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TABLE OF CONTENTS

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S1PR MODULATORS IN THE MANAGEMENT OF ULCERATIVE COLITIS: CONSIDERATIONS FOR PRACTICE

KEY TAKEAWAYS

- Data support S1PR modulators as effective therapies for the management of patients with moderate-to-severe UC
- They are safe, non-immunogenic, once daily oral therapies
- More head-to-head trials are needed to optimally place S1PR modulators in the treatment algorithm for UC

Introduction

Sphingosine-1-phosphate receptor (S1PR) modulators are novel oral small-molecule therapies that offer a unique profile compared to other advanced therapies in the treatment of ulcerative colitis (UC), including oral administration, linear pharmacokinetic profiles, reduced immunogenicity, and lower costs associated with manufacturing.[1]

The activation of S1P G-protein coupled receptors plays an inflammatory role in UC by promoting lymphocyte egress from lymphoid organs into circulation and colonic mucosa. S1PR modulators lead to internalization and degradation of these receptors, thereby reducing inflammation. Ozanimod was the first S1PR modulator approved for treating moderately-to-severely active UC and is also approved for multiple sclerosis. More recently, a second agent, etrasimod, was approved for UC. Etrasimod acts on different S1PR subtypes to avoid off target vascular and cardiac effects, has no up-titration regimen during initiation, a shorter half-life and less propensity for drug interactions. This review summarizes clinical trial and real-world data and provides guidance on the clinical uses of S1PR modulators.

Mechanism of Action of Sphingosine-1-Phosphate Receptor Modulators

S1PRs are G protein-coupled receptors that regulate immune cell trafficking. Among the five S1PR subtypes, S1PR1 is the most relevant for UC management. Sphingosine-1-phosphate (S1P) is a lipid signalling molecule that binds to S1PR1 on lymphocytes, facilitating their exit from lymphoid organs into the circulation. This leads to excessive lymphocyte migration into the intestinal mucosa as demonstrated in **Figure 1**.

Ozanimod is a selective agonist for S1P1 and S1P5 receptors which promotes S1P1 receptor internalization and degradation, decreasing T-cell migration from lymphoid organs. This results in a reduction of circulating B cells and CCR7+ T lymphocytes, thereby diminishing inflammation, mononuclear cell infiltration, and mucosal thickness. Certain traditional and advanced immune suppressive therapies affect multiple immune cell types and functions. S1PR modulators target lymphocyte egress as opposed to their function and their selective targeting of lymphocyte cells reduces the potential to develop certain toxicities and malignancies associated with other treatments. The current generation of S1PR modulators also has significantly less systemic side effects relative to previous generations. **Table 1** outlines various S1PR receptor subtypes, locations and their functions.[1,2]

Etrasimod is an S1PR modulator that selectively activates S1PR1, S1PR4, and S1PR5 with no activity on S1PR2 or S1PR3. By avoiding S1PR2, it prevents off target vascular side effects such as vasoconstriction. In addition, avoiding S1PR3 reduces the risks of bradycardia and hypertension, ensuring cardiovascular safety.[3]

Selective S1PR modulators, such as ozanimod and etrasimod, specifically target S1PR1 to prevent lymphocytes from exiting lymphoid tissues and infiltrating into the gut mucosa. This action decreases intestinal inflammation.[2] Unlike broad immunosuppressive therapies, S1PR modulators offer a targeted mechanism, minimizing systemic immune suppression while effectively controlling localized inflammation in the gastrointestinal tract. This makes them an attractive therapeutic option for patients with moderate-to-severe UC, who require long-term management of inflammation while limiting systemic side effects.

Efficacy of Ozanimod

In the phase 2 TOUCHSTONE trial, 197 adults with UC were randomly assigned to receive either a placebo, ozanimod 0.5 mg, or ozanimod 1 mg. The study's primary endpoint was clinical remission, defined as a Mayo score ≤2 without any individual subscore > 1 at 8 weeks.

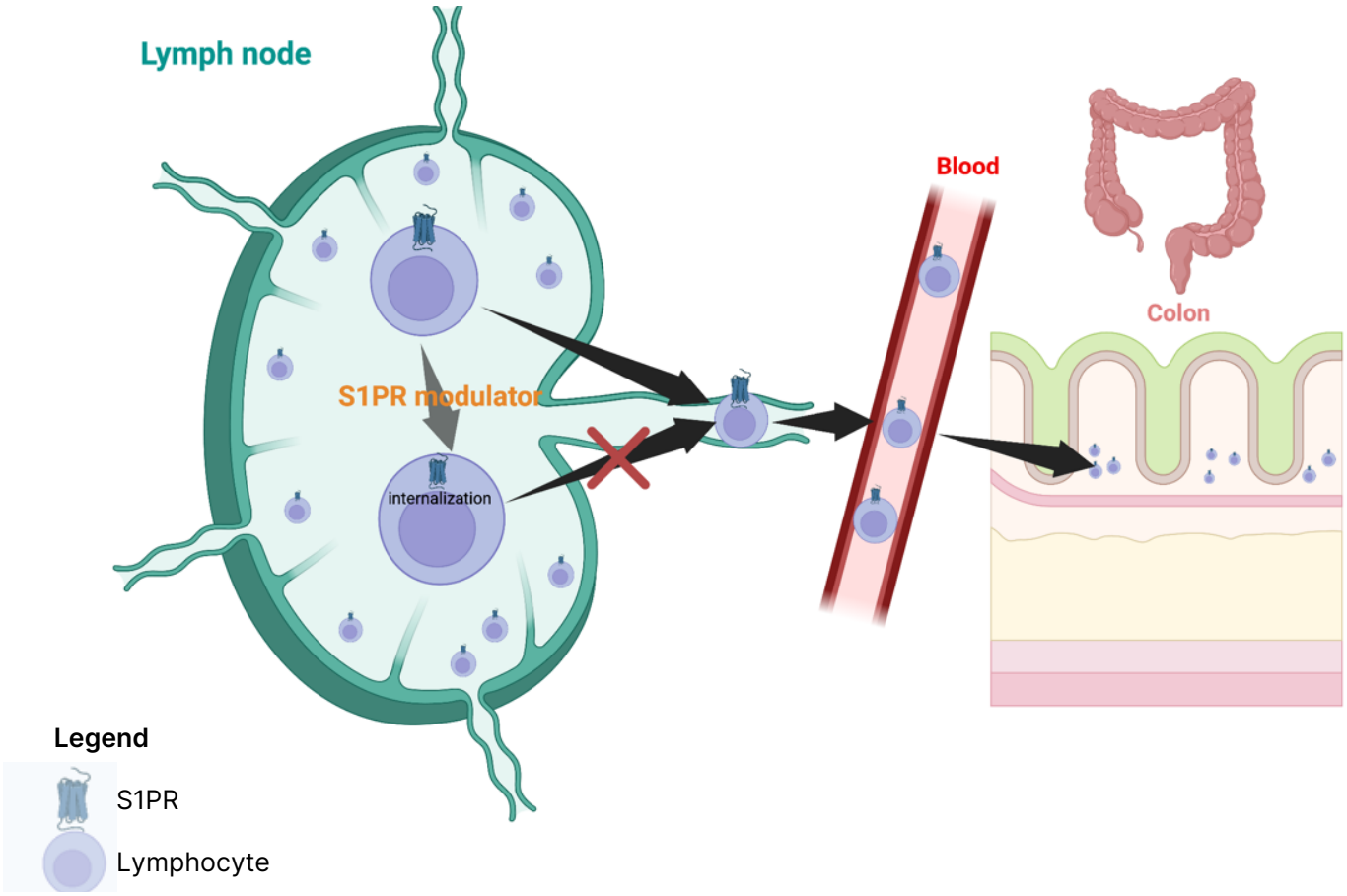

Figure 1: Mechanism of action of S1PR modulators; *courtsey of BioRender. Hass, A. (2024) BioRender.com/b88y627*

At week 8, 16% of patients on ozanimod 1 mg achieved clinical remission compared to 6% on placebo (P=.048). Additionally, 57% of the 1 mg group showed a clinical response vs. 37% in the placebo group. Mucosal healing was observed in 34% of patients on ozanimod 1 mg compared to 12% on placebo (P=.002).[4,5]

In the phase 3 True North trial, the primary endpoint of clinical remission was assessed at week 10 for the induction period and week 52 for the maintenance period. Clinical remission was defined using the three-component Mayo score (rectal bleeding subscore of 0, stool frequency subscore of ≤1 with a decrease of at least 1 point from baseline, and an endoscopy subscore of ≤1). At 10 weeks, remission was achieved in 18.4% of patients on ozanimod compared to 6% on placebo (P<0.0001). Secondary endpoints included clinical response (based on three-component Mayo subscore), endoscopic improvement (endoscopic subscore ≤1 without friability), and mucosal healing (endoscopic improvement plus histologic remission with mucosal endoscopy score of ≤1 and a Geboes score of <2). All secondary endpoints were significantly improved in the ozanimod group. The True North trial also showed sustained efficacy over time, with 37% of patients on ozanimod in clinical remission at week 52, compared to 18.5% in the placebo group (*P*<0.0001). This remission was accompanied by significant improvements in key secondary endpoints such as endoscopic improvement in the ozanimod group compared to placebo (45.7% vs. 26.4%; *P*<0.001) and corticosteroid-free clinical remission (31.7% vs. 16.7%; *P*<0.001).[4,6]

Efficacy of Etrasimod

The phase 2 12-week OASIS trial evaluated the efficacy of 2 mg of etrasimod in 156 patients with moderate-to-severe UC. The primary endpoint, which included improvements in Mayo Clinic scores (stool frequency, rectal bleeding and endoscopic appearance) was reached, along with endoscopic improvement.[7] In a 52-week open-label extension of this trial, 2 mg of etrasimod showed a 64% clinical response, 33% clinical remission, and 43% endoscopic improvement. This included patients who were on placebo during the original 12-week trial. Numerous patients who achieved a clinical response at 12 weeks maintained these benefits, while 22% of all patients achieved steroid-free remission.[8]

This was followed by two double-blind phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12. The primary endpoints of ELEVATE 52 were clinical remission at weeks 12 and 52. This trial used a treat-through trial design, comprising a 12-week induction

S1P Receptor Subtype	Primary Locations	Functions
S1PR1	Immune cells, endothelial cells, nervous system	Regulates lymphocyte egress from lymph nodes, vascular stability, and endothelial cell barrier integrity. Involved in immune cell migration.
S1PR2	Brain, endothelial cells, smooth muscle cells	Modulates vascular tone and endothelial permeability; influences brain and cardiovascular function. Plays a role in inflammatory responses.
S1PR3	Immune cells, heart, lungs, kidneys, vascular smooth muscle cells	Involved in inflammatory and immune responses, heart rate regulation, and vascular tone. Higher expression in organs involved in hemodynamic control.
S1PR4	Immune cells, especially in lymphoid tissues	Predominantly found in immune cells like T and B lymphocytes. Plays a role in immune regulation and modulation of inflammatory responses.
S1PR5	Central nervous system (CNS), especially oligodendrocytes; some expression in spleen and natural killer (NK) cells	Important in neural development, especially in myelination; involved in oligodendrocyte survival and function. Also plays a role in immune responses.

Table 1: Cell locations of various S1PR subtypes and reception functions; *courtsey of* Aaron Hass, MD, Laetitia Amar, MD, Robert Battat, MD, FRCPC

period followed by a 40-week maintenance phase without re-randomizing the induction responders. In the induction period of ELEVATE 52, the clinical remission rate was 27.0 % with etrasimod vs. 7 % with placebo ($p<0.0001$). At week 52, the remission rate was 32% with etrasimod vs. 7% with placebo ($p<0.0001$). Secondary endpoints were also achieved at both weeks 12 and 52. At 52 weeks, treatment with etrasimod led to symptomatic remission (24.9% higher than placebo; $p<0.0001$), endoscopic improvement, with an endoscopic subscore ≤1 (26.7% higher than placebo; $p<0.0001$), and mucosal healing with histologic remission incorporated (18.4% higher than placebo; $p<0.0001$). Some patients on etrasimod experienced steroid-free remission at 12 weeks (32% with etrasimod vs. 7% with placebo; $p<0.0001$), and sustained remission (18% with etrasimod vs. 2% with placebo; $p<0.0001$). The ELEVATE UC 12 trial was shorter in duration, ending at 12 weeks, and also demonstrated positive outcomes, including a clinical remission rate of 25% with etrasimod vs. 15% with placebo.[9]

What About Predictors of Efficacy?

