

Editorial: Postoperative management of Crohn's disease: One size does not fit all

It was in the late eighties and early nineties that the Leuven's group led by Paul Rutgeerts published a series of landmark studies describing the natural history of postoperative Crohn's disease (CD). These authors introduced the concept of postoperative recurrence (POR) as defined by the development of disease-related mucosal lesions at the neoterminal ileum after a "curative" ileocecal resection. They showed that this phenomenon occurs early after surgery in up to 80% of patients within the first 12 months and that there is a clear correlation between the severity of these lesions seen at ileocolonoscopy and the risk of developing symptoms (clinical POR), which in some patients may lead to a new intestinal resection (surgical POR).¹⁻³

Since then, many randomized, controlled studies have been performed to assess the efficacy of a number of drugs to prevent POR. To date, only thiopurines and anti-TNF agents have been demonstrated to be useful in the prevention of early endoscopic POR.⁴

But bearing in mind that not all the patients will develop POR (and in a significant proportion of those who will, only intermediate lesions carrying a low risk of clinical and surgical POR will occur) and that the use of immunosuppressive therapies carries a risk of adverse effects, the best strategy after intestinal resection is still under debate.

Systematic prevention with thiopurines and anti-TNF agents is supported by their demonstrated efficacy. Moreover, most of these patients already developed disease-related complications that drove them to surgery; therefore, leaving them without any maintenance therapy is against the current therapeutic goals that promote intensive treatment in those patients at risk of disabling disease.

On the other hand, some authors propose the so-called "endoscopy-driven strategy". Based on the benefits of treatment escalation in case of advanced endoscopic lesions,⁵ this strategy proposes early endoscopic monitoring and treatment with thiopurines or anti-TNF agents only in case of endoscopic POR. Although a statistically underpowered study found no differences in the rate of endoscopic POR after 2 years between this strategy and systematic prevention,⁶ it is also true that there is a risk of being late to reverse mucosal damage, leading to persistence or progression of mucosal lesions in up to 30%–50% of patients.⁷

Finally, given that there are some epidemiological and clinical features that have been associated with a higher risk of early POR, the

third strategy defends that the decision to start prevention or wait for endoscopic monitoring should be based on the presence or absence of risk factors. However, with the available risk factors in daily clinical practice, this strategy seems to be useless in improving postoperative outcomes.⁸ Recently, a prospective French research project on different POR issues found that the more risk factors, the higher the risk of endoscopic POR.⁹ As a consequence, these investigators decided to establish a decision-making protocol of POR prevention based on the number of risk factors. Unfortunately, this "stratification strategy" led to similar rates of endoscopic POR between those patients with no, one, or more than one risk factor in whom no prevention, thiopurines, and anti-TNF agents were started after surgery, respectively.¹⁰

In this issue of *United European Gastroenterology Journal*, Dragoni et al¹¹ explore a somewhat different aspect of this complex clinical scenario. The Italian Group in Inflammatory Bowel Disease designed a retrospective study to assess whether primary prevention or endoscopy-driven strategies work better in patients meeting only one risk factor for POR. Almost 200 adult CD patients who underwent ileocolic resection, met only one out of five well-established POR risk factors (i.e. previous intestinal resection, >50 cm small bowel resection, fistulising phenotype, history of perianal disease, or active smoking), and had at least one available ileocolonoscopy 6–12 months after surgery were included. The main endpoint was endoscopic POR within 12 months after surgery. The authors did not observe any difference in the rates of endoscopic POR (defined by a Rutgeerts score > i2a), severe endoscopic POR (Rutgeerts score i4), and clinical POR between the two study groups.

Although the study has some gaps related to its retrospective design (lack of central review of endoscopic examinations, different timings for endoscopic assessment, and different drug therapies in the primary prevention group), the observed results warrant a prospective evaluation of new decision-making approaches in the postoperative setting of CD. Both primary prevention and endoscopy-driven therapy strategies seem to be useful in the suitable patient...but how do we identify the patient? Maybe it is time to bring in histologic^{12,13} and microbiological¹⁴ data for decision-making.

