# IBD NYHETSBREV

## Scientific Newsletter

December 2023

Dear colleagues,

We live exciting times in Inflammatory Bowel Disease. We are gradually gaining understanding on the patho-physiology of the disease, we have better diagnostic tools, and we have more therapeutic options available than ever before to treat our patients.

For this last newsletter of the year, I selected 10 articles published during 2023 that I consider relevant for gastroenterologists with interest in IBD and that might have direct clinical applications. The articles are divided in 4 areas of interest:

**1.** PRE-CLINICAL IBD
**2.** NEW TREATMENTS
**3.** PATHOPHYSIOLOGY OF IBD
**4.** SURGERY

I hope you find them of interest, and I wish you all Merry Christmas and an excellent 2024!

*Ignacio Catalan Serra*

*Editor*

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# 1 PRE-CLINICAL IBD

## Anti-integrin αvβ6 autoantibodies are a novel biomarker that antedate ulcerative colitis

**LIVANOS AE, DUNN A, FISCHER J, et al. Gastroenterology 2023;164:619–29. doi: 10.1053/j.gastro.2022.12.042**

### Context of the Study

Ulcerative colitis (UC) has a pre-clinical phase that can be detected early using new biomarkers in subjects at risk. This might lead to early detection and eventually treatment with potentially better clinical outcomes. However, little is known about how to identify pre-symptomatic UC.

Previously, a novel autoantibody against integrin αvβ6 (that play a critical role in maintaining epithelial barrier integrity and suppressing inflammation) was described in the serum of UC patients. This study aimed to explore the potential of the detection of this autoantibody to predict UC diagnosis and clinical outcomes.

### Methods

The authors studied two pre-clinical cohorts and two well-characterised incident IBD cohorts. Longitudinal samples predating UC diagnosis by up to ten years were analysed in 82 individuals who developed UC and matched controls (who did not develop UC).

Serum anti-αvβ6 levels were measured at four time points (sample D: -10 years, sample C: -4 years, sample B: -2 years, sample A: at diagnosis). The authors also studied if anti-αvβ6 autoantibodies were significantly associated with adverse outcomes (combination of biologic therapy requirement, disease extension, systemic steroid use, IBD-related hospitalisation and/or surgery).

### Key findings

1. A significant elevation of anti-αvβ6 autoantibodies was observed in patients who later developed UC compared to controls ($p<0.001$, samples A–C; $p=0.0015$, sample D).
2. The percentage of seropositive individuals for anti-αvβ6 autoantibodies increased progressively during the pre-clinical phase in those who developed UC (ranging from 12.2% 10 years before diagnosis to 52.4% at diagnosis)
3. The predictive performance of anti-αvβ6 autoantibodies as a biomarker remained very good with consistently high areas under the curve (AUC) values across all three pre-diagnostic samples (0.89, 0.84 and 0.79 for samples A, B, C. and D, respectively).
4. The presence of anti-αvβ6 autoantibodies was significantly associated with extensive disease (E3) [(OR) 2.76; 95% (CI) 1.21–6.33] and with a more complicated disease course in two different incident UC cohorts.

### What is new?

The presence of of anti-αvβ6 autoantibodies antedates the diagnosis of UC by several years and is associated with worse clinical outcomes.

### How can it change clinical practice?

The possibility of diagnosing Ulcerative Colitis in a pre-symptomatic individuals at risk (like first-degree relatives) could avoid delays in the diagnosis and prevent later complications like hospitalizations and surgery.

The detection of anti-αvβ6 autoantibodies has good accuracy to detect those subjects that will develop UC, which might open the door for the introduction of preventive strategies in the future. In addition, anti-αvβ6 autoantibodies are a novel biomarker indicating worse outcomes which can be used to guide therapeutic decisions.

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# Gut Microbiome Composition Is Associated With Future Onset of Crohn's Disease in Healthy First-Degree Relatives.