S1PR modulators can inhibit lymphocyte egress while biologics can block specific pro-inflammatory cytokines. However, there has been no clear correlation to date between therapeutic effectiveness and lymphocyte counts. There are currently no predictors of responsiveness to therapy, though conducting analyses involving immunophenotyping of cell subtypes could be a worthwhile avenue to further explore.[10] In a study on Crohn's disease, ozanimod reduced circulating levels of all B-cell and most T-cell subsets but not monocytes or natural killer cells. This study also suggested that levels of non-switched memory B cells could serve as a biomarker for response, given their positive association with clinical, endoscopic, and histologic endpoints in Crohn's disease.[11]

Safety Profiles and Considerations

Although no direct comparisons exist, the safety profiles of ozanimod and etrasimod appear similar. In the phase 3 True North trial, treatment-emergent adverse events (TEAEs) with ozanimod were similar to placebo during the induction phase but were more frequent in the maintenance phase compared with placebo (49.1% vs 36.6%). Few serious adverse events led to discontinuation (1.3-3.8%). In the 3-year open-label extension (OLE) of True North, the most common cause of TEAEs causing discontinuation was herpes zoster (1.5%).[6,12] In the open-label extension of the

Baseline testing

- Complete blood count, including lymphocyte count
- Liver enzymes and liver function testing (hepatitis serologies prudent)
- VZV serology if no history of chickenpox or vaccination with varicella vaccine
- Latent tuberculosis screening in high-risk populations
- Ophthalmic exam (of fundus, including macula) if history of diabetes, uveitis or macular edema
- Electrocardiogram
- Pregnancy testing in women of child-bearing potential recommended
- Skin examination (baseline or shortly after initiation)

Monitoring during treatment

- Blood pressure should be monitored regularly while on treatment
- Complete blood count and lymphocyte counts periodically (often done every 3 months with liver testing) and after stopping therapy (at 3 months for ozanimod and 5 weeks for etrasimod)
- Liver transaminases and bilirubin levels at 1,3,6,9 and 12 months of therapy and then periodically
- Ophthalmic: Monitor for symptoms of macular edema and vision changes. Regular ophthalmic exams if history of diabetes, uveitis, or macular oedema
- Infections should be assessed for regularly during treatment and after treatment discontinuation (up to 3 months for ozanimod, up to 5 weeks for etrasimod)
- Pulmonary function (spirometry) testing if clinically indicated (eg., dyspnea)

Contraindications (Canada and US)

- Myocardial infarction, unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation, or class III or IV heart failure in the past 6 months
- Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker
- Concomitant use of an MAO inhibitor (eg., selegiline) with ozanimod
- There are some significant drug interactions which can be found in the product monograph or a drug interactions database

Additional Contraindications According to Canadian Product Labeling

- Hypersensitivity to ozanimod or any component to the formulation
- Patients at increased risk of opportunistic infection including those who are immunocompromised due to other treatments (eg. immunomodulating therapies and bone marrow transplant) or disease (eg., immunodeficiency syndrome)
- Severe active infections, including chronic bacterial, fungal or viral infections (eg., hepatitis or tuberculosis), until resolution of the infection
- Known active malignancy (excluding basal cell carcinoma)
- Pregnancy and women of childbearing years not using effective contraception

Some Practical Considerations

- There is an up-titration regimen with ozanimod, but not with etrasimod.
- Is the patient pregnant or do they plan to be pregnant?
- Does the patient have an active infection or malignancy?
- Is the patient on other immunosuppressive therapies?
- Is the baseline ECG normal? If the baseline ECG is normal, without known or new cardiac disease/ symptoms, no further ECGs are needed.
- Is the patient on drugs that could reduce AV node conduction? If they are in sinus rhythm and on a stable dose of beta blocker, etrasimod use is considered safe. In other cases, consider a cardiology referral.
- Is the patient on drugs that could interact with S1PR modulators? There are some important drug interactions other than with MAO-B inhibitors (ozanimod), related to effects on certain CYP enzymes; refer to a drug interaction database or product monograph for more information.

Table 2: Baseline testing, monitoring, contraindications and practical considerations for S1PR modulator use;[15] *courtsey of* Aaron Hass, MD, Laetitia Amar, MD, Robert Battat, MD, FRCPC

Abbreviations: AV: atrioventricular; **ECG:** electrocardiogram; **MAO:** monoamine oxidase; **VZV:** varicella zoster virus.

phase 2 TOUCHSTONE trial, TEAEs were similar in the ozanimod and placebo groups. The most commonly reported serious TEAEs were UC exacerbation (3.5%), anemia (1.2%), and ischemic stroke (1.2%).[13]

Etrasimod's safety profile was evaluated in the OLE of the phase II OASIS trial with 2 mg of etrasimod. The most common TEAEs were UC worsening (19%) and anemia (11%). Out of 112 patients, 14 experienced serious adverse events, and ten patients stopped the therapy (eight due to worsening UC).[8] In the ELEVATE UC 52 trial, 71% of patients experienced TEAEs with etrasimod compared to 56% with placebo, while in the shorter ELEVATE UC 12 trial, the event rates were similar (47% etrasimod vs. 47% placebo). The rate of adverse events leading to discontinuation was similar in the 52-week trial (4% with etrasimod vs. 5% with placebo), and in the 12-week trial (5% with etrasimod vs. 1% with placebo). Serious events were low and comparable to placebo.[9] Unlike ozanimod, no dose titration is needed for etrasimod.

Non-serious infections with ozanimod were more frequent in the maintenance phase of True North at 22.2% as compared to 10.1% with placebo, while a rate of 45.8% was observed in the OLE with ozanimod. The overall serious infection rate with ozanimod in the original True North trial was ≤1.6%. In the ELEVATE UC trials both non-serious and serious infection rates for etrasimod were each ≤1%. Patients on ozanimod experienced a 54% decrease in mean absolute lymphocyte counts from baseline at 10 weeks, while those on etrasimod had approximately a 50% decrease by week 12. No patients on ozanimod who developed serious or opportunistic infections had lymphocyte counts less than 200 cells/mm^3. During induction with ozanimod, 0.6% of patients experienced asymptomatic bradycardia and no patients had high-degree atrioventricular blocks, likely mitigated by the 7-day gradual dose escalation regimen used in the trial. In both ELEVATE trials, patients taking etrasimod had a ≤1% rate of bradycardia with two symptomatic, self-limited events leading to discontinuation. There was no up-titration regimen for the initiation of etrasimod. Less than 0.4% of patients on ozanimod developed macular edema which improved with the discontinuation of therapy. For etrasimod, rates were <1%, with one discontinuation. Asymptomatic liver enzyme elevations were more common with both ozanimod and etrasimod than placebo. These elevations infrequently led to discontinuation (<1%), and no patients met Hy's law criteria for drug-induced liver injury.[6,9]

There is a potential risk of drug-drug interactions with S1PR modulator use. Ozanimod has been shown to inhibit the monoamine oxidase B (MAO-B) enzyme in vitro, thus, concomitant use with MAO-B inhibitors is not recommended given the risk of precipitating serotonin syndrome and hypertensive crisis. Considering effects of S1PR modulators on certain cytochrome P450 (CYP450) enzymes, current recommendations are to avoid co-administration of these agents with medications such as gemfibrozil and rifampin. That said, in vitro studies suggest that etrasimod at 2 mg likely has a lesser impact on CYP450 enzymes compared to ozanimod. There is limited safety data on the use of S1PRs with arrhythmic and beta blocking agents. A cardiology opinion is prudent in such cases due to the additive effects on heart rate. However, etrasimod use in patients on stable beta blocker doses is considered a safe practice.[14] While unchanged etrasimod has a half-life of approximately 30 hours and is the primary circulating component in plasma, ozanimod has two major active metabolites in circulation each possessing a longer mean half-life of around 10 days. Therefore, ozanimod has a washout period of up to 3 months. Details on pre-initiation testing for S1PR modulators, monitoring during treatment, and some additional considerations for practice can be found in **Table 2**.

Future Perspectives of S1PR Modulators

S1PR modulators provide new treatment options for UC patients. They are now one of two classes of oral advanced therapies and may result in lower loss of response rates amongst responders due to their lack of immunogenicity. S1PR modulators may provide a lower infection risk, and do not have black box warnings for infection, malignancy or venous thromboembolism, unlike Janus kinase inhibitors.[16] Additionally, studies on etrasimod included patients with isolated ulcerative proctitis and demonstrated effectiveness, whereas these patients were generally excluded from other UC trials.[17]

Head-to-head randomized trials and analyses of cost-effectiveness between different S1PR modulators, biological agents, and small molecules are needed to help alter our current standards of care. A systematic review and meta-analysis by Lasa et al. showed that ozanimod had comparable efficacy to other small molecules and biologics in UC.[18] Another systematic review by Solitano et al. assessed oral small molecules, with S1PR modulators proven to be effective for clinical, endoscopic, and histologic end points (though etrasimod did not achieve the latter).[19]

While more head-to-head trials would be beneficial to optimally place S1PRs into our treatment algorithms for UC, these therapies remain as important modulators of the immune system that have shown promising data and are already used in clinical practice for this purpose. Cardiac concerns are rare and tend to occur within hours of treatment. Therefore, for patients without cardiac conduction disease, a history of heart failure, or myocardial infarction, a normal pre-treatment ECG should suffice. No further cardiac monitoring is necessary unless clinical changes or a cardiac event develop subsequent to therapy. Also, while lymphopenia is a pharmacodynamic effect reflecting S1PR modulation, it is not associated with an increased risk of infections, nor has it been proven to be related to drug efficacy. Lastly, there are many possibilities to explore for S1PR modulator use. Based on available

data and clinical experience, we believe that S1PR modulators should be evaluated in the future as an add-on therapy for UC patients with moderate disease activity who have failed to improve with mesalamine. The combination of S1PR modulators with biologics may be a promising future area of investigation as a therapy for UC.[20]

Conclusion

Sphingosine-1-phosphate receptor modulators are safe, effective, and well tolerated oral therapies for moderate-to-severe UC. With a novel mechanism of action, they could complement existing therapies. Their advantages include daily oral dosing, rapid action, lack of immunogenicity, and a low infection risk. These agents are generally easy to initiate, requiring some pre-initiation testing. Recent evidence of their safety, effectiveness, and ease of use is compelling, making them a consideration for early-line therapy in moderate-to-severe disease for those who have failed conventional treatments.

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References:

1. Tourkochristou E, Mouzaki A, Triantos C. Unveiling the biological role of sphingosine-1-phosphate receptor modulators in inflammatory bowel diseases. World J Gastroenterol. 2023;29(1):110-125. doi:10.3748/wjg.v29.i1.110
2. Scott FL, Clemons B, Brooks J, Brahmachary E, Powell R, Dedman H, et al. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. Br J Pharmacol. 2016;173(11):1778-1792. doi:10.1111/bph.13476
3. SandbornWJ, Feagan BG, D'Haens G. Safety and efficacy of etrasimod in ulcerative colitis: a randomized trial. N Engl J Med. 2016;374(23):2225-2236.
4. Choden T, Cohen NA, Rubin DT. Sphingosine-1 phosphate receptor modulators: the next wave of oral therapies in inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2022;18(5):265-271.
5. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016;374(18):1754-1762. doi:10.1056/NEJMoa1513248
6. Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021;385(14):1280-1291. doi:10.1056/NEJMoa2033617
7. Yarur AJ, Chiorean MV, Panés J, Jairath V, Zhang J, Rabbat CJ, et al. Achievement of clinical, endoscopic, and histological outcomes in patients with ulcerative colitis treated with etrasimod, and association with faecal calprotectin and c-reactive protein: results from the Phase 2 OASIS trial. J Crohns Colitis. 2024;18(6):885-894. doi:10.1093/ecco-jcc/jjae007
8. Vermeire S, Chiorean M, Panés J, Peyrin-Biroulet L, Zhang J, Sands BE, et al. Long-term safety and efficacy of etrasimod for ulcerative colitis: results from the open-label extension of the OASIS study. J Crohns Colitis. 2021;15(6):950-959. doi:10.1093/ecco-jcc/jjab016
9. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, Dubinsky MC, Panes J, Yarur A, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. [published correction appears in Lancet. 2023 Mar 25;401(10381):1000. doi: 10.1016/S0140-6736(23)00586-X]. Lancet. 2023;401(10383):1159-1171. doi:10.1016/S0140-6736(23)00061-2
10. Atreya R, Neurath MF. The sphingosine-1-phosphate receptor agonist etrasimod in ulcerative colitis. Lancet. 2023;401(10383):1132-1133. doi:10.1016/s0140-6736(23)00228-3
11. Harris S, Feagan BG, Hanauer S, Vermeire S, Ghosh S, Yan J, et al. Ozanimod differentially impacts circulating lymphocyte subsets in patients with moderately to severely active crohn's disease. Dig Dis Sci. 2024;69(6):2044-2054. doi:10.1007/s10620-024-08391-z
12. Danese S, Panaccione R, Abreu MT, Rubin DT, Ghosh S, Dignass A, et al. Efficacy and safety of approximately 3 years of continuous ozanimod in moderately to severely active ulcerative colitis: interim analysis of the True North open-label extension. J Crohns Colitis. 2024;18(2):264-274. doi:10.1093/ecco-jcc/jjad146
13. Sandborn WJ, Feagan BG, Hanauer S, Vermeire S, Ghosh S, Liu WJ, et al. Long-Term efficacy and safety of ozanimod in moderately to severely active ulcerative colitis: results from the open-label extension of the Randomized, Phase 2 TOUCHSTONE study. J Crohns Colitis. 2021;15(7):1120-1129. doi:10.1093/ecco-jcc/jjab012
14. Vieujean S, Peyrin-Biroulet L. Pharmacokinetics of S1P receptor modulators in the treatment of ulcerative colitis. Expert Opin Drug Metab Toxicol. 2024;20(9):881-892. doi:10.1080/17425255.2024.2402931
15. Sands BE, Schreiber S, Blumenstein I, Chiorean MV, Ungaro RC, Rubin DT. Clinician's guide to using ozanimod for the treatment of ulcerative colitis. J Crohns Colitis. 2023;17(12):2012-2025. doi:10.1093/ecco-jcc/jjad112
16. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316-326. doi:10.1056/NEJMoa2109927
17. Peyrin-Biroulet L, Dubinsky MC, Sands BE, Panés J, Schreiber S, Reinisch W, et al. Efficacy and safety of etrasimod in patients with moderately to severely active isolated proctitis: results from the Phase 3 ELEVATE UC Clinical Programme. [published correction appears in J Crohns Colitis. 2024 Aug 14;18(8):1356. doi: 10.1093/ecco-jcc/jjae098]. J Crohns Colitis. 2024;18(8):1270-1282. doi:10.1093/ecco-jcc/jjae038
18. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(2):161-170. doi:10.1016/s2468-1253(21)00377-0
19. Solitano V, Vuyyuru SK, MacDonald JK, Zayadi A, Parker CE, Narula N, et al. Efficacy and safety of advanced oral small molecules for inflammatory bowel disease: systematic review and meta-analysis. J Crohns Colitis. 2023;17(11):1800-1816. doi:10.1093/ecco-jcc/jjad100
20. Battat R, Chang JT, Loftus EV, Jr., Sands BE. IBD matchmaking - rational combination therapy. Clin Gastroenterol Hepatol. 2024. doi:10.1016/j.cgh.2024.05.051

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UC=ulcerative colitis; CD=Crohn's disease.