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Crohn's disease, endoscopy, gastroenterology, inflammatory bowel disease, surgery

CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Author elects to not share data.

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REFERENCES

- Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut*. 1984;25(6):665–72. <https://doi.org/10.1136/gut.25.6.665>
- Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99(4):956–63. [https://doi.org/10.1016/0016-5085\(90\)90613-6](https://doi.org/10.1016/0016-5085(90)90613-6)
- D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*. 1998;114(2):262–7. [https://doi.org/10.1016/s0016-5085\(98\)70476-7](https://doi.org/10.1016/s0016-5085(98)70476-7)
- Beelen EMJ, Nieboer D, Arkenbosch JHC, Regueiro MD, Satsangi J, Ardizzone S, et al. Risk prediction and comparative efficacy of anti-TNF vs thiopurines, for preventing postoperative recurrence in Crohn's disease: a pooled analysis of 6 trials. *Clin Gastroenterol Hepatol*. 2022;20(12):2741–52.e6. <https://doi.org/10.1016/j.cgh.2021.10.021>
- De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet*. 2015;385(9976):1406–17. [https://doi.org/10.1016/S0140-6736\(14\)61908-5](https://doi.org/10.1016/S0140-6736(14)61908-5)
- Ferrante M, Papamichael K, Duricova D, D'Haens G, Vermeire S, Archavlis E, et al. Systematic versus endoscopy-driven treatment with Azathioprine to prevent postoperative ileal Crohn's disease recurrence. *J Crohns Colitis*. 2015;9(8):617–24. <https://doi.org/10.1093/ecco-jcc/jjv076>
- Cañete F, Mañosa M, Pérez-Martínez I, Barreiro-de Acosta M, González-Sueyro RC, Nos P, et al. Antitumor necrosis factor agents to treat endoscopic postoperative recurrence of Crohn's disease: a nationwide study with propensity-matched score analysis. *Clin Transl Gastroenterol*. 2020;11(8):e00218. <https://doi.org/10.14309/ctg.0000000000000218>
- Joustra V, van Sabben J, van der Does de Willebois E, Duijvestein M, de Boer N, Jansen J, et al. Benefit of risk-stratified prophylactic treatment on clinical outcome in post-operative Crohn's disease. *J Crohns Colitis*. 2022;jjac139. <https://doi.org/10.1093/ecco-jcc/jjac139>
- Auzolle C, Nancey S, Tran-Minh ML, Buisson A, Pariente B, Stefanescu C, et al. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study. *Aliment Pharmacol Ther*. 2018;48(9):924–32. <https://doi.org/10.1111/apt.14944>
- Hammoudi N, Auzolle C, Tran Minh ML, Boschetti G, Bezault M, Buisson A, et al. Postoperative endoscopic recurrence on the neoterminal ileum but not on the anastomosis is mainly driving long-term outcomes in Crohn's disease. *Am J Gastroenterol*. 2020;115(7):1084–93. <https://doi.org/10.14309/ajg.0000000000000638>
- Dragoni G, Castiglione F, Bezzio C, Pugliese D, Spagnuolo R, Viola A, et al. Comparison of two strategies for the management of post-operative recurrence in Crohn's disease patients with one clinical risk factor: a multicentre IG-IBD study. *United Eur Gastroenterol J*. 2023.
- Li Y, Zhu W, Zuo L, Shen B. The role of the mesentery in Crohn's disease: the contributions of nerves, vessels, lymphatics, and fat to the pathogenesis and disease course. *Inflamm Bowel Dis*. 2016;22(6):1483–95. <https://doi.org/10.1097/MIB.0000000000000791>
- Tandon P, Malhi G, Abdali D, Pogue E, Marshall JK, de Buck van Overstraeten A, et al. Active margins, proctitis, and granulomas increase postoperative Crohn's recurrence: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(3):451–62. <https://doi.org/10.1016/j.cgh.2020.08.014>
- Wright EK, Kamm MA, Wagner J, Teo SM, Cruz P, Hamilton AL, et al. Microbial factors associated with postoperative Crohn's disease recurrence. *J Crohns Colitis*. 2017;11(2):191–203. <https://doi.org/10.1093/ecco-jcc/jjw136>