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ABOUT THE AUTHOR



Giada Sebastiani, MD, FAASLD

Dr. Giada Sebastiani is a Tenured Professor of Medicine in the Division of Gastroenterology and Hepatology at McGill University and a Clinician Scientist at the Research Institute of McGill University Health Centre. She is the President of the Canadian Association for the Study of the Liver (CASL) 2024–2026 and Fellow of the American Association for the Study of Liver Diseases (AASLD). She received a medical degree and specialized in internal medicine at the University of Padua, Italy. She had research training at Harvard Medical School (US), University College of London (UK), and University of Bordeaux (France). Her work focuses on steatotic liver disease (MASLD), liver fibrosis, and non-invasive diagnostic tools in liver disease. She is an author of 220 articles in peer-reviewed journals (including *Nature Reviews Gastroenterology & Hepatology*, *Lancet Gastroenterology and Hepatology*, *Lancet Regional Health*, *Lancet HIV*, *Gastroenterology, Hepatology*, *Journal of Hepatology*, *Clinical Infectious Diseases*, *Diabetes Care; h-index 56*), and 14 book chapters. Dr. Sebastiani is co-founder of the Canadian MASLD Network, Co-Chair of the first MASLD chapter of Diabetes Canada guidelines, and panelist of the first guidance on MASLD of the Canadian Association for the Study of the Liver. She is the sole North American representative in the guidelines of the European AIDS Clinical Society as a primary reviewer of the Liver Group. Dr Sebastiani holds the prestigious Merite Clinical Research Salary Award from Fonds Recherche Sante Quebec. Her research program is funded by the Canadian Institutes of Health Research, the Fonds Recherche Sante Quebec, Crohn's Colitis Canada, and the Montreal General Hospital Foundation.

Affiliations: *Division of Gastroenterology and Hepatology, Department of Medicine, McGill University Health Centre, Montreal, Canada*

Beyond the Gut: Metabolic Dysfunction-associated Steatotic Liver Disease in Inflammatory Bowel Disease

Giada Sebastiani, MD, FAASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a frequent and clinically meaningful comorbidity in inflammatory bowel disease (IBD). Once considered incidental, MASLD is increasingly recognized as a marker of systemic metabolic and inflammatory burden with important hepatic and extrahepatic consequences. Recent studies indicate that MASLD affects approximately 24–32% of patients with IBD, with similar prevalence in Crohn's disease and ulcerative colitis after adjustment for metabolic risk factors. Importantly, liver fibrosis, the key prognostic hallmark in chronic liver disease, is detected in a substantial subset of patients and appears to progress over time. The pathogenesis of MASLD in IBD reflects the convergence of classical metabolic dysfunction with IBD-specific factors, including chronic systemic inflammation, gut–liver axis alterations, and changes in body composition. Although IBD is not yet systematically included in MASLD screening recommendations, emerging epidemiological and longitudinal evidence supports adapting established metabolic screening pathways to the IBD population using a risk-stratified case- finding approach. Pragmatic two-step algorithms, employing simple serum-based scores followed by transient elastography in selected patients, offer scalable and implementation-ready strategies. Management of MASLD in patients with IBD should align with general population guidelines while accounting for disease-specific considerations. Lifestyle modification remains foundational, complemented by pharmacologic therapies in patients with fibrosis or high cardiometabolic risk. Integrating liver risk assessment into routine IBD care represents a critical step toward improving long-term hepatic and extrahepatic outcomes in this growing population.

Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated condition with a steadily rising global burden, with Canada reporting among the highest prevalence worldwide.[1] Once considered as a disorder confined to the gastrointestinal tract, IBD is now recognized as a systemic disorder characterized by chronic inflammation and a growing burden of extraintestinal comorbidities that influence long-term outcomes.[2] As disease control and survival improve, metabolic health has emerged as a key determinant of morbidity in people living with IBD.[3-6] In parallel, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease, has become the most prevalent chronic liver disease worldwide, affecting approximately one-third of adults.[7-9] In 2023, an international consensus redefined fatty liver disease under the umbrella term steatotic liver disease, within which MASLD represents the dominant subtype, characterized by hepatic steatosis in the presence of cardiometabolic risk factors.[8] This nomenclature shift reflects advances in understanding disease biology, removes stigmatizing terminology, and emphasizes the systemic, metabolism-driven nature of the condition. The convergence of IBD and MASLD is therefore increasingly relevant. Obesity, insulin resistance, type 2 diabetes (T2D), and dyslipidemia—once considered uncommon in IBD—are now increasingly prevalent as disease duration lengthens and treatment paradigms evolve.[3-6] In contemporary IBD cohorts, abnormal liver enzymes are observed in up to 30% of patients, with MASLD representing one of the most frequent underlying causes encountered in clinical practice.[10-12] Despite this, MASLD in IBD has often been regarded as a benign or incidental finding, overshadowed by concerns related to drug-induced liver injury or immune-mediated hepatobiliary disorders. Accumulating evidence challenges this perception. In patients with IBD, MASLD has been associated with liver fibrosis, cardiovascular disease, adverse hospitalization outcomes, and increased healthcare utilization.[13-15] This review synthesizes current evidence on the epidemiology, pathophysiology, natural history, and clinical implications of MASLD in IBD, with particular emphasis on longitudinal data and non-invasive diagnostic strategies that are reshaping care paradigms as we approach 2026 and beyond.