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* Comparative clinical significance has not been established.

References:
1. ENTYVIO® Product Monograph. Takeda Canada Inc. November 17, 2023. **2.** Data on file. Takeda Canada Inc. July 25, 2023.

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KEY TAKEAWAYS

- Complementary and Alternative Medicine (CAM) use is common among individuals living with inflammatory bowel disease (IBD)
- Most evidence-based consensus guidelines do not recommend the clinical use of CAM, including FMT, probiotics, cannabis, Curcumin, and PUFAs
- Recent advances in CAM research suggest a potential role for some forms of CAM, such as probiotics in preventing pouchitis or fecal microbiotia transplant for induction of remission in ulcerative colitis
- More research, specifically well-designed randomized control studies, are required in this field before results can be applied to the clinical treatment of IBD

RECENT ADVANCES IN COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR INFLAMMATORY BOWEL DISEASE

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory condition of the gastrointestinal (GI) tract, primarily comprised of 2 major types: Crohn's disease (CD) and ulcerative colitis (UC).[1] The pathogenesis of IBD is not fully elucidated but is thought to be multifactorial involving genetic,

environmental, and immunological contributors.[2] The incidence of IBD has been rising worldwide, particularly in developed nations. Canada, in particular, has one of the highest prevalence rates of IBD globally, with recent data indicating that over 320,000 Canadians are living with IBD, making it a significant public health concern.[3,4]

The chronic nature of IBD, along with the severity of its symptoms, and the adverse effects occasionally attributed to management (e.g. immunosuppression, corticosteroids, surgical complications) can significantly reduce the quality of life for those affected.[5] As such, many patients with IBD use complementary and alternative medicine (CAM) due to safety concerns of conventional therapy and a sense of greater control over their disease.[6] CAM refers to a broad range of healthcare practices, such as herbal medicine, acupuncture, homeopathy, fecal microbiota transplants, and probiotics, which are not typically considered part of conventional western medicine.[7] The use of CAM among patients with IBD is high, with current or past use of CAM ranging from 21-60% of IBD patients.[6] Given the propensity of patients with IBD to seek CAM and the unfamiliarity that many medical practitioners have with the evidence of benefit/harm from these practices, this review seeks to summarize recent advances in clinical research on CAM use for IBD.

Probiotics

Probiotics are living microorganisms that can be ingested to confer a health advantage to the host. They have been an attractive target in the treatment of IBD given that patients with this condition have been demonstrated to have less diverse/altered GI microbiota (dysbiosis). However, the science and clinical implications of probiotics in IBD treatment continues to be explored.[8,9] The 2019 Canadian Association of Gastroenterology (CAG) clinical practice guidelines for CD strongly recommend against the use of probiotics to induce or maintain symptomatic remission in CD, citing a lack of evidence at that time.[10] The 2015 CAG clinical practice guidelines for the management of UC also recommend against probiotics to induce or maintain remission.[11] More recently, the 2019 British Society of Gastroenterology (BSG) consensus guidelines on the management of IBD is in agreement with previous guidelines regarding the use of probiotics in CD, but states that there may be modest benefit for UC, specifically in maintaining remission, although routine use of probiotics is not recommended.[12] An important limitation of the literature evaluating probiotics is the variation of bacterial strain combinations (most often *Lactobacillus GG, Lactobacillus johnsonii, Escherichia coli* strain Nissle 1917, or *Saccharomyces boulardii*) used in studies, which makes pooled analyses challenging. Additionally, the studies exhibit wide inter-study variability as well as small sample sizes.[10] These limitations have led to the consensus among most gastroenterology providers that more research is required into the use of probiotics as a therapeutic option for IBD at the time.

Research in probiotics for IBD has continued since the publication of the above-mentioned guidelines. A recent meta-analysis of 13 studies (N=930 patients),[13] reported no statistical difference between probiotic and placebo groups in the rates of inducing remission in UC patients. No statistical difference was observed in the maintenance of clinical remission, clinical course, change in the Ulcerative Colitis Disease Activity Index (UCDAI) scores, or mucosal healing outcomes between the 2 groups. Interestingly, for UC patients, the probiotic group showed a statistically significant decrease in relapse rates (OR 0.34; 95% CI 0.14–0.79; P = 0.01). Importantly, there were no statistically significant differences in adverse events between the 2 groups. Additionally, Estevinho et al. conducted a systematic review and updated meta-analysis of randomized controlled trials (RCTs) that analyzed data from 22 systematic reviews and 45 RCTs, making it the largest meta-analysis performed on probiotics in IBD to date.[14] The findings indicated that the effects of probiotics were positive for induction of clinical remission in patients with UC (OR 2.00; 95% CI 1.28–3.11; I_2 = 57%), but the effect was not significant in CD (OR 1.61, 95% CI 0.21–12.50, I^2 = 65%). With regards to maintenance, the study found that probiotics had a protective effect against relapsing pouchitis (OR 0.03; 95% CI 0.00–0.25) and exhibited a tendency to maintain remission in UC (OR 0.65; 95% CI 0.42–1.01), but not in CD. Subgroup analysis determined that the most efficacious use of probiotics occurred with multi-strain formulations. Further, combining 5-amino salicylic acid (5-ASA) and probiotics vs 5-ASA alone was superior for the induction of remission. However, this analysis was limited by significant heterogeneity. Importantly, this study also found that the likelihood of experiencing adverse events was comparable to that of the placebo group.

Pouchitis, a phenotype of IBD, is an area where probiotics have perhaps been better studied and are more commonly used in clinical practice. Alphonsus et al. conducted a systematic review of 20 RCTs investigating medical therapy for the treatment and prevention of pouchitis.[15] In regards to probiotics, they pooled 2 studies (N=20) that used the De Simone Formulation (a specific multispecies probiotic combination that consists of a mixture of 8 strains of bacteria). They found that 90% (18/20) of participants using the De Simone Formulation did not develop pouchitis compared with 60% (12/20) of placebo participants (RR 1.50; 95% CI 1.02–2.21). Thus, there are signals in the literature that suggest probiotics may play a role in specific subtypes of IBD, particularly UC and pouchitis, but more study is needed before these therapies can be recommended.

Fecal Microbiota Transplant

Fecal microbiota transplant (FMT) is the transplantation of feces, and the microbiome present within, from a healthy donor to the recipient via enema or nasogastric tube. The advantages of FMT over probiotic supplementation for restoring a healthy colonic microbiome include a vastly higher number of administered organisms, greater heterogeneity of the bacterial species, and the elimination of concerns over probiotic bacterial strains adapting to an ex-vivo environment.[16]

The current recommendations from the CAG clinical practice guidelines for UC advise against the use of FMT to induce or maintain complete remission outside the setting of clinical trials, citing insufficient data.[11] The recently published BSG consensus guidelines on managing IBD in adults comments that the initial data on FMT is promising, citing evidence of improved remission in UC, but recommends it only as an investigational treatment at this time.[12] Among the larger trials used to inform these recommendations includes a RCT by Moayyedi et al., which found that patients with UC treated with FMT were significantly more likely to achieve induction of remission compared to placebo.[17]

More recent evidence since the publishing of these guidelines include a meta-analysis by Tan et al. of 14 trials using FMT in UC.[18] The authors noted that FMT had a statistically significant increase in inducing remission compared with placebo (RR1.44; 95% CI 1.03–2.02; I^2 = 38%, P = 0.03), with minimal study heterogeneity. Additionally, FMT resulted in a statistically significant clinical response (most commonly defined as a reduction in the Mayo score and improved endoscopic findings) compared with placebo (RR 1.34; 95% CI 0.9–1.94; I^2 = 51%; P = 0.12) with moderate study heterogeneity. Regarding safety, symptoms of gastrointestinal distress were the most common adverse events, however all were self-limiting, no major adverse events were attributed to FMT. While these results are promising and the mechanism of action of FMT is an area of significant interest in elucidating the pathogenesis of IBD, it is generally not performed outside of research studies. The nature of researching FMT is challenging given the difficulty standardizing aspects of therapy, such as the microbiome of the donor and dosing, which can contribute to significant variability. Larger studies will be required with control over factors such as route of administration, timing, preceding antibiotics, and number of administrations to better define the optimal role of FMT in patients with IBD.

Cannabis

Cannabis, typically from the *Cannabis stativa* plant, contains cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD). These compounds interact with the body's endocannabinoid system and are theorized to have beneficial effects on inflammation, appetite, and pain, making them an attractive therapeutic option under investigation for IBD.[19]

The current recommendations from the CAG consensus on clinical practice guidelines for CD recommend against the use of cannabis for inducing or maintaining symptomatic remission, citing the poor quality of evidence available at the time of publication.[10] The BSG consensus guidelines on managing IBD in adults recommend further research into the effects of cannabis extracts in IBD. They acknowledge that literature to date has demonstrated a positive influence on self-reported symptomology but lacks statistical significance in the under-powered blinded studies that are available.[12]

Since the publishing of these guidelines, Doeve et al. conducted a meta-analysis including 15 nonrandomized clinical trials and 5 RCTs.[20] They found that cannabinoids were not effective at inducing remission (RR 1.56; 95% CI 0.99–2.46), and that they had no effect on inflammatory biomarkers. However, in keeping with pre-existing research, they did find that clinical symptoms (abdominal pain, general well-being, nausea, diarrhea, and poor appetite) all improved with cannabinoids.

At this time, evidence for cannabis and the use of cannabinoids in the treatment of IBD remains underpowered and lacking validity in dose, extract, and formulation, but is consistent in that it has not been found to induce remission or prevent relapse. Some studies do point towards symptomatic benefit, although this may be in part due to the un-maskable psychotropic effects of the treatment, making blinded studies difficult to facilitate.

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6 fatty acids are natural compounds often found in fish oil and plant oils.[21] They are theorized to have anti-inflammatory properties, and although clear mechanistic evidence in this regard is lacking, their proposed benefit to the inflammatory nature of IBD has long been of interest. The current recommendations from the CAG consensus on clinical practice guidelines for CD recommend against using omega-3 fatty acids for inducing or maintaining symptomatic remission, citing 2 key systematic reviews that concluded that omega-3 fatty acids (primarily as monotherapy) were likely no more effective than placebo for maintenance therapy in CD.[10] The BSG consensus guidelines on managing IBD in adults reiterates the same message, citing that the most comprehensive study at the time, published by Feagan et al., did not demonstrate any benefit of omega-3 fatty acid supplementation in CD.[12,22]

Recent advances in the research on PUFA supplementation for treating IBD includes the largest and most comprehensive meta-analysis of RCTs

to date by Ajabnoor et al., which included 83 RCTs with 41,751 participants.[21] In this analysis, omega-3 fatty acid supplementation showed a trend toward improvement in the risk of IBD relapse (RR 0.85; 95% CI 0.72–1.01), however, it did not reach statistical significance. In addition, the outcomes for other PUFAs, such as omega-6 fatty acid and alpha-linolenic acid, were not statistically significant.

Natural Compounds

Curcumin is a substance found in the rhizomes of the plant *Curcuma longa* (Aka. turmeric) as well as other Curcuma species, which has been used for centuries in Asia, both in traditional medicine and in cooking due to its vibrant yellow colour.[23] It contains natural compounds termed curcuminoids, thought to have anti-inflammatory properties.[24] Current guidelines regarding the therapeutic use of curcumin in IBD is lacking in Canadian guidelines, however the BSG consensus guidelines on IBD comment that no recommendations can be made due to lack of sufficient high-quality evidence regarding efficacy and dose and larger studies are needed, but that there have been some promising signals from pilot studies.[12] QingDai (QD), also known as Indigo naturalis, is a natural compound isolated from plants such as *Strobilanthes cusia* and *Isatis tinctoria*, which contains natural ingredients such as indigo, indirubin, isoindigotin, and nimbosterol.[25] Originally used as a natural blue dye since ancient times, it has been used to treat various inflammatory disorders including UC, primarily in China.[26] QD is not mentioned in Canadian or British IBD guidelines, however preexisting evidence for its use in IBD includes a small Japanese trial demonstrating dose dependant clinical response and an American dose-escalation study without a placebo groupand with patients (N=11) patients demonstrating clinical response.[26, 27]

Recent evidence for natural compounds includes a double-blind RCT by Ben-Horin et al. In part 2 of the trial they randomized patients (n=42) with moderate-serve UC to receive enteric coded Curcumin-QD (1.5 g of each compound) combination therapy vs placebo, with the primary outcome being induction of remission, defined by a clinical response (reduction in the Simple Clinical Colitis Activity Index of ≥3 points) and an objective response (Mayo endoscopic subscore improvement of ≥1 or a 50% fecal calprotectin reduction). Here, they found that the curcumin-QD arm had a statistically significant increase in achieving remission, with 12 of 28 patient (43%) in the treatment arm vs 1 of 13 patients (8%) in the placebo arm meeting this primary outcome (P = .033; RR, 1.62; 95% CI, 1.13–2.31).[28]

Ultimately, although there are promising signals towards the treatment of UC, sample sizes remain small and standardization of the proposed therapeutic compounds within these herbal compounds remains elusive. More research will be required before results can be applied to the clinical treatment of IBD.