**RAYGOZA GARAY JA, TURPIN W, LEE SH et al. Gastroenterology. 2023 Sep;165(3):670-681. doi: 10.1053/j.gastro.2023.05.032.**

## Context of the Study

Crohn´s disease (CD) has a pre-symptomatic phase that can be detected via several biomarkers years before diagnosis (like the presence of plasmatic Anti-Saccharomyces cerevisiae antibodies (ASCA) or increased permeability tests). Dysbiosis is a common feature in IBD. However, it is unclear whether alterations of gut microbiome are associated with future onset of CD or a result of the inflammation. The characterization of early changes in the microbiota composition can help identify patients that will develop CD early avoiding late complications like abscesses, fistulae or strictures. In addition, it can also and provide clues on the role of the microbiome in CD.

## Methods

The investigators studied a prospective cohort study of 3483 healthy first-degree relatives of patients with CD from the the Crohn's and Colitis Canada Genetic Environmental Microbial (GEM) cohort. The subjects were monitored for a median of 5.4 years.

The authors applied machine learning to the analysis of the gut microbiome composition (based on 16S ribosomal RNA sequencing) to define a microbial signature that associates with future development of CD. The authors developed the Microbial Composition Risk Score (MRS) to compare between those who developed CD and those who did not to provide insight in the microbial determinants of CD pathogenesis.

## Main findings

1. Microbial Composition Risk Score is associated with future risk of developing CD. In the validation cohort, the microbiome risk score (MRS) model yielded a hazard ratio of 2.24 (95% confidence interval, 1.03-4.84; P = .04)
2. The 5 most important taxa contributing to the MRS included *Ruminococcus torques*, *Blautia*, ***Colidextribacter***, an uncultured genus-level group from *Oscillospiraceae*, and *Roseburia*.
3. Microbial Composition Risk Score Predicts CD up to 5 years Before Disease Onset (area under the curve > 0.65).
4. The Microbiome Risk Score was associated with CD independently of Fecal Calprotectin, suggesting an independent effect.

## What is new?

This study is the first to demonstrate that the gut microbiota composition is associated with future onset of CD and suggests that the bacterial component of the gut microbiota is a contributor in the pathogenesis of CD. In addition, the authors found that the microbial community rather than individuals' taxa are associated with risk of CD.

## How can it change clinical practice?

This study suggests that the determination of the bacterial microbiota (Microbiome Risk Score) could help stratify healthy at-risk individuals who would benefit from interventions aimed at modifying this dysbiosis.

This might lead to preventive strategies to correct these early changes and modify the disease course by avoiding the development of late complications. Diet modifications, Fecal Microbiota Transplantation or phage therapy could have a role in asymptomatic subjects at-risk who present these alterations.

# 2 NEW TREATMENTS

## Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): A randomised, double-blind, controlled, phase 2, proof-of-concept trial

**FEAGAN BG, SANDS BE, SANDBORN WJ, et al. Lancet Gastroenterol Hepatol 2023;8:307–20**

### Context of the Study

Despite the plethora of advanced therapies for Ulcerative Colitis (UC), a substantial part of the patients do not achieve a sustained clinical remission over time and many need treatment escalation or surgery. Combination therapy utilising dual biologic or small molecules has been proposed to improve outcomes and break the therapeutic ceiling in in selective refractory patients. Both TNF-α inhibitors and IL-23 inhibitors have demonstrated efficacy in the treatment of UC. However, there is a scarcity of good-quality data on the efficacy and safety of the combination of these two biological agents in UC.

### Methods

This is a multi-center randomised double-blinded controlled phase 2 trial aimed to determine the efficacy and safety of combination therapy with guselkumab (GUS), an IL-23 p19 antagonist, plus golimumab (GOL), a TNF-α inhibitor, compared with either monotherapy in UC.

A total of 214 patients with moderate to severe UC, were randomised into three treatment arms (1:1:1): (1) combination therapy with GUS and GOL induction therapy followed by GUS maintenance (71 patients), (2) GOL monotherapy (72 patients) and (3) GUS monotherapy (71 patients). Efficacy was assessed following induction at week 12 and also at week 38. Safety was analysed up to week 50.

Patients on combination therapy received: s.c. GOL 200 mg at week 0 followed by s.c. GOL 100 mg (at weeks 2, 6 and 10) and i.v. GUS 200 mg (at weeks 0, 4, and 8) followed by s.c. GUS 100 mg every 8 weeks for 32 weeks.