Epidemiology of MASLD in IBD

Canada has one of the highest IBD prevalence rates globally, with 1 in 140 Canadians living with Crohn's disease or ulcerative colitis. Over 270,000 Canadians were affected in 2018, a number projected to exceed 400,000 by 2030.[1,16] As the IBD population grows, metabolic health

is worsening: obesity now affects 15% to 40% of patients,[3] and the incidence of T2D and dyslipidemia is higher than that observed in the general population.[4-6] Together with chronic intestinal inflammation and exposure to hepatotoxic therapies, these factors likely elevate the risk of steatotic liver disease. Globally, MASLD affects approximately 32% of adults and represents the most common chronic liver disease.[7-9] Its growing burden parallels the global epidemics of obesity and T2D, which are the primary drivers of hepatic steatosis and fibrosis progression. MASLD is a heterogeneous condition, with clinical presentation and prognosis shaped by metabolic risk, systemic inflammation, and extrahepatic disease states.[7-9] Within this context, MASLD is frequently observed among patients with IBD. Reported prevalence estimates typically range between 24% and 32%, though values vary widely (6.9%–53.8%) depending on diagnostic methods, study design, and population characteristics.[17] Studies relying on administrative codes or conventional ultrasonography consistently underestimate disease burden, whereas those using modern non-invasive tools—such as transient elastography or validated biomarker-based scores—report substantially higher prevalence estimates. A meta-analysis including more than 14,000 individuals from 18 countries reported a pooled MASLD prevalence of approximately 36% among patients with IBD, comparable to that observed in the general population.[18] These findings underscore the dominant role of metabolic dysfunction, while highlighting IBD as a population in which MASLD is frequently underrecognized. Prospective screening cohorts using transient elastography have provided important clarity into disease burden. In a Canadian cohort of 384 adults with IBD who underwent systematic transient elastography screening, MASLD was identified in 32.8% of patients despite a relatively young median age, and was accompanied by a substantial prevalence of significant liver fibrosis (12.2%).[19] From a global perspective, the intersection of IBD and MASLD is likely to intensify as IBD incidence rises in newly industrialized regions alongside rapid increases in obesity and T2D. These populations remain underrepresented in current studies, suggesting that the true global burden of MASLD in IBD is likely underestimated.

Pathophysiology: Why MASLD is More Complex in IBD

The pathogenesis of MASLD in IBD extends beyond classical metabolic dysfunction and reflects the convergence of metabolic, inflammatory, and intestine-derived mechanisms (**Figure 1**). While insulin resistance and adipose tissue dysfunction remain central drivers, IBD-specific factors may modify disease susceptibility and progression. Chronic systemic inflammation is a shared hallmark of both conditions. Persistent inflammatory signalling promotes hepatic lipid accumulation, oxidative stress, and fibrogenesis.[17,20] In IBD, recurrent disease flares may amplify these pathogenic pathways, although direct associations between disease activity indices and MASLD severity remain inconsistent. The gut–liver axis plays a pivotal role. Increased intestinal permeability, dysbiosis, and altered bile acid signalling enhance hepatic exposure to microbial products and pro-inflammatory mediators.[17] These mechanisms may be particularly relevant in Crohn's disease with small-bowel involvement, where transmural inflammation and mesenteric adipose tissue activation further contribute to metabolic dysregulation. Additional complexity is introduced by alterations in body composition. Sarcopenia is common in IBD, even among individuals with normal or elevated body mass index, contributing to the increasingly recognized phenotype of lean MASLD.[21,22] The impact of IBD therapies on MASLD development and progression remains incompletely defined. Corticosteroid exposure may promote visceral adiposity and insulin resistance, thereby amplifying hepatic steatosis and fibrotic risk, and is widely considered a modifiable contributor. Although methotrexate is not a primary driver of MASLD, it may increase susceptibility to liver injury in the presence of underlying steatosis, underscoring the importance of baseline liver risk stratification. Thiopurines are not associated with steatosis but may cause alternative hepatic complications, including cholestasis and nodular regenerative hyperplasia.[17,18] Biologic therapies, including anti-tumour necrosis factor (TNF) agents, vedolizumab, and ustekinumab, are generally considered metabolically neutral, while emerging data suggests that TNF inhibition may confer potential protective metabolic effects. Janus kinase inhibitors are associated with lipid profile