Conclusion

In summary, most forms of CAM lack consistent moderate or high-quality evidence to support their routine use in the induction and maintenance of IBD. However, some subtypes of IBD show stronger signals of benefit from CAM, such as probiotics in preventing pouchitis or FMT for induction of remission in UC. More research is needed to define the role of these therapies. Nonetheless, patients are increasingly using CAM, and providers should familiarize themselves with the various forms of CAM. Moreover, providers should make a point to ask about CAM use, as patients may not volunteer this information. Ultimately, research into CAM will require large-scale RCT data before their specific role can be better defined. This remains a key area of research given the high use of CAM among patients with IBD.

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References:

1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet Lond Engl. 2007;369(9573):1641–1657.
2. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology. 2014;146(6):1489–1499.
3. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet Lond Engl. 2017;390(10114):2769–2778.
4. Coward S, Benchimol EI, Kuenzig ME, Windsor JW, Bernstein CN, Bitton A, et al. The 2023 impact of inflammatory bowel disease in Canada: epidemiology of IBD. J Can Assoc Gastroenterol. 2023;6(Suppl 2):S9–S15.
5. Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-part I. Inflamm Bowel Dis. 2018;24(4):742–751.
6. Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis. 2015;9(1):86–106.
7. Ernst E. The role of complementary and alternative medicine. BMJ. 2000;321(7269):1133–1135.
8. Zhou Y, Xu ZZ, He Y, Yang Y, Liu L, Lin Q, et al. Gut Microbiota offers universal biomarkers across ethnicity in inflammatory bowel disease diagnosis and infliximab response prediction. mSystems. 2018;3(1):e00188-17. doi:10.1128/mSystems.00188-17
9. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD:

causation or correlation? Nat Rev Gastroenterol Hepatol. 2017;14(10):573–584.
10. Panaccione R, Steinhart AH, Bressler B, Khanna R, Marshall JK, Targownik L, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Luminal Crohn's Disease. Clin Gastroenterol Hepatol. 2019;17(9):1680–1713.
11. Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical Practice Guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148(5):1035-1058.e3.
12. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–106.
13. Wang X, Zhou C, Zhang S, Ma Y, Xiao W, Guo Y. Additive efficacy and safety of probiotics in the treatment of ulcerative colitis: a systematic review and meta-analysis. Eur J Nutr. 2024;63(5):1395–1411.
14. Estevinho MM, Yuan Y, Rodríguez-Lago I, Sousa-Pimenta M, Dias CC, Barreiro-de Acosta M, et al. Efficacy and safety of probiotics in IBD: An overview of systematic reviews and updated meta-analysis of randomized controlled trials. United Eur Gastroenterol J. 2024;12(7):960–981.
15. Alphonsus L, De Silva TA, Ma C, MacDonald JK, Hanzel J, Beaton M, et al. Systematic review and meta-analysis of randomised controlled trials: medical therapies for the treatment and prevention of pouchitis. Aliment Pharmacol Ther. 2023;58(3):268–282.
16. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. Nat Rev Gastroenterol Hepatol. 2011;9(2):88–96.
17. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology. 2015;149(1):102-109.e6.
18. Tan XY, Xie YJ, Liu XL, Li XY, Jia B. A systematic review and meta-analysis of randomized controlled trials of fecal microbiota transplantation for the treatment of inflammatory bowel disease. Evid-Based Complement Altern Med. 2022;2022:8266793. doi:10.1155/2022/8266793
19. Ambrose T, Simmons A. Cannabis, cannabinoids, and the endocannabinoid system—is there therapeutic potential for inflammatory bowel disease? J Crohns Colitis. 2019;13(4):525–535.
20. Doeve BH, Van De Meeberg MM, Van Schaik FDM, Fidder HH. A systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for inflammatory bowel disease: what can we learn from randomized and nonrandomized studies? J Clin Gastroenterol. 2021;55(9):798–809.
21. Ajabnoor SM, Thorpe G, Abdelhamid A, Hooper L. Long-term effects of increasing omega-3, omega-6 and total polyunsaturated fats on inflammatory bowel disease and markers of inflammation: a systematic review and meta-analysis of randomized controlled trials. Eur J Nutr. 2021;60(5):2293–2316.
22. Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC randomized controlled trials. JAMA. 2008;299(14):1690–1697.
23. Hanai H, Sugimoto K. Curcumin has Bright Prospects for the Treatment of Inflammatory Bowel Disease. Curr Pharm Des. 2009 Jun 1;15(18):2087–94.
24. Vecchi Brumatti L, Marcuzzi A, Tricarico P, Zanin V, Girardelli M, Bianco A. Curcumin and Inflammatory Bowel Disease: Potential and Limits of Innovative Treatments. Molecules. 2014 Dec 16;19(12):21127–53.
25. Suzuki H, Kaneko T, Mizokami Y, Narasaka T, Endo S, Matsui H, et al. Therapeutic efficacy of the Qing Dai in patients with intractable ulcerative colitis. World J Gastroenterol. 2013 May 7;19(17):2718–22.
26. Naganuma M, Sugimoto S, Mitsuyama K, Kobayashi T, Yoshimura N, Ohi H, et al. Efficacy of Indigo Naturalis in a Multicenter Randomized Controlled Trial of Patients With Ulcerative Colitis. Gastroenterology. 2018 Mar;154(4):935–47.
27. Saiki JP, Andreasson JO, Grimes KV, Frumkin LR, Sanjines E, Davidson MG, et al. Treatment-refractory ulcerative colitis responsive to indigo naturalis. BMJ Open Gastroenterol. 2021 Dec;8(1):e000813
28. Ben-Horin S, Salomon N, Karampekos G, Viazis N, Lahat A, Ungar B, et al. Curcumin-QingDai Combination for Patients With Active Ulcerative Colitis: A Randomized, Double-Blinded, Placebo-Controlled Trial. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2024 Feb;22(2):347-356.e6.

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Reference:

1. STELARA/STELARA I.V. Product Monograph. Janssen Inc., April 5, 2023.

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MANAGEMENT OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Introduction

Anemia is one of the most common complications of inflammatory bowel disease (IBD), with estimates of its prevalence varying from 9-74%.[1] It is estimated to affect more than 1.2 billion people worldwide and evidence suggests that the incidence of anemia in people with IBD is almost double that of people without IBD (92.75 people with IBD per 1000 person-years vs 51.18 without IBD per 1000 person-years).[2,3] Having a thorough approach to anemia in IBD is important because it is common and potentially dangerous, and because of its potential to arise from multiple different pathological and/or physiological processes.

Definitions

The parameters by which we define anemia are somewhat arbitrary because they are defined more by deviation from the mean rather than by clinical effects. Most laboratories report normal reference values that are sometimes modified to reflect average differences in age and sex. Other factors such as ethnicity or living at higher altitudes are sometimes considered; as a result, normal values can therefore vary from institution to institution. The normal values are not different for patients with IBD.

The normal values for measures of hemoglobin (HGB) concentration have changed over time but remain near the original cutoffs of 130 g/L in men and 120 g/L in women. Other red blood cell (RBC) indices that may be useful include the mean corpuscular volume (MCV) and the reticulocyte distribution width (RDW). The normal MCV is considered to be between 80-100 fL, however, the normal values for RDW are not well-defined.[4] Total body iron stores are considered to be low when serum ferritin levels are 30 mg/L or below.[3]

Evaluation

The management of anemia in IBD is dependent on establishing all underlying causes. With so many potential underlying and interconnected causes for anemia, having a structured approach can help avoid missing a contributing factor. Several conceptual approaches exist, with one of the most common consisting of considering causes that result in macrocytic, microcytic, or normocytic RBCs (the "morphological approach"). This narrows down the most common etiologies for macrocytosis and microcytosis, although the differential diagnosis for normocytic anemia remains large, and each category encompasses unrelated etiologies. Perhaps a more physiology-based conceptual structure, the "kinetic approach," involves categorizing causes of anemia as resulting from decreased production of erythrocytes, increased destruction of erythrocytes, and destruction of erythrocytes.[5] A list of some causes for anemia are provided in **Table 1**, with the etiologies of particular concern in IBD shown in bold font. It is worth noting that these etiologies can be related or independent of each other. Gastrointestinal (GI) malignancy can cause bleeding but can also cause anemia of inflammation. A patient with active IBD can also have medication- or infection-related anemia. The clinician should also consider artifactual anemia, i.e., adequate HGB concentration diluted by physiological processes such as pregnancy or iatrogenic processes such as intravenous fluid resuscitation.

Abnormal Production	Increased Destruction	Increased Loss
Chronic Inflammation • **Active IBD** • **Extraintestinal manifestations** • **Other IMIDs†** • Chronic heart failure • COPD • Chronic kidney disease Metabolic Disease • Hypothyroidism • Adrenal insufficiency Nutrient deficiency • **Iron** • **B12** • Folate Malabsorption • **Short gut syndrome** • Celiac • Bariatric surgery Bone Marrow disorders • Myelodysplasia • Aplastic anemia • Infection (HIV, hepatitis) • Infiltration	Mechanical • Artificial heart valve Hemolytic anemia • Acquired (immune, **medications**) • Inherited (hemoglobinopathies, G6PD deficiency, spherocytosis) Physiological • Hypersplenism o Cirrhosis o **Lymphoma**	GI blood loss • **Active IBD** • **Intestinal surgical anastomoses** • Peptic ulcer disease • **GI malignancy** • Angiodysplasia • GAVE • Ischemia Non-GI blood loss • Hematuria • Menorrhagia • Epistaxis • Blood donation

Table 1: Etiologies of anemia; *courtsey of Chris Sheasgreen, MD, FRCPC*
Abbreviations: COPD: chronic obstructive pulmonary disease; **G6PD:** glucose-6-phosphate dehydrogenase; **GAVE:** gastric antral vascular ectasia; **GI:** gastrointestinal; **HIV:** human immunodeficiency virus; **IBD:** inflammatory bowel disease; **IMIDs:** immune-mediated inflammatory diseases
Etiologies of particular concern in patients with IBD are in bold font.
† Immune-mediated inflammatory disease

Evaluation of anemia in IBD, as in all clinical situations, requires consideration of the individual patient's clinical context. It should begin with a thorough history with particular attention to major milestones in the IBD natural history such as surgeries and medication exposures. The history should include a review of symptoms with attention paid to common symptoms of severe anemia such as fatigue, shortness of breath, orthostatic dizziness, pallor, palpitations, and chest pain. Less dangerous complications such as rashes can provide clues to the underlying etiology.

A dietary review is crucial as many IBD patients have significant dietary restrictions. Patients may adopt these restrictions as a means of symptom control based on their own idiosyncratic reactions to foods in the past or because of perceived benefit for overall health and flare avoidance. There is insufficient data to comment on the risk of anemia or specific micronutrient deficiencies from these dietary strategies. Regardless, clinicians should remain aware that dietary restriction is common in IBD patients, may lead to micronutrient deficiencies, and has been associated with decreased quality of life.[6,7]

A review of medications is necessary as some can lead to anemia as well as morphological changes to the RBCs. These changes can provide clues to the etiology but can also confuse the situation in cases in which there are multiple contributing factors to the anemia. For example, methotrexate is an antifolate medication that can result in macrocytosis. This could offset microcytosis caused by iron deficiency. A list of anemia-associated medications common in IBD or the general population is provided in **Table 2.**

Assessment of clinical disease activity is paramount and can be imperfectly quantified by tools such as the Mayo score or the Harvey Bradshaw Index.[8] Particular attention should be dedicated to inquiring about GI blood loss such as hematochezia, melena, or even hematemesis. The gastroenterologist should not forget extraintestinal blood loss sources such as menorrhagia, epistaxis, and hematuria. Inpatient status can have diagnostic value because intravenous fluid administration for resuscitation can cause a dilutional effect on serum lab results.