### Key Findings

1. The rate of clinical response at week 12 in the combination therapy group was significantly higher than that in the GOL monotherapy group (83% vs 61%; p=0.0032) but similar to GUS monotherapy (75%) (p=0.2155).
2. Similar results were reported at week 38 with rates of clinical response similar between GUS monotherapy and combination therapy (72% vs 69%) but higher than GOL monotherapy (58%).
3. Rates of endoscopic improvement were also higher in the combination therapy group at weeks 12 and 38 than in either monotherapy group.
4. Regarding safety, the rates of adverse events, infection and serious infection were similar across groups with no new safety signals associated with combination therapy.

### What is new?

The use of combination of IL-23 and TNF-α inhibition (guselkumab pluss golimumab) is very effective in UC, with no new safety signals. However, patients on guselkumab monotherapy also achieved high rates of clinical remission (not statistically significant compared to the combination).

### How can it change clinical practice?

Highly refractory UC patients can benefit from the combination of IL-23 and TNF-α inhibition without increasing the risk profile (until week 38). Patients on combination therapy achieved numerically higher rates of clinical, biochemical, endoscopic and histological improvement.

However, the use of Guselkumab alone was also very effective, with no statistically significant differences with the combination group. Thus, a strict patient selection, costs and long-term safety should be considered before deciding to use combination therapy with these agents.

# Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis

D'HAENS G, DUBINSKY M, KOBAYASHI T et al. N Engl J Med. 2023 Jun 29;388(26):2444-2455. doi: 10.1056/NEJMoa2207940.

## Context of the Study

Ustekinumab, a monoclonal antibody targeting the p40 subunit of interleukin-12 and interleukin-23, has been approved and in clinical use for the treatment of ulcerative colitis (UC). The exclusive inhibition of IL-23 with the novel p19-directed antibodies represents a promising new therapeutic approach for patients with UC, with several agents being tested on clinical trials. Mirikizumab, a humanized IgG4-variant monoclonal antibody that specifically binds to subunit p19 of interleukin-23, has shown efficacy in a phase 2 trial in UC.

## Methods

This is a two phase 3, randomized, double-blind, placebo-controlled trials of mirikizumab in adults with moderately to severely active ulcerative colitis.

In the induction trial, patients were randomly assigned in a 3:1 ratio to receive 300 mg i.v. mirikizumab or placebo every 4 weeks for 12 weeks. In the maintenance trial, patients with a response to mirikizumab induction were randomly assigned in a 2:1 ratio to receive mirikizumab 200 mg or placebo s.c. every 4 weeks for 40 weeks.

The primary end points were clinical remission at week 12 and week 40 in the induction and maintenance trial, respectively.

## Key Findings

1. The authors report significantly higher percentages of clinical remission in the mirikizumab group than in the placebo group at week 12 of the induction trial (24.2% vs. 13.3%, P<0.001) and at week 40 of the maintenance trial (49.9% vs. 25.1%, P<0.001).
2. The criteria for all the major secondary end points (clinical response, endoscopic remission, and improvement in bowel-movement urgency) were met in both trials.
3. Nasopharyngitis and arthralgia were reported more frequently with mirikizumab than with placebo. Opportunistic infection or cancer occurred in a small number of patients treated with mirikizumab: 15 had an opportunistic infection (6 with herpes zoster) and 8 had cancer (3 colorectal cancer). Depression was reported in four patients who received mirikizumab and in no patient who received placebo in the maintenance trial.

## What is new?

Mirikizumab, a novel IL-23 inhibitor, was more effective than placebo in inducing and maintaining clinical remission in patients with moderately to severely active UC. Opportunistic infection or cancer were more frequent than placebo, but their absolute frequency was low.

## How can it change clinical practice?

This study was the foundation for the approval of Mirikizumab for moderately-to-severe UC patients. Mirikizumab offers a new therapeutic alternative in UC, with high rates of clinical remission. The positioning of the novel p-19 inhibitors in the therapeutic algorithm for UC (especially in patients with failure to anti-TNF) needs to further study.

# Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies.