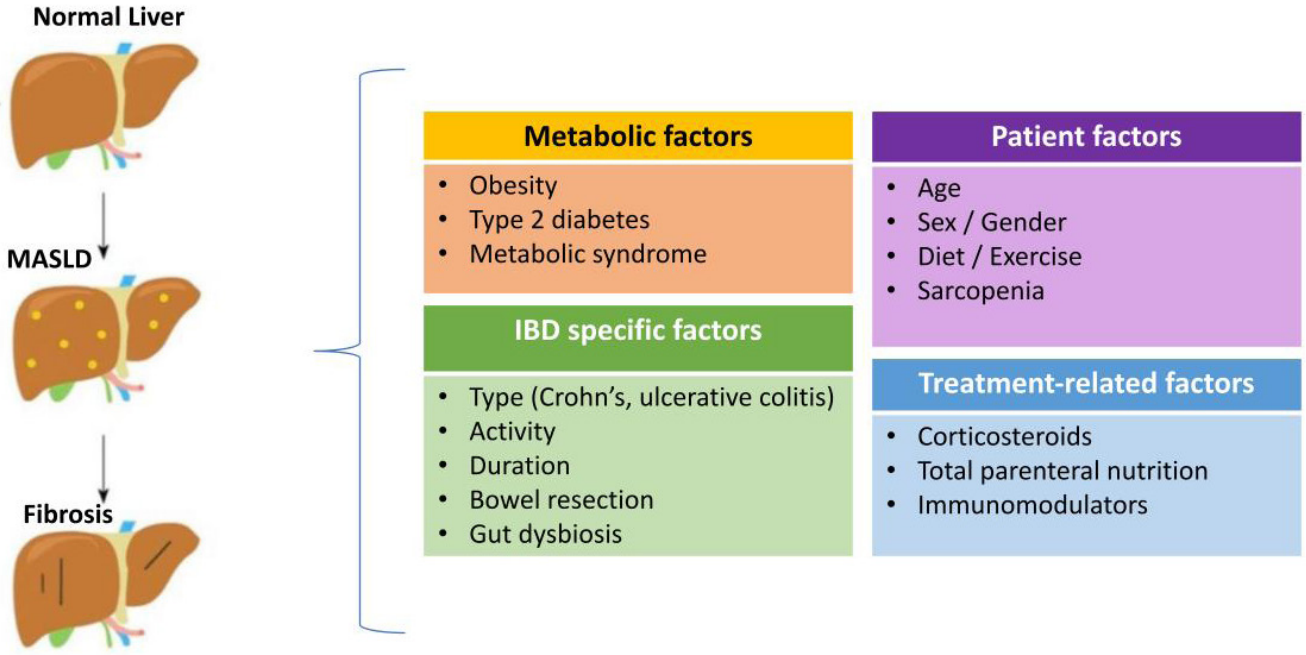


Figure 1. Factors implicated in the development of MASLD; *courtesy of Giada Sebastiani, MD, FAASLD.*

Abbreviations: MASLD: metabolic-dysfunction-associated steatotic liver disease

changes; however, their long-term hepatic impact remains unknown.[17]

Collectively, these mechanisms support the concept that MASLD in IBD is not a coincidental comorbidity, but rather the result of intersecting metabolic and inflammatory processes. Despite disease-specific pathogenic pathways, epidemiological studies consistently demonstrate similar MASLD prevalence in Crohn's disease and ulcerative colitis after adjustment for metabolic risk factors. Across IBD populations, older age, male sex, obesity, T2D, and dyslipidemia remain the most consistently reported associated factors associated with MASLD burden.[17-19]

Diagnostic Considerations, Fibrosis Risk Stratification, and Disease Progression

Although MASLD is common in IBD, its natural history was long considered relatively benign. Early cross-sectional studies reported low prevalence of advanced fibrosis, reinforcing this perception. However, more recent longitudinal studies using contemporary non-invasive tools challenge this view. In cohorts systematically assessed with transient elastography, liver fibrosis has been detected in 12%–14% of unselected IBD patients—rates that appear higher than those reported in the general population.[19,23] Longitudinal follow-up with serial biomarkers further demonstrates that fibrosis progression is not uncommon, with reported rates of approximately 0.5 per 100 person-years, while steatosis progression may exceed 9 per 100 person-years.[24] These findings suggest that fibrosis risk in IBD has been underestimated due to short follow-up, inconsistent diagnostic approaches, and selection bias. Although fibrosis progression appears primarily driven by metabolic risk rather than IBD activity alone, a subset of patients develops fibrosis in the absence of overt MASLD, pointing to additional contributory factors, including inflammatory, nutritional, or treatment-related influences. MASLD in IBD is increasingly recognized as a marker of systemic risk. Cardiovascular disease is of particular concern, with higher rates of incident events observed among IBD patients with MASLD, especially in those with fibrosis, lean MASLD, or combined metabolic dysfunction.[13,14] MASLD has also been associated with worse hospitalization outcomes, including longer length of stay, increased complication rates, and greater healthcare

utilization, reinforcing its role as a marker of global metabolic and inflammatory burden.[15]

Current clinical practice guidelines increasingly recommend case-finding for MASLD-related advanced fibrosis in high-risk metabolic populations, particularly individuals with prediabetes or T2D, in whom fibrosis is the key determinant of hepatic and extrahepatic outcomes.[25,26] These guidelines endorse the Fibrosis-4 index (FIB-4) as a first-line triage tool, followed by second-line testing, most commonly transient elastography, for individuals with indeterminate or high-risk results. In these care pathways, pragmatic thresholds are typically applied: an FIB-4 score <1.3 indicates a low likelihood of advanced fibrosis and supports periodic reassessment and cardiometabolic risk management; values between 1.3 and 2.67 suggest indeterminate risk warranting further evaluation; and an FIB-4 score >2.67 supports referral for specialist assessment due to higher probability of advanced fibrosis. Although IBD is not yet systematically included in MASLD screening recommendations, accumulating epidemiological and natural-history data support adapting established metabolic screening pathways to IBD using a risk-stratified case-finding approach rather than universal screening. In clinical practice, this strategy may prioritize IBD patients with readily identifiable triggers, including: **a)** steatosis detected on imaging (ultrasound, computed tomography, or magnetic resonance imaging); **b)** persistently abnormal liver enzymes after exclusion of alternative etiologies and acute drug-induced liver injury; **c)** overweight or obesity, including central adiposity; **d)** prediabetes or T2D; and **e)** a high cardiometabolic risk profile, such as multiple metabolic comorbidities and increasing age. Operationally, an IBD-adapted algorithm can mirror the scalable two-step screening pathways already used in metabolic populations. This approach employs the FIB-4 index calculated from routinely available laboratory tests as a first-line assessment, followed by transient elastography (or an alternative validated second-line test where available) for patients with indeterminate or high FIB-4 scores or compelling clinical suspicion.[25,26] This strategy relies on widely accessible, low-cost tools that integrate seamlessly into gastroenterology workflows, while reserving elastography capacity and hepatology referral for those most likely to benefit. As the global metabolic disease burden rises in parallel with IBD incidence, such implementation-ready strategies will be essential to prevent delayed diagnosis of advanced fibrosis and to embed liver health within comprehensive IBD care.