More objective measures of disease activity include C reactive protein (not GI specific) and fecal calprotectin. Cross sectional imaging, including enterography or intestinal ultrasound, can provide promising and accessible assessments of IBD intestinal activity. Endoscopy (usually colonoscopy or flexible sigmoidoscopy, keeeping upper endoscopy in mind for patients with documented or possible upper GI

- Methotrexate (antifolate)
- Azathioprine (bone marrow suppression)
- Janus kinase inhibitors (erythropoiesis suppression)
- Mesalamine (bone marrow suppression)
- Antibiotics (autoimmune)
- Cyclosporine (autoimmune)
- Prednisone (autoimmune)
- TNF Inhibitors
- Risankizumab
- Ozanimod

Table 2: Medications (mechanisms) associated with anemia in inflammatory bowel disease; *courtsey of Chris Sheasgreen, MD, FRCPC*

Crohn's disease) allows assessment of disease activity as well as other sources of bleeding such as surgical anastomoses and malignancy.[8]

Two of the most important laboratory tests are the complete blood count (CBC) and iron studies. Regarding the CBC, take note of other cell lineages (pancytopenia might suggest a bone marrow disorder). As mentioned above, MCV can help steer the diagnosis toward certain etiologies (e.g., iron deficiency tends toward microcytosis whereas myelodysplasia, vitamin B12 and folate deficiency, and the drug effect from methotrexate and azathioprine can lead to macrocytosis). Remember that reticulocytes are larger than mature erythrocytes and can skew the MCV high.[9]

Iron deficiency is the most common cause of anemia in patients with IBD, therefore, interpreting serum iron stores is of paramount importance. However, a Scandinavian study has found that most causes of anemia were attributed to both iron deficiency and chronic inflammation.[10] In addition to serum ferritin as a marker of iron deficiency, transferrin saturation can be calculated to confirm that the body iron stores are low (<20%). However, in the context of anemia of chronic inflammation (usually normocytic), ferritin levels can be normal or high, but the transferrin saturation might still be low.[5] In these situations, a low transferrin saturation with a ferritin level as high as 100 mg/L might be considered to have iron deficiency. A trial of iron replacement in these patients could be considered diagnostic as well as therapeutic, rather than proceeding to bone marrow biopsy as gold standard for diagnosis.[17]

Vitamin B12 and folate deficiencies can lead to macrocytic anemias. However, in Canada, flour is fortified with folate, thus the rates of folate deficiency are below 1%.[11] Combined micronutrient deficiencies (or other factors such as the medication effect) could affect RBC morphology in opposite ways, resulting in normocytosis.[9] Some studies have shown an association between low levels of zinc and copper with anemia. Therefore, these micronutrients could be considered as part of an extended workup in this population at risk for micronutrient deficiencies.[12] Similar to most patients with anemia, serology for celiac disease and thyroid-stimulating hormone (TSH) should be considered, along with creatinine, testosterone, cortisol, and hemoglobin A1c (HbA1c) in selected cases.[13]

Treatment

Anemia of any degree should be treated when discovered and the investigations will steer the clinician toward appropriate therapy.[1] Severe (HGB <70 g/L) anemia should be treated with transfusion of packed RBCs to avoid complications. More liberal transfusion thresholds exist for patients with acute coronary syndromes (HGB 80 g/L) or early sepsis (HGB 100 g/L).[14]

Iron deficiency can be treated with dietary interventions, oral iron supplementation, and intravenous infusion. Dietary interventions should be considered for all patients but may not be sufficient in those with severe anemia or an ongoing etiology. Referral to a registered dietician should be considered. Evidence regarding the effectiveness of dietary interventions (as opposed to supplementation) is lacking. However, it is worth noting that while vegetarian diets are widely considered to predispose to iron deficiency, evidence suggests that there is no statistically significant difference in the amount of iron consumed among vegetarian or non-vegetarian diets, and that even strict vegetarians meet minimum requirements.[15]

Various dietary tips and tricks can be considered to prevent or treat anemia. In general, iron fortification in foods such as flour and noodles can be effective. Cooking in iron pots may also be effective.[16] Intestinal absorption of iron can be improved with concomitant vitamin C, either via supplementation or with drinks such as orange juice. Tea, coffee, and calcium e.g., dairy) can decrease the absorption of iron.[17]

There are various oral iron supplements available in Canada ranging in price from $5-35 per 100 mg of elemental iron. Examples of oral iron supplements available in Canada are provided in **Table 3**. Iron supplements are recommended to be taken between meals. Side effects including abdominal pain, nausea, and constipation are common.[17] QOD dosing of oral iron may decrease side effects and result in improved iron indices compared to daily dosing. This may occur from limiting the rise in hepcidin triggered by even slight rises in serum iron concentrations. Hepcidin is a circulating hormone that inhibits iron export from the liver and absorption of dietary iron through intestinal enterocytes. Dosing of oral iron on alternate days has been shown to result in lower rises in serum hepcidin compared to daily dosing.[3] It may take 3-6 months to achieve a response with oral iron so consider assessing for response at this interval.[17] Evidence is lacking to prove that newer oral iron formulations are more effective.[18] Folate deficiency can be corrected by oral or intravenous supplementation, but the underlying cause should be sought out given its rarity.

Formulation	Dose per tablet (mg)	Elemental iron per tablet (mg)	Dose
Ferrous gluconate	240	27	1-3 tablets daily or every other day*
Ferrous sulfate	325	65	1-2 tablets daily or every other day
Ferrous fumarate	325	106	1 tablet daily
Heme iron polypeptide (Proferrin)	398	11	1-3 tablets daily
Polysaccharide iron complex (Feramax)	150	150	1 tablet daily

Table 3: Oral iron formulations* available in Canada; Adapted from Ning, S et al 2019.[17]
*Take on empty stomach; avoid taking with antacid medications or proton pump inhibitors

Supplementation of other deficient micronutrients has been described elsewhere.[19]

Intravenous iron formulations are also available and are often preferable in the context of malabsorption, symptomatic anemia, intolerance to oral formulations, or when rapid replenishment is required for an intervention like surgery. IV formulations are preferred for patients with IBD for their increased efficacy as well as increased tolerability and potential for decreasing oxidative damage to the intestinal wall. It is also preferred for patients with chronic kidney disease using erythropoietin.[3] However, access to IV formulations may be limited by cost, location, and tolerability. The patient's iron deficit can be calculated using the Ganzoni formula (patient weight in kilograms x [desired HGB– current HGB g/dL] x 2.4 + 500 for adult patients). Some evidence shows that the average total iron deficit for general patients with iron deficiency anemia was about 1500 mg. Iron isomaltoside (Monoferric) allows for the fastest infusion of the most elemental iron (1000 mg or more) in a single session. Other formulations available in Canada include iron sucrose (Venofer, 300 mg) and ferrous gluconate (Ferrelict, 125 mg). These can be administered weekly until the desired amount is infused and serum HGB and iron studies can be repeated as early as 4 weeks to determine if further replenishment is necessary.[17]

Evidence of active IBD should prompt the initiation or optimization of therapy.[8] However, certain medications **(Table 2)** may need to be held or discontinued entirely if no other cause is found for the anemia.

As provided in **Table 1**, many causes of anemia are unrelated to GI pathology. Given this information, it then behooves the gastroenterologist to ensure referral or collaboration with colleagues of other disciplines. Anemia of chronic inflammation from uncontrolled extraintestinal manifestations merits collaboration with other specialties such as rheumatology and dermatology. A hematology referral could be considered if blood tests show evidence of schistocytes, pancytopenia, or macrocytic anemia without a micronutrient deficiency. A surgical referral may be required if there are surgical anastomotic issues or along with an oncology referral in the context of malignancy. The clinician should follow up after appropriate interventions to ensure resolution of the anemia and provide follow up care as necessary.

Conclusion

Management of anemia in IBD patients can be challenging because there can be multiple causes both related to and independent of the disease. Evaluation merits special attention to issues specific to and more common to patients with IBD, such as surgery, certain malignancies, and the malabsorptive and dietary issues inherent in the disease. However, iron deficiency remains the most common cause for anemia in these patients and the IBD may merit preference of IV replenishment rather than oral dosing. Irrespective of the cause, anemia should be recognized and managed without delay so as to avoid complications.

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References:

1. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol. 2008;103(5):1299-1307. doi:10.1111/j.1572-0241.2008.01846.x
2. Patel D, Yang YX, Trivedi C, Kavani H, Xie D, Medvedeva E, et al. Incidence, duration, and management of anemia: a nationwide comparison between IBD and non-IBD populations. Inflamm Bowel Dis. 2020;26(6):934-940. doi:10.1093/ibd/izz206
3. Camaschella C. Iron deficiency. Blood. 2019;133(1):30-39. doi:10.1182/blood-2018-05-815944
4. Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol. 2016;38 Suppl 1:123-132. doi:10.1111/ijlh.12500
5. Milovanovic T, Dragasevic S, Nikolic AN, Markovic AP, Lalosevic MS, Popovic DD, et al. Anemia as a problem: GP approach. Dig Dis. 2022;40(3):370-375. doi:10.1159/000517579
6. Day AS, Yao CK, Costello SP, Andrews JM, Bryant RV. Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: a systematic scoping review. Appetite. 2021;167:105650. doi:10.1016/j.appet.2021.105650
7. Limdi JK. Dietary practices and inflammatory bowel disease. Indian J Gastroenterol. 2018;37(4):284-292. doi:10.1007/s12664-018-0890-5
8. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583. doi:10.1053/j.gastro.2020.12.031
9. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. Mayo Clin Proc. 2003;78(10):1274-1280. doi:10.4065/78.10.1274
10. Bager P, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, et al. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. Scand J Gastroenterol. 2011;46(3):304-309. doi:10.3109/00365521.2010.533382
11. Colapinto CK, O'Connor DL, Tremblay MS. Folate status of the population in the Canadian Health Measures Survey. Cmaj. 2011;183(2):E100-106. doi:10.1503/cmaj.100568
12. Gold SL, Manning L, Kohler D, Ungaro R, Sands B, Raman M. Micronutrients and their role in inflammatory bowel disease: function, assessment, supplementation, and impact on clinical outcomes including muscle health. Inflamm Bowel Dis. 2023;29(3):487-501. doi:10.1093/ibd/izac223
13. Means RTJ, Brodsky RA. Diagnostic approach to anemia in adults. In: UptoDate, Elmore JG, (Editor): Wolters Kluwer; 2024.
14. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program. 2013;2013:638-644. doi:10.1182/asheducation-2013.1.638
15. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. J Acad Nutr Diet. 2013;113(12):1610-1619. doi:10.1016/j.jand.2013.06.349
16. da Silva Lopes K, Yamaji N, Rahman MO, Suto M, Takemoto Y, Garcia-Casal MN, et al. Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews. Cochrane Database Syst Rev. 2021;9(9):Cd013092. doi:10.1002/14651858.CD013092.pub2
17. Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019;2019(1):315-322. doi:10.1182/hematology.2019000034
18. Moe S, Grill AK, Allan GM. Newer iron supplements for anemia. Can Fam Physician. 2019;65(8):556.
19. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis. 2012;18(10):1961-1981. doi:10.1002/ibd.22906

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KEY TAKEAWAYS

- Post-operative recurrence (POR) is extremely common after Crohn's disease (CD) surgery, and the severity of recurrence predicts future need for surgery, therefore POR monitoring is vital.
- The current gold standard for monitoring POR is ileocolonoscopy however there is poor patient compliance.
- Emerging data support combining intestinal ultrasound with fecal calprotectin as a new non-invasive tool for monitoring POR.
- Further research to fully elucidate the utility of non-invasive investigations in post-operative CD management is warranted.

CAN NON-INVASIVE MONITORING REPLACE ILEOCOLONOSCOPY FOR POSTOPERATIVE RECURRENCE OF CROHN'S DISEASE?

Introduction

The therapeutic landscape for Crohn's disease (CD) has been reshaped by improvements in disease management and medical therapy, leading to a decrease in the necessity for intestinal resection.[1] However, surgical intervention still plays a crucial role in treating medically refractory disease or

complications such as strictures or fistulae.[2] Recent biologic-era population studies have shown that the rate of CD-related abdominal surgery over 10 years is up to 49.9% in adult-onset CD and 37.7% in pediatric onset CD.[3]

Why is Postoperative Monitoring Important?

Although clinical remission is often achieved after surgery, endoscopic postoperative recurrence (POR) is detected in as many as 90% of cases within 3 years after surgery and up to 70% of patients require further surgery within 10 years if appropriate treatment is not instigated.[4] Disease recurrence occurs in the neo-terminal ileum or anastomosis and it usually manifests with endoscopic findings prior to clinical symptoms.[1] The severity of endoscopic recurrence 1 year after surgery is often predictive of later clinical recurrence and the need for future surgery.[4] Postoperative recurrence is thought to be triggered by the presence of intestinal contents and bacteria in the lumen that lead to mucosal invasion by inflammatory cells.[1]

Current Surveillance for CD Recurrence

The current gold standard for monitoring CD postoperatively is ileocolonoscopy performed at 6-12 months post-surgery.[5] **(Figure 1)** The landmark POCER trial supported the central role of endoscopy postoperatively. In this study, patients were randomized to either the 'active care' arm with a 6 month ileocolonoscopy and step-up therapy if there was endoscopic recurrence or the 'standard care' arm with symptom-based management and no ileocolonoscopy. At 18 months follow up, patients in the 'active care' endoscopy group exhibited significantly lower endoscopic recurrence rates compared to the 'standard care' group (49% vs 67% respectively, p=0.03).[6] There is limited research to guide endoscopic surveillance beyond 12 months postoperatively but given high POR rates it has been suggested that repeat ileocolonoscopy could take place every 1-2 years to guide management.[7] Endoscopic mucosal findings are graded using the Rutgeerts score, which predicts clinical recurrence and categorizes disease severity from i0 to i4 according to the presence and extent of aphthous ulcers in the neo-terminal ileum and anastomosis.[1] The modified Rutgeerts and REMIND scores were recently developed to separate aphthous lesions in the neo-terminal ileum from those confined to the anastomosis as questions remain about whether anastomotic lesions are related to post-surgical ischemic change rather than CD progression.[8] These scores continue to be evaluated and may aid prediction of postoperative long-term outcomes.

Ileocolonoscopy cannot be replaced by non-invasive methods in all circumstances as endoscopic evaluation allows biopsies to assess histological activity and dysplasia. However, Ileocolonoscopy is invasive and leads to high costs, procedural risks and logistical issues such as operating room availability. Additionally, it cannot easily assess proximal small bowel disease, and the frequency of endoscopy is limited. It requires bowel preparation and it can be poorly tolerated by patients.[9] As a result, patient compliance with recommended postoperative surveillance is poor with only 30-54% of patients undergoing ileocolonoscopy within 12 months of surgery. Given the importance of preventing and promptly treating POR to avoid bowel damage, non-invasive assessment methods for POR monitoring are warranted.