**SANDBORN WJ, VERMEIRE S, PEYRIN-BIROULET L et al. Lancet. 2023 Apr 8;401(10383):1159-1171. doi: 10.1016/S0140-6736(23)00061-2.**

## Context of the Study

There is a need for new effective oral treatments for ulcerative colitis (UC). The modulation of sphingosine 1-phosphate (S1P) receptor has proven to be effective by limiting the egress of activated lymphocytes from the lymph nodes. Ozanimod, a selective S1P1,5 receptor modulator, is approved for the treatment of multiple sclerosis and UC.

Etrasimod is an oral, once-daily, selective, sphingosine 1-phosphate receptor (S1P1,4,5) modulator that proved to be effective for moderately to severely active UC in a phase 2 trial.

## Methods

This article presents the results of two independent randomised, multicentre, double-blind, placebo-controlled, phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12. Patients with active moderate-to-severe UC and an inadequate or loss of response or intolerance to at least one approved therapy were randomly assigned (2:1) to once-daily oral etrasimod 2 mg or placebo.

ELEVATE UC 52 comprised a 12-week induction period followed by a 40-week maintenance period. ELEVATE UC 12 independently assessed induction at week 12. The full analysis set of ELEVATE UC 52 comprised 289 patients assigned to etrasimod and 144 to placebo and 238 patients were assigned to etrasimod and 116 to placebo In ELEVATE UC 12.

The primary efficacy endpoints were the proportion of patients with clinical remission at weeks 12 and 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12

## Key Findings

1. A significantly greater proportion of patients in the etrasimod group achieved clinical remission compared with placebo at week 12 (27% vs 7% of patients; p<0·0001) and at week 52 (32% vs 7%); p<0·0001) in ELEVATE UC 52.
2. Of note, ELEVATE UC 52 is the first phase 3 treat-through design trial of S1P receptor modulators in which all patients enrolled in the trial were included in the efficacy evaluation at the end of the 40-week without re-randomisation.
3. In ELEVATE UC 12, 25% of patients in the etrasimod group had clinical remission compared with 15% in the placebo group at week 12. This difference was not statistically significant (p=0.026).
4. Key secondary endpoints for both trials, including endoscopic improvement, endoscopic improvement–histological remission, and sustained clinical remission were achieved in patients treated with etrasimod.
5. Adverse events were reported in 71% of patients treated with etrasimod vs 56% in the placebo group in ELEVATE UC 52. No deaths or malignancies were reported.

## What is new?

Etrasimod is an effective and well tolerated novel oral therapy in patients with UC, with a good safety profile. Etrasimod might offer two advantages in comparison with ozanimod: 1) faster wash-out period of 1 week (with faster normalization of lymphocyte counts within 2 weeks after cessation of treatment); and 2) it can be used in full dose from day one, not needing dose titration.

## How can it change clinical practice?

Etrasimod is a new oral agent that will be soon available for clinicians to add to the current armamentarium for UC, with a favourable safety profile. As with Ozanimod, patients should obtain and ECG and an ophthalmic exam if they present a history of diabetes, macular oedema, or uveitis. The positioning of S1P modulators needs further study, especially in patients that failed anti-TNF.

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# Efficacy and safety of fecal microbiota transplantation in the treatment of ulcerative colitis: a systematic review and meta-analysis.

**Feng J, Chen Y, Liu Y et al. Sci Rep. 2023 Sep 3;13(1):14494. doi: 10.1038/s41598-023-41182-6.**

## Context of the Study

Fecal Microbiota Transplantation (FMT) is a promising new therapeutic alternative for patients with ulcerative colitis (UC). However, it has not reached clinical practice outside clinical trials yet. Some aspects like long-term efficacy and safety have not been well-studied.

## Methods

The authors performed a comprehensive systematic review and meta-analysis of high-quality randomized controlled trials (RCT) that explored the efficacy and safety of FMT as a treatment approach for UC.

A total of 13 RCTs on the efficacy of FMT in patients with UC were included in the study, in which 580 patients participated, including 293 patients treated with FMT and 287 control subjects.