Management and Treatment of MASLD in IBD

Management of MASLD in patients with IBD should align with principles established in the general population, while accounting for IBD-specific factors that may influence feasibility, adherence, and risk-benefit considerations. Current guidelines emphasize a stage-specific approach, with particular focus on patients with liver fibrosis, given its central role in determining liver-related and extrahepatic outcomes. Lifestyle modification remains the cornerstone of MASLD management.[25,26] Sustained weight loss is the most effective intervention for reducing hepatic steatosis and improving fibrosis, with evidence indicating that a ≥7%–10% reduction in body weight is associated with histological improvement and fibrosis regression. Dietary interventions should prioritize caloric reduction and cardiometabolic benefit rather than restrictive, disease-specific exclusion diets. A Mediterranean-style diet, rich in mono- and polyunsaturated fats, fibre, and plant-based foods, has been associated with improvements in hepatic steatosis and cardiovascular risk and is generally well tolerated in patients with stable IBD.[27] Regular aerobic and resistance exercise (targeting 150–200 minutes per week across 3–5 sessions) improves insulin sensitivity and reduces liver fat and should be encouraged even in the absence of substantial weight loss.[25,26] In IBD populations, particular attention is warranted for sarcopenia and altered body composition, as weight loss strategies that exacerbate muscle loss may worsen functional status and metabolic risk.[21,22] Multidisciplinary care involving dietitians familiar with both MASLD and IBD is therefore essential. Pharmacologic therapy should be considered in patients with MASLD who have moderate-to-advanced fibrosis, progressive disease despite lifestyle intervention, or high cardiometabolic risk. Among available options, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) currently have the strongest evidence base. In 2025, Health Canada approved semaglutide for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with stage 2–3 fibrosis, based on results from the

phase 3 ESSENCE trial.[28] Beyond liver-specific benefits, GLP-1 RAs reduce major adverse cardiovascular events and improve glycemic control, positioning them as dual-purpose agents in MASLD management. Although data in IBD-specific populations remain limited, available evidence does not suggest increased risk of IBD disease activity. Nonetheless, careful monitoring during treatment initiation is advised, particularly in patients with active disease or prominent gastrointestinal symptoms.

MASLD is a strong marker of systemic cardiometabolic risk, and cardiovascular disease remains the leading cause of mortality in this population.[26] Accordingly, aggressive management of cardiovascular risk factors is a core component of MASLD care in patients with IBD. Statins are safe and recommended in patients with MASLD, including those with compensated liver cirrhosis, and should not be withheld because of mild liver enzyme elevations.[26] Statin therapy reduces cardiovascular events and may also confer modest hepatic benefit. Blood pressure control, glycemic optimization, and smoking cessation should likewise be addressed systematically as part of an integrated care strategy.

Importantly, MASLD management should not be siloed from IBD care. Treatment decisions should be integrated into routine gastroenterology follow-up, with close coordination among IBD specialists, hepatologists, endocrinologists, and primary care providers. Minimizing cumulative corticosteroid exposure, optimizing IBD control, and selecting therapies that do not exacerbate metabolic risk are key complementary strategies. As pharmacologic options for MASH continue to evolve, patients with IBD and MASLD—particularly those with fibrosis—represent a priority group in whom early identification and treatment may substantially alter long-term hepatic and extrahepatic outcomes.

Clinical Implications and Future Directions

The recognition of MASLD as a common and clinically meaningful comorbidity in IBD has important implications for clinical practice (**Figure 2**). Universal screening is unlikely to be feasible or cost-effective. Instead, a targeted, risk-stratified approach focused on patients with metabolic risk factors, persistently abnormal liver enzymes, or incidental findings of steatosis on imaging is warranted. In this context, non-invasive tools, including serum-based scores and transient elastography, provide practical and scalable options for liver risk assessment within IBD clinics. MASLD management should be integrated into routine IBD care rather than treated as a parallel condition. Lifestyle interventions, optimization of metabolic risk factors, and minimization of corticosteroid exposure remain foundational. Key research priorities include defining IBD phenotypes at highest risk for fibrosis progression, clarifying interactions between IBD therapies and liver outcomes, and evaluating whether MASLD-targeted interventions improve hepatic and extrahepatic outcomes. As the global prevalence of both IBD and metabolic disease continue to rise, MASLD will increasingly shape long-term outcomes in this population. Recognizing and addressing MASLD as a common comorbidity represents a critical step toward more comprehensive, patient-centred IBD care.