Non-invasive Modalities for Monitoring CD Activity Postoperatively

Clinical Disease Indices

Clinical indices such as the Crohn's Disease Activity Index do not correlate well with the presence of recurrent endoscopic disease postoperatively.[9] Endoscopically identified disease recurrence often occurs before clinical symptoms develop.[1] Moreover, there are many symptomatic confounders postoperatively such as bile-salt malabsorption, small bowel bacterial overgrowth, adhesions, dysmotility, and fat malabsorption that falsely elevate clinical indices.[7]

Serum Biomarkers and the Endoscopic Healing Index

Serum biomarkers such as C-reactive protein and erythrocyte sedimentation rate have been shown to be insensitive to detecting localized POR.[1,10] However, the Endoscopic Healing Index, a score derived from a blood test analyzing 13 biomarkers postulated to reflect mucosal inflammation (ANG1, ANG2, CRP, SAA1, IL17, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGF-α, CEACAM1, and VCAM), has been developed and validated to identify patients in endoscopic remission. The accuracy of the Endoscopic Healing Index has been evaluated for the presence of postoperative endoscopic recurrence. After six months, both the Endoscopic Healing Index <20 and fecal calprotectin <100 µg/g showed comparable sensitivity (81.8% and 90.9%, respectively) and negative predictive value (84.0% and 91.7%, respectively) for the detection of endoscopic recurrence. However, at 18 months, the Endoscopic Healing Index was unable to reliably distinguish between remission and recurrence, unlike fecal calprotectin, with a negative predictive value of 64.9% vs 89.7%, respectively.[4] This was postulated to be attributed to the matrix remodelling markers being more prominent in the early postoperative phase. Although this test is promising, it currently has limited availability and further research validating its cost effectiveness and utility to predict POR in the real world is warranted.

Fecal Biomarkers

Growing evidence points to fecal calprotectin as a useful adjunctive tool for monitoring activity of CD

after surgery. Boschetti et al. studied 86 asymptomatic postoperative CD patients after a mean interval of 8.2 +/- 0.5 months. They reported that patients experiencing endoscopic recurrence had significantly elevated levels of fecal calprotectin compared to those in endoscopic remission (mean 473 µg/g vs 115 µg/g; P < 0.0001). Additionally, they observed a significant correlation between fecal calprotectin levels and Rutgeerts scores (r = 0.65, P < 0.0001).[11] Fecal calprotectin thresholds from 100 to 150 µg/g have demonstrated sensitivity of 70-89% and specificity of 58-69% in detecting endoscopic recurrence.[12] The high negative predictive value of fecal calprotectin >90% suggests that a threshold below 100 µg/g could avoid systematic ileocolonoscopies in 30% of asymptomatic postoperative CD patients. Moreover, existing literature indicates that serial fecal calprotectin trends over time can forecast early endoscopic and clinical recurrence in both pediatric and adult cohorts.[13] Therefore, fecal calprotectin could play a role in perioperative risk assessment, proactive monitoring and evaluating treatment effectiveness in postoperative CD. European Crohn's and Colitis Organization (ECCO) guidelines recommend initiating fecal calprotectin measurements three months after surgery and consider subsequent endoscopic evaluation based on its levels and trends during follow-up.[14] However, the optimal cutoff value to predict POR is still to be determined and adherence with stool tests can be challenging.[4]

Intestinal Ultrasound

Intestinal ultrasound (IUS) is emerging as a non-invasive alternative for ileocolonoscopy in diagnosing POR, defined as a Rutgeerts score >i2, with a sensitivity of 94% and specificity of 84%.[15,16] **(Figure 2)**. Scores like the Simple Ultrasound Activity Score for Crohn's Disease (SUS-CD), the International Bowel Ultrasound Segmental Activity Score (IBUS-SAS) and the Simple Ultrasound Score demonstrate high accuracy in POR diagnosis with all three showing area under the curve of over 80%.[17] Increased bowel wall thickness, bowel wall hyperemia and the presence of lymph nodes have all correlated with the endoscopic Rutgeerts score.[9,18] The utility of IUS postoperatively to detect complications has not been studied. However, various studies have determined the role of IUS in detecting stenosis affecting the small bowel and by using surgery as a comparator they reported sensitivity of between 75-100% and specificity between 89-93%.[18]

Given that CD is transmural, it is more thoroughly evaluated by imaging which can assess the entire intestinal wall and extraluminal manifestations, unlike colonoscopy which can only assess mucosal damage. Moreover, imaging may be able to detect active inflammation in the proximal small bowel. An important advantage of non-invasive methods like IUS is the ability to be repeated multiple times, potentially improving accuracy for this test, as well as facilitating close patient monitoring and minimizing delays in diagnosis and treatment. Earlier treatment has the potential to reshape the trajectory of disease in postoperative CD patients and minimize risk of POR. Intestinal ultrasound is operator dependent and is more challenging with larger body habitus. However, it is inexpensive, non-irradiating, and provides valuable point of care information. Recent ECCO guidelines suggest IUS as an alternative method for detecting POR, especially after small bowel resection with an anastomosis that is beyond the accessibility of endoscopy.[18] International CD postoperative consensus

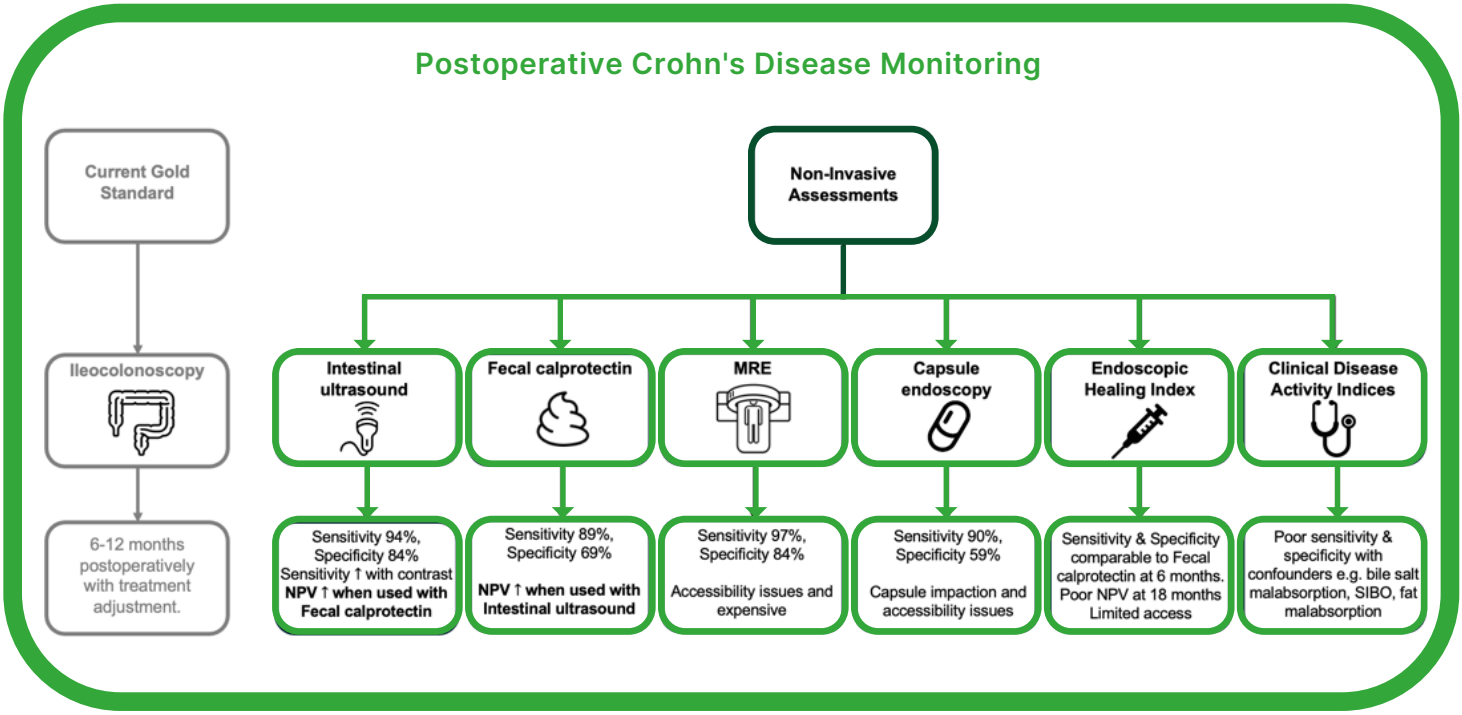

Figure 1: Postoperative Crohn's disease monitoring; *courtesy of Dr. Shreya Kishore MD, Dr. Sally Lawrence MBChB, FRCPCH, FRCPC*
Abbreviations: NPV: Negative predictive value; **MRE:** Magnetic resonance enterography; **SIBO:** Small intestinal bacterial overgrowth.

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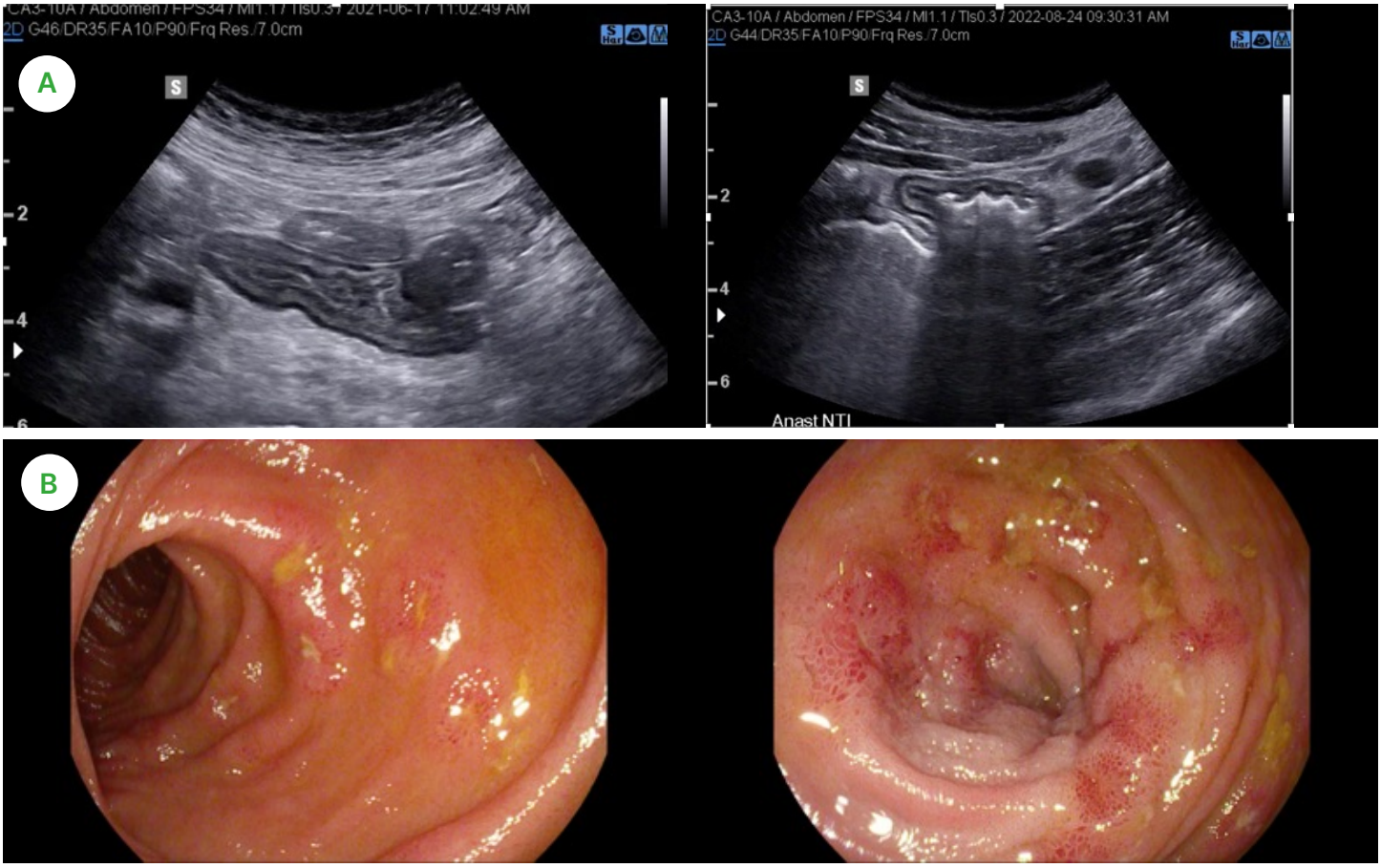

Figure 2: Postoperative Crohn's disease assessment 6 months post-ileocecal resection with side-to-side anastomosis in high-risk patient on postoperative prophylactic biologic therapy. **A.** Intestinal ultrasound showing side-to-side anastomosis with normal colonic mucosa and increased bowel wall thickness on the ileal side with surrounding bright inflammatory fat. **B.** Endoscopic images confirmed Rutgeerts score i3 recurrence in the neo-terminal ileum; *courtesy of Dr. Kerri Novak*.

guidelines for IUS parameters are currently underway and they will further bolster the use of this modality in the postoperative setting.