## Key Findings

1. Clinical remission was significantly better in the FMT group than in the control group [RR = 1.73; 95% CI = (1.41, 2.12); P < 0.00001].
2. Endoscopic remission was significantly better in the FMT group than in the control group [RR = 1.74; 95% CI = (1.24, 2.44); P = 0.001].
3. The study confirms a very good safety profile of FMT. No significant differences in the incidence of adverse reactions between the two groups [RR = 1.00; 95% CI = (0.86, 1.15); P = 0.96].

## What is new?

This large meta-analysis with more than 500 patients included in 13 RCT confirms the efficacy of FMT in UC, with higher clinical remission rates than placebo. Notably, FMT was also more effective in achieving endoscopic remission and showed a favorable safety profile in the long-term.

## How can it change clinical practice?

This study adds to previous meta-analysis confirming the efficacy of FMT for UC. Importantly, no new safety signals were shown in the meta-analysis which is reassuring for clinical implementation. FMT represents a safe and affordable therapeutic modality that avoids immune suppression and has great potential to improve outcomes in UC. In addition, FMT could be used in combination with current advanced therapies (or for maintenance of remission by correcting dysbiosis). However, some key aspects like the most effective route of administration, donor selection or schedule protocols need to be further studied.

# 3 PATHOPHYSIOLOGY OF IBD

## The enteric nervous system relays psychological stress to intestinal inflammation

**SCHNEIDER KM, BLANK N, ALVAREZ Y et al. Cell. 2023 Jun 22;186(13):2823-2838.e20. doi: 10.1016/j.cell.2023.05.001..**

### Context of the Study

It is well established that mental health profoundly impacts inflammatory responses in the body. Patients with IBD suffer from several psychological issues like anxiety and depression; and psychological stress is associated with disease flares. However, the exact mechanisms behind this are not fully understood.

The authors aim to uncover several mechanisms by which psychological stress influences bowel inflammation via the enteric nervous system (ENS).

### Methods

The authors study several mouse models of intestinal inflammation and patient data from the UK biobank with an external validation cohort of dutch IBD patients and a prospective stress cohort analyzing colonoscopy biopsies.

### Key Findings

1. The authors discover a critical role for the enteric nervous system (ENS) in mediating the aggravating effect of chronic stress on intestinal inflammation.
2. Psychological stress leads to monocyte-mediated exacerbation of gut inflammation.
3. Chronically elevated levels of glucocorticoids drive the generation of an inflammatory subset of enteric glia that promotes monocyte- and TNF-mediated inflammation via colony stimulating factor-1 (CSF1).
4. Stress provokes transcriptional immaturity in enteric neurons and dysmotility. Glucocorticoids cause transcriptional immaturity in enteric neurons, acetylcholine deficiency, and dysmotility via TGF-β2.
5. This novel connection between the psychological state, intestinal inflammation, and dysmotility was verified in three cohorts of IBD patients.

### What is new?

This study offers for the first time a mechanistic explanation for the impact of the brain on peripheral inflammation and reveals the key role of the the enteric nervous system as a relay between psychological stress and gut inflammation.

### How can it change clinical practice?

This study helps clinicians understand the bi-directional relationship between stress and intestinal inflammation and provides a new explanation of the clinical observation of stress provoking flares of IBD.

These findings also highlight enteric neurons and glia as possible therapeutic targets and underscores the relevance of stress management as a valuable component of IBD care. Furthermore, it provides strong evidence for the inclusion of a clinical psychologists as part of the multi-disciplinary team in our IBD units.

# Genetic coding variant in complement factor B (CFB) is associated with increased risk for perianal Crohn's disease and leads to impaired CFB cleavage and phagocytosis.

**Akhlaghpour M, Haritunians T, More SK et al. Gut. 2023 Nov;72(11):2068-2080. doi: 10.1136/gutjnl-2023-329689.**

## Context of the Study

Perianal Crohn's disease is a common feature that occurs in up to 40% of patients with CD and is associated with repeated surgeries and poor quality of life. The etiology of perianal CD is poorly understood.

CD is associated with a dysfunction in several mechanisms of the innate immunity (macrophages, intraepithelial lymphocytes, neutrophils etc.). The complement factor B (CFB) is a component of the alternative pathway of complement activation and facilitates phagocytosis by several immune cells, including macrophages. CFB has been previously associated with CD in Genome-wide association studies, but the mechanism contributing to intestinal inflammation is not known.