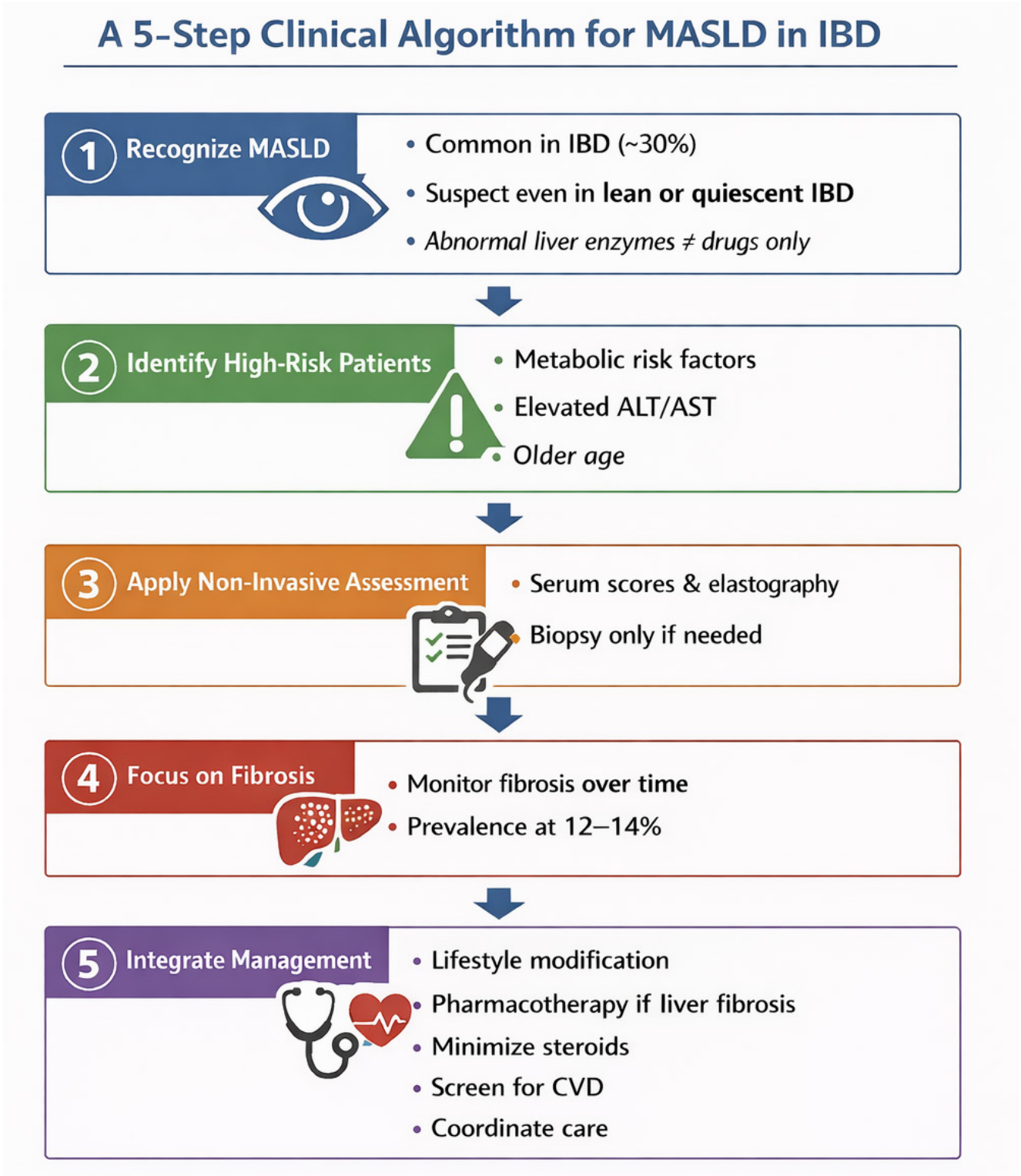


Figure 2. Five-step clinical algorithm for MASLD in IBD; *courtesy of Giada Sebastiani, MD, FAASLD.*

Abbreviations: CVD: cardiovascular disease; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **IBD:** inflammatory bowel disease; **MASLD:** metabolic-dysfunction-associated steatotic liver disease

Correspondence

Giada Sebastiani, MD, FAASLD
Email: giada.sebastiani@mcgill.ca

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ABOUT THE AUTHORS



Thilini Delungahawatta, MD, MSc

Dr. Thilini Delungahawatta is a Gastroenterology resident at McMaster University. She earned a Master of Science degree from McMaster University, completed her medical degree at the University of Limerick (Limerick, Ireland), and subsequently trained in Internal Medicine at MedStar Health–Georgetown University (MD, USA), where she participated in the Health Equity Track. Her academic interests now focus on inflammatory bowel disease (IBD), with particular emphasis on health equity and improving clinical outcomes in IBD populations.

Affiliations: *Department of Internal Medicine / Division of Gastroenterology McMaster University, Hamilton, ON, Canada*



Neeraj Narula, MD

Dr. Neeraj Narula is an Associate Professor of Medicine at McMaster University and Staff Gastroenterologist at Hamilton Health Sciences, with a clinical and research focus in Inflammatory Bowel Diseases (IBD). He is the director of the IBD clinic and IBD fellowship program at McMaster University. He completed the Present-Levison Advanced Inflammatory Bowel Diseases Fellowship at Mount Sinai Hospital (New York, NY) in 2015 and a Masters of Public Health at Harvard TH Chan School of Public Health (Boston, MA) in 2018. He has over 190 peer-reviewed publications and 4 book chapters. He has been awarded over $4 million in research funding and grants. His research interests are predominantly in clinical epidemiology, nutrition, and pharmaceutical trials in IBD. He has held leadership roles in national organizations including Past-President of the Canadian IBD Research Consortium and VP-Treasurer for the Canadian Association of Gastroenterology (CAG). His recent awards include the CAG Early Career Investigator Award (2025), the Canadian IBD Research Consortium Distinguished Achievement Award (2025), Crohn's and Colitis 360 Research Award (2025) and the McMaster Mid-Career Research Award (2025).