A recent multicentre prospective study assessed a non-invasive approach combining IUS and fecal calprotectin. It demonstrated that bowel wall thickness (BWT) ≥3 mm and fecal calprotectin ≥50 µg/g correctly identified 75% of POR patients, with a false positive rate of 2.5%.[9] Conversely, the combination of BWT <3 mm and fecal calprotectin <50 ug/g correctly classified 74% patients with just 4.5% of patients falsely classified as not having POR. This suggests that there is potential for patients with evidence of POR on IUS and elevated fecal calprotectin to initiate biologic therapy without undergoing ileocolonoscopy. Similarly, patients with normal calprotectin values and without IUS abnormalities could potentially continue their follow-up without undergoing endoscopic evaluation.

Ultrasound with Contrast

Small intestine contrast ultrasonography (SICUS) and contrast-enhanced ultrasound (CEUS) have also been used to assess POR in CD. SICUS utilizes an oral contrast (polyethylene glycol) to assess bowel wall changes and complications. CEUS requires intravenous contrast, enabling detailed evaluation of the intestinal wall vasculature. A recent meta-analysis found that SICUS is more sensitive than IUS (99% vs 82%, respectively) but less specific (74% vs 88%, respectively).[1] A recent study reported that the already high sensitivity of 89.7% in detecting POR by IUS could be increased to 98% using CEUS.[18] However, the modest gain in sensitivity must be balanced with the increased invasiveness, additional time required and lack of access. Therefore, both contrast-enhanced ultrasound methods currently do not appear to offer significant advantages over IUS.[16]

Capsule Endoscopy

The value of capsule endoscopy (CE) for POR in CD has been evaluated in several studies. It has been reported that the sensitivity of CE in detecting recurrence in the neo-terminal ileum is inferior to that of ileocolonoscopy, although it is able to detect lesions outside the scope of ileocolonoscopy in up to two-thirds of patients.[1] Nonetheless, CE carries a risk of capsule impaction, and it is more expensive than traditional endoscopy. CE may be useful as a non-invasive technique for POR in CD, but further studies are required.[1]

Magnetic Resonance Enterography

Magnetic resonance enterography (MRE) has the potential for evaluating CD disease activity without the radiation exposure associated with computed tomography scans. The MONITOR index was recently

validated to predict POR in patients with CD using MRE. The score is calculated using seven criteria: bowel wall thickness, contrast enhancement, T2 signal increase, diffusion-weighted signal increase, edema, ulcers, and the length of the diseased segment. It has been found to be efficient and easy to use, demonstrating an area under the curve of 0.80 in predicting POR.[19]

A meta-analysis by Yung et al. evaluated the diagnostic accuracy of CE, MRE, and IUS in detecting endoscopic recurrence in postoperative CD. Both MRE and IUS demonstrated comparable accuracy in predicting POR, with area under the curve values of 0.98 and 0.93, respectively.[20] A significant advantage of IUS is that it can be performed by gastroenterologists, providing immediate information and guiding therapeutic decisions. In contrast, MRE requires evaluation by radiologists, leading to longer wait times for both the procedure and reporting. In addition, the examination is expensive, and the use of intravenous gadolinium contrast has been linked to long-term contrast retention in the brain.[18] The use of MRE is limited by accessibility challenges, poor patient acceptance due to claustrophobia and the need for bowel preparation.

Conclusion

POR remains one of the most challenging aspects in the management of CD. Preventing and promptly treating POR is crucial to avoid bowel damage. Non-invasive monitoring could play a fundamental role in reducing the number of endoscopic procedures postoperatively in CD, decreasing the burden on patients. Fecal calprotectin, IUS plus other imaging modalities, and the Endoscopic Healing Index are minimally invasive monitoring methods emerging for identifying POR. Moreover, combining non-invasive assessments such as IUS and fecal calprotectin holds promise as it has been shown to be accurate and reliable for monitoring POR in CD, facilitating close patient monitoring and minimizing delays in diagnosis and treatment. Larger prospective trials are required to determine how IUS and fecal calprotectin can be integrated into the monitoring of POR in CD. However, these tests add to the diagnostic armamentarium after CD surgery and may reduce the need for invasive endoscopies in routine surveillance in the near future.

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References:

1. Yamamoto T. Diagnosis and monitoring of postoperative recurrence in Crohn's disease. *Expert Rev Gastroenterol Hepatol*. 2015 Jan 2;9(1):55-66.
2. Spinelli A, Sacchi M, Fiorino G, et al. Risk of postoperative recurrence and postoperative management of Crohn's disease. *World J Gastroenterol*. 2011 Jul 7;17(27):3213
3. Kurowski JA, Milinovich A, Ji X, et al. Differences in biologic utilization and surgery rates in pediatric and adult Crohn's disease: results from a large electronic medical record-derived cohort. *Inflamm Bowel Dis*. 2021 Jul 1;27(7):1035-44.
4. Hamilton AL, De Cruz P, Wright EK, et al. Non-invasive serological monitoring for Crohn's disease postoperative recurrence. *J Crohns Colitis*. 2022 Dec 1;16(12):1797-807.
5. Nguyen GC, Loftus EV, Hirano I, et al. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. Gastroenterol. 2017;152:271-5. Most recent AGA guidelines specifically evaluating the postoperative management of Crohn's disease.
6. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015 Apr 11;385(9976):1406-17.
7. Battat R, Sandborn WJ. Advances in the comprehensive management of postoperative Crohn's disease. *Clin Gastroenterol Hepatol*. 2022 Jul 1;20(7):1436-49.
8. Dasharathy SS, Limketkai BN, Sauk JS. What's new in the postoperative management of Crohn's disease? *Dig Dis Sci*. 2022 Aug;67(8):3508-17.
9. Furfaro F, D'Amico F, Zilli A, et al. Noninvasive assessment of postoperative disease recurrence in Crohn's disease: a multicenter, prospective cohort study on behalf of the italian Group for Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2023 Nov 1;21(12):3143-51.
10. Fasulo E, D'Amico F, Osorio L, et al. The management of postoperative recurrence in Crohn's disease. *J Clin Med*. 2023 Dec 25;13(1):119.
11. Boschetti G, Moussata D, Stefanescu C, et al. Levels of fecal calprotectin are associated with the severity of postoperative endoscopic recurrence in asymptomatic patients with Crohn's disease. *Am J Gastroenterol| ACG*. 2015 Jun 1;110(6):865-72.
12. Tham YS, Yung DE, Fay S, et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. *Therap Adv Gastroenterol*. 2018 Jun 30;11:1756284818785571.
13. Boube M, Laharie D, Nancey S, et al. Variation of faecal calprotectin level within the first three months after bowel resection is predictive of endoscopic postoperative recurrence in Crohn's disease. *Dig Liver Dis*. 2020 Jul 1;52(7):740-4.
14. Dragoni G, Allocca M, Myrelid P, et al. Results of the eighth scientific workshop of ECCO: Diagnosing postoperative recurrence of Crohn's disease after an ileocolonic resection with ileocolonic anastomosis. *J Crohns Colitis*. 2023 Sep 1;17(9):1373-86.
15. Taylor SA, Mallett S, Bhatnagar G, et al. Magnetic resonance enterography compared with ultrasonography in newly diagnosed and relapsing Crohn's disease patients: the METRIC diagnostic accuracy study. *Health Technol Assess*. 2019 Aug;23(42):1.
16. Rispo A, Imperatore N, Testa A, et al. Diagnostic accuracy of ultrasonography in the detection of postsurgical recurrence in Crohn's disease: a systematic review with meta-analysis. *Inflamm Bowel Dis*. 2018 Apr 23;24(5):977-88.
17. Amor Costa C, Suarez Ferrer C, Poza Cordon J, et al. P485 Do intestinal ultrasound scores have a role in the diagnosis of postoperative recurrence? *J Crohns Colitis*. 2024 Jan 1;18(Supplement_1):i971-2.
18. Kucharzik T, Maaser C. Intestinal ultrasound and management of small bowel Crohn's disease. *Therap Adv Gastroenterol*. 2018 Apr 30;11:1756284818771367.
19. Schaefer M, Laurent V, Grandmougin A, et al. A magnetic resonance imaging index to predict Crohn's disease postoperative recurrence: the MONITOR index. *Clin Gastroenterol Hepatol*. 2022 May 1;20(5):e1040-9.
20. Yung DE, Har-Noy O, Tham YS, et al. Capsule endoscopy, magnetic resonance enterography, and small bowel ultrasound for evaluation of postoperative recurrence in Crohn's disease: systematic review and meta-analysis. *Inflamm Bowel Dis*. 2018 Jan 1;24(1):93-100.

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- reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of RENFLEXIS® have not been established in patients less than 6 years of age.

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References: 1. Organon Canada. Data on file. October 2023. **2.** RENFLEXIS® Product Monograph, Samsung Bioepis, October 4, 2023. Distributed by Organon Canada Inc.

† Comparative clinical significance unknown.
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A REVIEW OF PEDIATRIC TO ADULT TRANSITION OF CARE IN INFLAMMATORY BOWEL DISEASE

The Epidemiology of Childhood Onset Inflammatory Bowel Disease

Canada is reported to have one of the highest rates of both incidence and prevalence of inflammatory bowel disease (IBD). Benchimol et al. conducted a population-based cohort study from 1999-2008 using health administrative data from Ontario, Canada, and reported that the prevalence of IBD in Canada in 2008 was 534.3 per 100,000 people (68,017 affected individuals among 12,738,350 Ontario residents).[1] Between 1999 and 2008, the incidence of IBD increased annually in children under the age of 10 (9.7% per year, p<0.0001) and in those aged 10-19 (3.8% per year, p<0.0001).[2,3]

Coward et al. published a similar population based health administrative data study using data from eight provinces in Canada. In this study the national incidence of IBD was estimated to be 29.9 per 100,000 (95% PI 28.3-31.5) in 2023.ll The incidence of IBD in pediatric patients was found to be increasing (average annual percentage change (AAPC) 1.27%; 95% CI 0.82-1.67). The prevalence of IBD was 843 per 100,000 (95% PI 716-735) in 2023 with forecasted increases (AAPC 2.43%;95% CI 2.32-2.54). In pediatric patients the prevalence in 2023 was 82 (95% PI 77-88) and the forecasted AAPC was 1.91 (1.46-2.31).

According to the 2023 Impact of IBD in Canada Report by Crohn's and Colitis Canada, an estimated 322,600 Canadians are living with IBD, with 11,000 new diagnoses expected in 2023.[4,5]

The global incidence and prevalence of IBD has been rising. In 2011, Benchimol et al. published a systematic review detailing international trends in IBD.[6] The review demonstrated a 60% increase in Crohn's disease (CD) and a 20% increase in ulcerative colitis (UC) across both developing and developed countries. Benchimol et al. also published the results of a health administrative data analysis evaluating children with a diagnosis of IBD between 1999-2010 across five Canadian provinces, which together account for 79.2% of the Canadian population.[7] They reported that incidence of IBD in children aged five and under increased during the study period (annual percentage increase [APC] +7.19%; 95% CI, +2.82% to +11.56%). The prevalence of IBD also increased significantly during the study period (APC+4.56%; 95% CI, +3.71% to +5.42%).[7]

The Dilemma of Transition of Care

Considering its low mortality, children diagnosed with IBD will eventually be required to transition from pediatric oriented health services to adult care. Kaplan et al. provided a thorough explanation of this phenomenon, outlining the compounding prevalence within the context of IBD. With the life expectancy of individuals in the Western world into the 80s and young patients being diagnosed regularly, the prevalence of IBD in the Western world is steadily increasing.[8]

Pediatric to adult transition of care is defined as *"the purposeful planned movement of adolescents*

and young adults with chronic physical and medical conditions from child centered to adult oriented healthcare systems (Blum 1993).[9]" It is recognized that in pediatric healthcare systems both the child and their care partner participate in the process, with the care partner usually responsible for medical decision making. In the adult healthcare system, there is an expectation of patient autonomy with the experience focused on the patient themselves, with less attention paid to the expectations and needs of their care partner. This divergence in focus and care delivery creates the opportunity for adverse health outcomes. Added to this is the overlap of healthcare transfer of care upon milestones such as completing secondary education, beginning either a vocation or post-secondary education, potentially leaving the family household, and gaining financial independence, all of which can create additional stress and burden to a young adult managing a lifelong, complex chronic disease.

In contrast, transfer of care specifically refers to the handover of care to the adult healthcare team.

Access to Transition of Care Services

The child and adolescent health measurement initiative published data from their 2021-2022 National Survey of Children's Health (NSCH), an American national survey, funded by the Health Resources and Services Administration's Maternal and Child Health Bureau.[10] A total of 104,995 surveys were completed in 2021 and 2022 combined. Across 50 states and the District of Columbia, the estimated percentage of patients who received transition of care services between the ages of 12 and 17 (after application of sampling weights) ranged from 9.8 to 30.5%.[10]

Jawaid et al. conducted a national qualitative survey assessing the access and quality of transition of care resources for children moving from pediatric to adult care across Canada.[11] The study involved targeted sampling of gastroenterologists with expertise in IBD transition care who treat adults. Researchers conducted 25 anonymous surveys and 17 semi-structured interviews across nine adult IBD centres and six Canadian provinces. They reported that four out of five centres offered an IBD transition clinic, with most transition-aged patients being preferentially transferred to an adult IBD centre within a tertiary care academic institution. The number of transition-aged patients transferring annually ranged between 12-100, according to these preferred providers. Challenges during the transition of care period included a consistent lack of access to multi-disciplinary healthcare resources. In addition, participants agreed that a comprehensive referral package and access to shared patient data, for example through a shared electronic medical record, eased the transfer of care process.[11]

Outcomes in Pediatric to Adult Transition of Care in IBD

Traditionally healthcare outcomes have been disease focused, with a focus on endoscopic and clinical remission, and normalization of serological markers of inflammation. There is now a broader understanding that a patient's perceived sense of wellness and overall quality of life is a foundational target outcome that ultimately allows a young person with IBD to achieve their personal potential. Interventions to improve these patient reported outcomes are now a critical component of our approach to IBD care.