## Methods

The authors performed a genetic association study comparing CD subjects with and without perianal disease and subsequently performed functional follow-up studies for a pCD associated SNP in Complement Factor B (CFB).

Immunochip-based meta-analysis on 4056 pCD and 11 088 patients with CD from three independent cohorts was performed. Several methods were performed in to assess the mechanistic function of the risk allele rs4151651, including introduction in human plasmid and cell-free assays to study the cleavage of C3B and flow cytometry to assess macrophage phagocytosis.

## Key Findings

1. The study of serological and clinical variables showed that perianal complications were associated with colonic involvement, OmpC and ASCA serology.
2. The authors identify a novel genetic association for pCD (rs4151651), a non-synonymous SNP (G252S) in CFB, in all three cohorts of CD patients.
3. Perianal CD-associated variant rs4151651 leads to glycine to serine amino acid substitution in CFB (G252S CFB) and confers significantly impaired binding to complement factor 3b and subsequent cleavage of CFB into Ba and Bb subunits.
4. Serum from homozygous risk subjects (S252/S252) confers significantly decreased macrophage phagocytosis of zymosan particles compared with homozygous protective subjects (G252/G252).

## What is new?

The authors identified a novel risk allele for the development of perianal CD.

This study shows how this genetic variant (recombinant S252 CFB) decreases macrophage phagocytosis and cytokine secretion, revealing a new alteration in innate immunity leading to a defective clearance of antigens in CD.

## How can it change clinical practice?

The perianal CD-associated variant rs4151651 could be used as a biomarker to monitor patients at risk to develop this devastating complication in the future.

This study suggests that targeting the alternative complement pathway may be a novel therapeutic approach for treating perianal CD.

# 4 SURGERY FOR IBD

## KONO-S Anastomosis Is Not Superior to Conventional Anastomosis for the Reduction of Postoperative Endoscopic Recurrence in Crohn's Disease.

**TYRODE G, LAKKIS Z, VERNEREY D et al. Inflamm Bowel Dis. 2023 Sep 30:izad214. doi: 10.1093/ibd/izad214.**

### Context of the Study

A high proportion of CD Patients still need surgery during the disease course. Reducing postoperative recurrence (POR) is challenging, especially in patients with risk factors (i.e. smokers) or several surgeries.

The Kono-S anastomosis is new surgical technique (a terminal, antimesenteric, ileocolic handsewn anastomosis with a support column to prevent distortion and anastomosis stenosis), that may reduce postoperative recurrence in CD after ileal resection. A recent Italian RCT showed promising results of Kono-S in reducing post-operative recurrence (POR).

### Methods

The aim of the study was to compare the endoscopic POR rate after Kono-S vs standard ileocolic anastomosis.

The study included all consecutive CD patients operated for ileocolic resection with a Kono-S anastomosis between February 2020 and March 2022. They were prospectively followed, and colonoscopy was performed 6 to 12 months. Patients were compared with a historical cohort of patients operated on with a conventional anastomosis in the same center.

The primary end point was endoscopic POR (Rutgeerts score ≥i2) and factors associated with POR were assessed. A total of 85 patients were included, 30 in the Kono-S group and 55 in the control group, with no significant differences in risk factors or use of biologics.

### Key Findings

1. At 6 to 12 months, endoscopic POR rate did not differ significantly between groups (56.7% in the Kono-S group vs 49.1% in the control group; P = 0.50), nor did endoscopic POR according to the modified Rutgeerts score ≥i2b (46.7% in the Kono-S group vs 40% in the control group; P = 0.55).
2. Severe endoscopic POR rates were 23.3% and 18.2% in each group, respectively. Clinical recurrence rate was similar in both groups, and no recurrent surgery occurred.
3. The type of anastomosis was not associated with endoscopic POR by multivariable analysis (OR, 1.229; 95% CI, 0.461-3.274, P = .68); however, postoperative treatment with anti-TNF was (OR, 0.337; 95% CI, 0.131-0.865 P = 0.02).
4. The surgical approach was mostly laparoscopic, for 71.8% of procedures. There was no significant difference in operative time , length of bowel resection, length of hospital stay or complications between groups.