Affiliations: *Department of Internal Medicine / Division of Gastroenterology McMaster University, Hamilton, ON, Canada*

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Recent Clinical Trials in Acute Severe Ulcerative Colitis:

Can We Improve the Chances of Success of Corticosteroids and Rescue Therapies?

Thilini Delungahawatta, MD, MSc
Neeraj Narula, MD

Key Takeaways

1. Don't withhold intravenous (IV) steroids waiting for the stool infectious workup to come back. Many patients with infectious etiologies for exacerbation will require antimicrobials plus steroids to manage severe relapses.

2. When considering infliximab rescue therapy, a 10 mg/kg dose likely leads to higher response rates among patients with hypoalbuminemia (<25 g/L) and elevated CRP (≥50 mg/L) than a 5 mg/kg dose

3. JAK inhibitors can be considered as an adjunct to IV steroids, or as rescue therapy in steroid-refractory patients with a history of anti-TNF failure.

Introduction

Worldwide, there are over 5 million individuals with ulcerative colitis (UC), a chronic inflammatory disease of the large intestine, with rising incidence in developing countries.[1] Acute severe ulcerative colitis (ASUC) represents a life-threatening disease flare associated with an overall mortality of approximately 1% and necessitates hospitalization to prevent complications and avoid colectomy.[1,2] The diagnostic criteria for ASUC were first defined by Truelove and Witts in 1955 and include ≥6 bloody stools per day with systemic toxicity, such as fever (>37.8°C), tachycardia (>90 beats/min), anemia (<105 g/L), or elevated inflammatory markers (erythrocyte sedimentation rate >30 mm/hour; later modified to use C-reactive protein (CRP) >30 mg/L).[1] Approximately 20% of UC patients will require hospitalization for ASUC during their disease course, and up to 15% will experience recurrent episodes.[2] With the emergence of quick onset medical rescue therapies, continuous refinement of ASUC management algorithms is warranted to reduce disease morbidity and mortality.

First-Line Therapy

Intravenous corticosteroids (IVCS) remain the first-line therapy for ASUC; however, approximately one-third of patients fail to respond.[1,2] In a meta-regression analysis by Turner et al.,[3] daily corticosteroid doses across studies ranged from the equivalent of 40–100 mg of methylprednisolone for an average adult body weight of 70 kg. Doses exceeding 60 mg/day of methylprednisolone showed no additional benefit in reducing colectomy risk. Clinical response to IVCS is typically observed within one week in approximately 70% of patients, thus, early identification of steroid non-response is critical to facilitate timely initiation of second-line therapy.[4] The Oxford criteria[5] remain the most widely validated tool for predicting steroid failure at day 3 of treatment. According to these criteria, 85% of patients with more than eight stools per day, or three to eight stools per day accompanied by a CRP level >45 mg/L, ultimately require colectomy.

Recent evidence suggests a role for Janus kinase (JAK) inhibitors with IVCS during the initial management of ASUC. In a retrospective

case-control study of 40 biologic-experienced ASUC patients, adjunctive tofacitinib administered with intravenous methylprednisolone was associated with a significantly lower 90-day colectomy rate compared with controls (15% vs 20.4%; hazard ratio [HR]: 0.28), with the greatest benefit observed using three-times-daily dosing (HR: 0.11).[6] The TACOS single-centre randomized controlled trial further demonstrated that adding tofacitinib (10 mg three-times-daily for 7 days) to intravenous hydrocortisone significantly improved the clinical response at day 7 compared with placebo (83.0% vs 58.8%; odds ratio [OR]: 3.42), reduced the need for rescue therapy (OR: 0.27), and conferred sustained benefit through day 90.[7] Another multicenter observational study of 25 ASUC patients treated with upadacitinib and IVCS reported a 90-day colectomy rate of 24%, with 83% of patients who avoided colectomy achieving steroid-free clinical remission.[8]

In contrast, other corticosteroid-based combination strategies have not demonstrated clinical benefit in the management of ASUC. In a multicentre randomized controlled trial comparing IVCS alone versus IVCS with mesalamine (4 g/day), no significant differences were observed in clinical response rates (72.6% vs 76.3%; OR: 0.82), length of hospitalization, or colectomy rates through day 90.[9] Similarly, a randomized controlled trial from the United Kingdom evaluating adjunctive anakinra, an interleukin-1 receptor antagonist, failed to reduce the need for rescue therapy within 10 days or colectomy rates by day 98 compared with IVCS alone.[10] Furthermore, three randomized controlled trials (n = 144) evaluated adjunctive antibiotics with IVCS versus placebo in ASUC and demonstrated no significant difference in colectomy rates at hospital discharge (relative risk [RR]: 1.00).[11] Lastly, although exclusive enteral nutrition (EEN) appears safe and well tolerated, with a signal toward improved corticosteroid responsiveness in ASUC (75% vs 57% with standard care, $p = 0.051$),[12] pooled evidence shows no significant benefit in remission induction (risk ratio [RR] 1.15, 95% CI 0.71–1.85), corticosteroid failure (RR 0.76, 95% CI 0.48–1.20), or colectomy rates (RR 0.88, 95% CI 0.51–1.51) compared with standard care.[13] Furthermore, an RCT evaluating EEN with adjunctive albumin versus EEN alone, along with standard therapy, demonstrated no differences in corticosteroid failure (33.3% vs 41.9%, $p = 0.49$), colectomy (10% vs 9.7%, $p = 1$), or response to salvage therapy (88.9% vs 76.9%, $p = 0.62$).[14]