Patient and Provider Reported Outcomes

Bihari et al. evaluated definitions of transition success according to patients, parents, and healthcare providers during the transition of care period.[12] Using purposive sampling, they conducted 17 semi-structured interviews with patients, 13 with parents, and 15 with healthcare providers. This process identified several themes that define a successful transition. Key criteria included independent engagement (self-advocacy, taking responsibility for appointments, being aware of health-related events). Active involvement in disease management was also identified, including adherence to treatments, investigations, and coordinating with the healthcare team during disease flares. The development of a supportive and trusting relationship with the healthcare team was identified. A flexible approach by the adult care team is essential, acknowledging the challenges of transitioning from a pediatric healthcare system and the demands of post-secondary programs that might limit attendance or engagement. Providers valued having a comprehensive disease-specific knowledge base. Patients emphasized the importance of a regularly available adult healthcare provider and disease stability.[12]

Transition Related Readiness

One of the key factors thought to encompass the critical skills needed for transition is transition readiness. These skills include self-management, medication and disease-related knowledge, health literacy, and self-efficacy. Johnson et al. conducted a systematic review of factors affecting transition readiness skills in IBD patients that included 16 studies.[13] These factors were divided into provider related, demographic, other, and disease-related factors. Among provider related factors, the duration of the transition (before transfer of care occurred) was positively associated with self-efficacy. Fourteen studies demonstrated a positive association between age and self-management behaviours as well as disease-related knowledge. Three studies have shown a positive relationship between self-efficacy, knowledge, and self-management behaviours. Depression and anxiety were associated with lower self-efficacy, while a family history of IBD was found

to be positively associated with self-efficacy. Three studies reported that female gender was positively associated with self-management.[13]

Health Service Utilization

Botema et al. conducted a cohort study using a Dutch insurance database that covered approximately 4.2 million people, or 25% of the Dutch population, from 2007 to 2014.[10] They followed patients aged 16-18 until the age of 19 or when they transferred to adult care. The study reported that steroids and biological advanced IBD therapies were used less frequently in pediatric care, and that there were fewer overall IBD-related hospitalizations while under the care of a pediatric provider.[14]

Zhao et al. used health administrative data in Ontario, Canada from 1998 to 2008 to evaluate IBD-specific and IBD-related outpatient visits, emergency department visits, hospitalizations, and laboratory visits.[15] They compared the relative incidence (RI) in the last two years of pediatric care with the first two years of adult care. The study included 536 patients (388 with CD and 148 with UC). The findings showed that emergency department visits ([CD RI, 2.12; 95% CI, 1.53-2.93], [UC RI 2.34; 95% CI, 1.09-5.03]), outpatient visits ([CD RI, 1.56; 95% CI, 1.42-1.72], [UC RI, 1.48; 95% CI, 1.24-1.76]), and laboratory investigations were all significantly higher in the adult period.

Interventions to Optimize Healthcare Outcomes During Transition of Care.

There is a paucity of level one evidence rigorously evaluating the impact of targeted interventions aimed at improving transition-specific healthcare outcomes.

Bollegala et al. have published the protocol for a randomized controlled trial evaluating the impact of a multimodal intervention to improve the transition of patients with IBD from pediatric to adult care.[16] This type 1 hybrid effectiveness-implementation trial aimed at patients aged 16-17.5 and evaluates the role of a four part model including 1) individualized assessment, 2) a transition navigator, 3) virtual patient skill building, and 4) a virtual education program. The primary outcome is the IBD disability index. This study has not yet entered into the analytic phase and preliminary results are not yet available. In the absence of level one data to support transition programming, this intervention has elected to focus on the role of a transition navigator and a comprehensive transition focused educational platform. This was also the intervention supported by the Canadian Consensus Statements on the Transition of Adolescents and Young Adults with Inflammatory Bowel Disease from Pediatric to Adult Care.

Erős et al. published a systematic review on the transition of care from pediatric to adult.[17] The most commonly studied intervention was the role of a joint visit between the adult gastroenterologist, the pediatric gastroenterologist, the patient, and their care partner. The number of visits, the duration of time over which they occur, and their locations varied across studies. The members of the healthcare team participating in these visits also varied. In some studies, multi-disciplinary team members such as dieticians, IBD nurses, and psychologists were present. The purpose of these visits could range from a comprehensive review of the patient's medical history and upcoming treatment plans to disease-specific education and the development of skills such as communication.

Corsello et al. conducted an observational study in Rome, Italy which evaluated the impact of a two-part transition of care process.[18] The first visit took place at the pediatric centre with parents and both adult and pediatric providers present. The second visit occurred at the adult centre. The study included 82 IBD patients with a mean transition age of 20.2 ± 2.7 years. Notably, 75% of participants expressed a positive opinion about this transition strategy. The authors recommended an optimal age range for these visits, prioritizing their occurrence during a period of remission.

Marani et al., acknowledged the limited scope of literature on transition-specific interventions for IBD, and expanded their literature review to include any transition interventions across all pediatric-onset chronic diseases.[19] They identified 26 studies and two broad categories of intervention, which included multi-disciplinary transition clinics and transition programs led by facilitators. Both interventions featured elements such as educational interventions, social programs and peer support, enhanced communication strategies, and targeted efforts to improve transition readiness.

Reviews of the literature in this area have identified variability in outcome measurements, and heterogeneity in the measurement scales of these outcomes. They identified a need for greater consistency to identify significant differences and to take subsequent targeted steps to improve the quality of care.

Canadian Consensus Statements on the Transition of Adolescents and Young Adults with Inflammatory Bowel Disease from Pediatric to Adult Care.

Canadian Consensus Statements on the Transition of Adolescents and Young Adults with Inflammatory Bowel Disease from Pediatric to Adult Care.

In the absence of clear evidence, most guideline statements in this area are based on expert opinion and consensus.

Several guidelines in this area have been published. Vernon-Roberts et al. released guidelines for Australia and New Zealand in May 2024.[20] The United Kingdom's IBD transition guidelines were published in 2017 by Brooks et al.[21]

The recent Canadian guidelines were developed by a comprehensive multi-disciplinary group from across Canada, representing a variety of practice settings and incorporating patient partners.[22] They

issued 15 statements emphasizing the importance of individualized structured transition programs focused on skill building in behaviour, knowledge, and abilities. The guidelines recognized the need to support care partners during this process of emerging independence and addressed the training needs of adult healthcare providers managing this complex phenotype. Importantly, they identified the role of a primary care provider as a stable figure during a period of change and an important ally in managing adolescent-specific issues that may be unfamiliar to the adult gastroenterologist. The guidelines also emphasized the importance of a comprehensive transfer of care letter from the pediatric care provider.[18]

Conclusions

The transition of IBD patients from pediatric to adult care is a complex process involving multiple stakeholders. An emerging body of literature is exploring effective interventions to optimize healthcare outcomes in this area. Ultimately, gaining an appreciation for the complexities of this period, prioritizing these patients by adult gastroenterologists, and improving transition-specific skills provide the necessary foundation for successful outcomes.

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References:

1. Benchimol EI, Manuel DG, Guttmann A, Nguyen GC, Mojaverian N, Quach P, et al. Changing age demographics of inflammatory bowel disease in Ontario, Canada: a population-based cohort study of epidemiology trends. Inflamm Bowel Dis. 2014;20(10):1761-1769. doi:10.1097/mib.0000000000000103
2. Coward S, Benchimol EI, Bernstein CN, Avina-Zubieta A, Bitton A, Carroll MW, et al. Forecasting the incidence and prevalence of inflammatory bowel disease: a Canadian nationwide analysis. Am J Gastroenterol. 2024 Aug 1;119(8):1563-1570. doi: 10.14309/ajg.0000000000002687
3. Kuenzig ME, Fung SG, Marderfeld L, Mak JWY, Kaplan GG, Ng SC, et al. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. Gastroenterology. 2022 Apr;162(4):1147-1159.e4. doi: 10.1053/j.gastro.2021.12.282
4. Windsor JW, Kuenzig ME, Murthy SK, Bitton A, Bernstein CN, Jones JL, et al. The 2023 impact of inflammatory bowel disease in Canada: executive summary. J Can Assoc Gastroenterol. 2023 Jun 1;6(Suppl 2):S1-S8. doi: 10.1093/jcag/gwad003. Erratum in: J Can Assoc Gastroenterol. 2023 Nov 13;6(6):255. doi: 10.1093/jcag/gwad038
5. El-Matary W, Carroll MW, Deslandres C, Griffiths AM, Kuenzig ME, Mack DR, et al. The 2023 impact of inflammatory bowel disease in Canada: special populations-children and adolescents with IBD. J Can Assoc Gastroenterol. 2023 Sep 5;6(Suppl 2):S35-S44. doi: 10.1093/jcag/gwad016
6. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis. 2011;17(1):423-439. doi:10.1002/ibd.21349
7. Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based Provincial health administrative databases. Am J Gastroenterol. 2017;112(7):1120-1134. doi:10.1038/ajg.2017.97
8. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021 Jan;18(1):56-66. doi: 10.1038/s41575-020-00360-x
9. Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. J Adolesc Health. 1993;14(7):570-576. doi:10.1016/1054-139x(93)90143-d
10. Child and Adolescent Health Measurement Initiative. 2021-2022 National Survey of Children's Health (NSCH) data query. Data Resource Center for Child and Adolescent Health, supported by the U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB); 2022. Available from: https://www.childhealthdata.org/browse/survey/results?q=10623&r=1.
11. Jawaid N, Jeyalingam T, Nguyen G, Bollegala N. Paediatric to adult transition of care in IBD: understanding the current standard of care among Canadian adult academic gastroenterologists. J Can Assoc Gastroenterol. 2020;3(6):266-273. doi:10.1093/jcag/gwz023
12. Bihari A, Hamidi N, Seow CH, Goodman KJ, Wine E, Kroeker KI. Defining transition success for young adults with inflammatory bowel disease according to patients, parents and health care providers. J Can Assoc Gastroenterol. 2022;5(4):192-198. doi:10.1093/jcag/gwac004
13. Johnson LE, Lee MJ, Turner-Moore R, Grinsted Tate LR, Brooks AJ, Tattersall RS, et al. Systematic review of factors affecting transition readiness skills in patients with inflammatory bowel disease. J Crohns Colitis. 2021;15(6):1049-1059. doi:10.1093/ecco-jcc/jjaa245
14. Bottema RWB, de Vries H, Houwen RHJ, van Rheenen PF. Impact of paediatric versus adult care setting on health care utilization in adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2019;69(3):310-316. doi:10.1097/mpg.0000000000002399
15. Zhao X, Bjerre LM, Nguyen GC, Mack DR, Manuel DG, Hawken S, et al. Health services use during transition from pediatric to adult care for inflammatory bowel disease: a population-based study using health administrative data. J Pediatr. 2018;203:280-287.e284. doi:10.1016/j.jpeds.2018.08.021
16. Bollegala N, Barwick M, Fu N, Griffiths AM, Keefer L, Kohut SA, Kroeker KI, Lawrence S, Lee K, Mack DR, Walters TD, de Guzman J, Tersigni C, Miatello A, Benchimol EI. Multimodal intervention to improve the transition of patients with inflammatory bowel disease from pediatric to adult care: protocol for a randomized controlled trial. BMC Gastroenterol. 2022 May 18;22(1):251. doi: 10.1186/s12876-022-02307-9.
17. Erős A, Soós A, Hegyi P, Szakács Z, Erőss B, Párniczky A, et al. Spotlight on transition in patients with inflammatory bowel disease: a systematic review. Inflamm Bowel Dis. 2020;26(3):331-346. doi:10.1093/ibd/izz173
18. Corsello A, Pugliese D, Bracci F, Knafelz D, Papadatou B, Aloi M, et al. Transition of inflammatory bowel disease patients from pediatric to adult care: an observational study on a joint-visits approach. Ital J Pediatr. 2021;47(1):18. doi:10.1186/s13052-021-00977-x
19. Marani H, Fujioka J, Tabatabavakili S, Bollegala N. Systematic narrative review of pediatric-to-adult care transition models for youth with pediatric-onset chronic conditions. Children and Youth Services Review. 2020;118:105415. doi:https://doi.org/10.1016/j.childyouth.2020.105415
20. Vernon-Roberts A, Chan P, Christensen B, Havrlant R, Giles E, Williams AJ. Pediatric to adult transition in inflammatory bowel disease: consensus guidelines for Australia and New Zealand. Inflamm Bowel Dis. 2024. doi:10.1093/ibd/izae087
21. Brooks AJ, Smith PJ, Cohen R, Collins P, Douds A, Forbes V, et al. UK guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. Gut. 2017;66(6):988-1000. doi:10.1136/gutjnl-2016-313000
22. Fu N, Bollegala N, Jacobson K, Kroeker KI, Frost K, Afif W, et al. Canadian consensus statements on the transition of adolescents and young adults with inflammatory bowel disease from pediatric to adult care: a collaborative initiative between the Canadian IBD Transition Network and Crohn's and Colitis Canada. J Can Assoc Gastroenterol. 2022;5(3):105-115. doi:10.1093/jcag/gwab050

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