Lancet 2015)

- The patients on active care showed a lower endoscopic recurrence rate than those on standard care (49% vs. 67%, p = 0.03).
- Patients who dropped out because of symptomatic clinical recurrence were similar in both groups (11% vs. 17%, p = 0.23, active vs. standard care, respectively)
- The percentage of patients with clinical recurrence defined as CDAI > 200 did not reach significant differences (27% vs. 40%, p = 0.008, active vs. standard care, respectively).
- **Interpretation:** Treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of postoperative Crohn's disease recurrence

Vedolizumab to prevent postoperative recurrence of Crohn's disease (REPREVIO): a multicentre, double-blind, randomised, placebo-controlled trial. (D'Haens et al. Lancet Gasro Hep 2025)

- Conducted at 13 academic or teaching hospitals in France, Italy, the Netherlands, and Spain
- Eligible participants ≥18 yrs with Crohn's disease who underwent ileocolonic resection and had one or more risk factors for recurrence
- Patients were randomly assigned within 4 weeks of surgery (1:1 ratio) to receive intravenous vedolizumab (300 mg) or placebo at weeks 0, 8, 16, and 24
- 84 patients were randomly assigned to treatment, of whom four did not receive study treatment, leaving 43 patients in the vedolizumab group and 37 in the placebo group.

Vedolizumab to prevent postoperative recurrence of Crohn's disease (REPREVIO): a multicentre, double-blind, randomised, placebo-controlled trial. (D'Haens et al. Lancet Gasro Hep 2025)

- Ileocolonoscopy was performed at week 26,
- At week 26, the probability of a lower modified Rutgeerts score with vedolizumab versus placebo was 77·8% (95% CI 66·4 to 86·3; p<0·0001)
- Severe endoscopic recurrence was observed in ten (23·3%) of 43 patients in the vedolizumab group versus 23 (62·2%) of 37 patients in the placebo group (difference -38·9% [95% CI -56·0 to -17·3]; p=0·0004).
- Vedolizumab treatment within 4 weeks of ileocolonic resection was more likely to prevent endoscopic Crohn's disease recurrence than placebo, making this an attractive option for postoperative management in patients with risk factors for recurrence.

Ustekinumab

- A small-scale comparative study where patients receiving UST had a lower endoscopic POR rate at six months than those on azathioprine (28% vs. 54.5%, p = 0.029), though the difference was primarily driven by moderate disease (Rutgeerts i2) rather than severe recurrence (≥i3)
- When comparing UST to vedolizumab (VDZ), both drugs showed similar rates of endoscopic success (50.0% for UST vs. 47.6% for VDZ) and clinical failure (27.3% for UST vs. 32.8% for VDZ).

1.Buisson A. et al. Ustekinumab Is More Effective than Azathioprine to Prevent Endoscopic Postoperative Recurrence in Crohn's Disease. United Eur. Gastroenterol. J. **2021**, 9, 552–560.

2.Olteanu A.O.et al. Managing Crohn's Disease Postoperative Recurrence Beyond Prophylaxis: A Comprehensive Review with Meta-Analysis. Biomedicines **2024**, 12,2434.

Other Advanced therapies

- Although no direct studies have evaluated the use of these advanced therapies for the prevention of POR in CD, their demonstrated efficacy in induction and maintenance trials suggests a potential role in this setting
  - Upadacitinib
  - Risankizumab
  - Infliximab SC
  - Vedolizumab SC
  - Mirikizumab
  - Guselkumab

Minimal or No benefit

- Aminosalicylates
- Budesonide
- Probiotics
- Vitamin D
- Curcumin (active compound in turmeric)

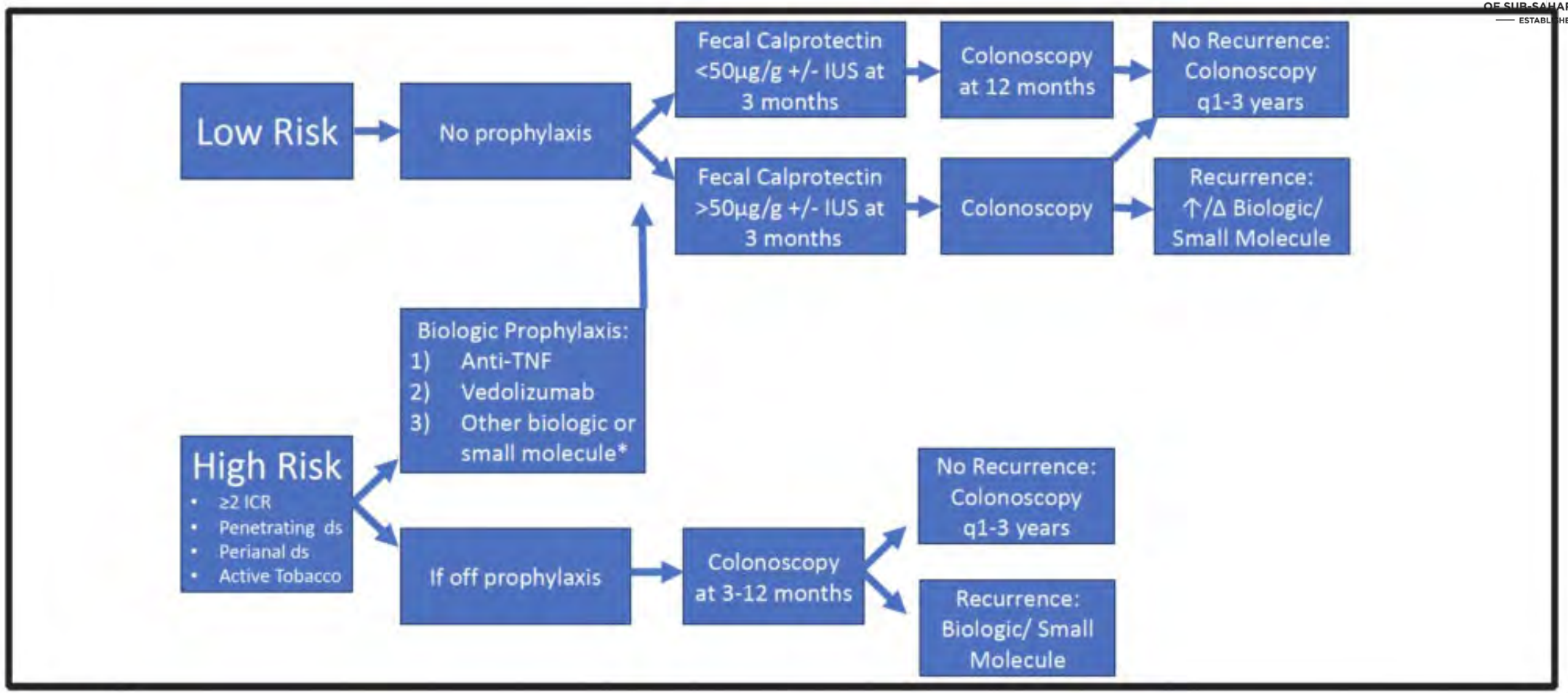


Figure 2.

Reguero M et al. A review on the Practical management of postoperative Crohn's disease. Practical gastro 2024

CONCLUSION

- Early intervention and proactive monitoring are crucial for optimizing long-term results in the postoperative setting of CD
- Smoking is the only modifiable environmental factor
- Personalized treatment plans based on individual risk factors and biomarkers are crucial.
- For high-risk patients, IFX is recommended as the first-line treatment, with UST and VDZ as second-line options
- Further studies are needed to provide evidence-based treatment algorithms and validate tools to risk-stratify patients

G-ECHO

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