Rescue Therapy

Intravenous cyclosporine, a calcineurin inhibitor that suppresses T-cell activation via inhibition of interleukin-2 transcription, was first reported in 1990 to be effective for treating ASUC at a dose of 4 mg/kg/day.[15] This finding was subsequently confirmed in a randomized controlled trial of 20 corticosteroid-refractory patients, in which cyclosporine (4 mg/kg/day) induced clinical response in 9 of 11 patients (82%) within a mean of 7 days, compared with 0 of 9 patients receiving placebo ($P < 0.001$).[16] A subsequent randomized trial demonstrated comparable efficacy between cyclosporine doses of 2 mg/kg/day and 4 mg/kg/day, with evidence suggesting a potentially improved safety profile at the lower dose.[17]

The anti–tumour necrosis factor (TNF)-α monoclonal antibody infliximab represents another well-established rescue therapy.[18] In a pilot placebo-controlled study by Sands et al.,[18] 8 patients with severe steroid-refractory UC received a single infusion of infliximab (5–20 mg/kg), with 50% achieving treatment success at 2 weeks compared with no responders in the placebo group. Subsequently, the landmark randomized controlled trial by Järnerot et al.,[19] demonstrated that infliximab (5 mg/kg) significantly reduced colectomy rates compared with placebo (29% vs 67%; OR: 4.9).

In ASUC, disruption of the epithelial barrier and heightened inflammation lead to increased infliximab loss and accelerated drug clearance, resulting in low serum drug levels and providing a rationale for dose intensification of infliximab.[20] Interestingly, the PREDICT-UC study of steroid-refractory ASUC demonstrated similar clinical response rates at day 7 with infliximab dosed at 5 mg/kg and 10 mg/kg. Intensified or accelerated induction strategies did not improve outcomes at month 3 compared with standard dosing, despite earlier achievement of clinical and biochemical remission in post hoc analyses.[2] However, among patients with hypoalbuminemia (<25 g/L) and elevated CRP (≥50 mg/L) day-7 response rates were numerically higher with the 10 mg/kg dose compared with 5 mg/kg, suggesting a potential role for biomarker-guided dosing. Supporting this approach, a post-hoc analysis of PREDICT-UC demonstrated that lower infliximab concentrations on day 3 were