### What is new?

Kono-S anastomosis did not reduce postoperative recurrence in a prospective cohort of CD patients undergoing ileal resection, with systematic review of postoperative colonoscopy.

Kono-S technique was safe and feasible. However, these results contradict the previous positive results, which highlights the need for randomized multicenter studies to confirm its value in reducing postoperative recurrence.

### How can it change clinical practice?

Due to the relative high rates of post-operative recuerrence, the implementation of new surgical techiques that might prevent it is of high interest.

In this study, Kono-S anastomosis was technically feasible, with no differences in terms of operative time, conversion to laparotomy, length of resection, or postoperative outcome, which might make this approach appealing in CD.

However, the positive results of the previous RCT from Italy were not confirmed in this series from France. Thus, more data is needed before we can adopt this technique as a standard procedure in patients with CD.

Other surgical techniques for preventing POR, especially involving mesenteric extensive resections, are currently under evaluation and will help clarify the role of the mesenterium in the natural history of POR in CD.

# Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study.

**Agrawal M, Ebert AC, Poulsen G et al. Gastroenterology. 2023 Oct;165(4):976-985.e3. doi: 10.1053/j.gastro.2023.05.051.**

## Context of the Study

There is a window of opportunity to treat Crohn´s disease (CD) early after diagnosis and prevent complications and disease progression.

Although surgical management is traditionally recommended in complicated CD or for patients nonresponsive to or intolerant of medications, there is evidence of the efficacy of early surgery in selected patients. In the Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Recurrent Distal Ileitis in Crohn's Disease (LIR!C) trial, the improvement in quality of life with ileocecal resection was comparable to infliximab as a first-line therapy for limited, nonstricturing ileocecal CD at 1 year.

However, in the real world, the long-term impact of early ileocecal resection remains largely unexplored.

## Methods

This study used longitudinal real-world data to compare long-term outcomes of primary ICR and anti-TNF therapy for ileocecal CD. The authors used cross-linked nationwide registers from Denmark to identify all individuals diagnosed with ileal or ileocecal CD between 2003 and 2018 and treated with ICR or anti-TNF agents within 1 year of diagnosis.

The primary outcome was a composite of ≥1 of the following: CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, and perianal CD.

## Key Findings

1. 1279 individuals fulfilled the inclusion criteria (45.4% underwent ICR and 54.6% received anti-TNF)
2. The composite outcome occurred in 273 individuals (incidence rate, 110/1000 person-years) in the ICR group and in 318 individuals (incidence rate, 202/1000 person-years) in the anti-TNF group.
3. The primary outcome (complications of the disease) was 33% lower with ICR compared with anti-TNF (adjusted hazard ratio, 0.67; 95% confidence interval, 0.54–0.83).
4. ICR was associated with reduced risk of systemic corticosteroid exposure and CD-related surgery, but not other secondary outcomes.
5. The proportion of individuals on immunomodulator, anti-TNF, who underwent subsequent resection, or were on no therapy 5 years post-ICR was 46.3%, 16.8%, 1.8%, and 49.7%, respectively.

## What is new?

The study demonstrates that the risk of the composite outcome (including hospitalization, repeat Crohn's disease-related surgery, systemic corticosteroid exposure, and perianal CD) was 33% lower with ileocaecal resection compared with anti-tumor necrosis factor agents as primary therapy.

Of individuals who underwent ileocaecal resection, approximately half were on no treatment at 5 years of follow-up.

## How can it change clinical practice?

This real-world longitudinal data suggest that ileocecal resection may have a role as first-line therapy in CD management and challenge the current paradigm of reserving surgery for complicated CD.

Intriguingly, almost 50% of patients that underwent an early ileocecal resection in this large sample were on no treatment at 5 years of follow-up. The characterization of this subpopulation of good responders after resection deserves further investigation to avoid over-treatment.

Identifying clinical and biological (-omics) characteristics of patients that could benefit the most from an early resection is paramount to guide the management of CD in the first year after diagnosis, avoiding potential complications.