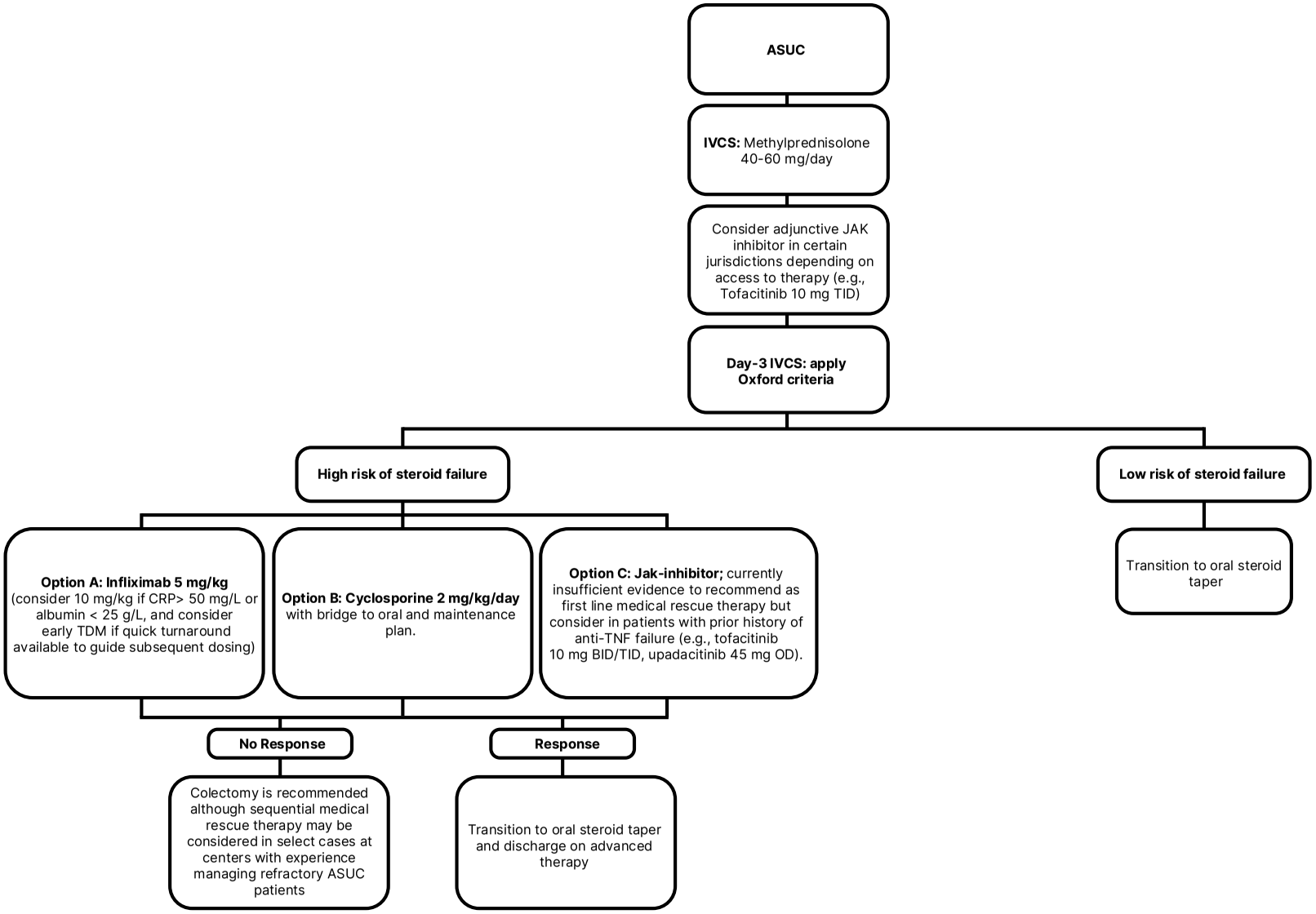


Figure 1. Treatment Algorithm for Hospitalized Patients with Acute Severe Ulcerative Colitis; *courtesy of Thilini Delungahawatta, MD and Neeraj Narula, MD.*

Abbreviations: ASUC: acute severe ulcerative colitis; **BID:** twice a day; **CRP:** C-reactive protein; **IVCS:** intravenous corticosteroids; **JAK inhibitor:** Janus kinase inhibitor; **OD:** once a day; TDM: therapeutic drug monitoring; **TID:** Three times a day; **TNF:** tumour necrosis factor

significantly associated with induction failure by day 14 and colectomy by month 3.[21] A day 3 infliximab level ≤53.6 µg/mL predicted induction failure (NPV 80.8%), while ≤57.9 µg/mL predicted colectomy (NPV 96.9%). Collectively, these findings suggest that early therapeutic drug monitoring or dosing strategies according to the individual patient's predicted drug clearance, may identify highrisk patients who could benefit from prompt dose intensification or early use of higher dosing. Indeed, patients with high early infliximab clearance showed higher day14 response rates when re-dosed early with 10 mg/kg compared with 5 mg/kg (38% vs 11%; RR: 3.43).[21] Nonetheless, data from a meta-analysis has shown no significant reduction in short-term colectomy risk with intensive infliximab dosing strategies compared with standard induction regimens (RR: 1.61; 95% confidence interval: 0.74–3.52).[22] Additionally, randomized trials summarized in recent meta-analyses have not shown a definitive difference between infliximab and cyclosporin, but the assessed observational studies suggest infliximab may be associated with improved treatment responses and a lower risk of colectomy at 12 months.[11,23,24]

JAK inhibitors such as tofacitinib and upadacitinib are approved for treating moderate to severe UC and possess several theoretical benefits that may support their use for ASUC, including rapid oral onset, efficacy irrespective of prior antiTNF exposure, and avoidance of the inflammationrelated colonic drug loss observed with biologics.[11] In a systematic review of 148 pooled cases of ASUC, tofacitinib was associated with colectomy-free survival of 86% at 90 days, clinical remission rates of up to 69%, and endoscopic remission in 55% of patients.[25] Additional prospective evidence comes from the multicenter, open-label TRIUMPH trial conducted across five Canadian hospitals, in which 24 hospitalized patients with steroid-refractory ASUC received tofacitinib 10 mg twice daily as rescue therapy; clinical response at day 7 was achieved in 58.3% of patients, with a mean time to response of 2.4 days.[26] Colectomy occurred in 25% of patients by 6 months, with no additional colectomies thereafter. Building on these results, the ongoing RESCUE-UC trial (**Clinicaltrials.gov** NCT06660693) is comparing an upadacitinib-first rescue strategy, with infliximab reserved for non-responders, to conventional infliximab-based rescue therapy in patients with steroid-refractory ASUC.

Conclusion

Despite major therapeutic advances, ASUC remains a highrisk clinical emergency requiring timely, evidencebased escalation of care. Intravenous corticosteroids remain the foundation of initial therapy; however, approximately onethird of patients fail to respond, underscoring the importance of early prognostic assessment and initiation of medical rescue therapy or surgery in non-responders. Adjunctive JAK inhibitors appear to enhance corticosteroid efficacy in ASUC, improving early clinical response and reducing need for rescue therapy, whereas other combination strategies including mesalamine, antibiotics, anakinra, and exclusive enteral nutrition (with or without albumin) have not demonstrated consistent benefit in corticosteroid response, remission rates, or colectomy outcomes. Recent clinical trials also highlight the growing role of JAK inhibitors as rescue options in those who are steroid-refractory, demonstrating rapid onset of action, encouraging remission rates, and potential synergy with corticosteroids. Among established rescue therapies, infliximab and cyclosporine show comparable short- and long-term efficacy, though emerging data suggest that personalized approaches, including biomarkerguided infliximab dosing and early therapeutic drug monitoring, may improve outcomes in selected highrisk patients. **Figure 1** provides a proposed algorithm for managing patients with ASUC based on the currently available evidence. Ongoing prospective trials will be essential for understanding how to position JAK inhibitors within treatment algorithms and in identifying strategies to maximize therapeutic success.

Correspondence

Neeraj Narula, MD
Email: neeraj.narula@medportal.ca

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ABOUT THE AUTHOR



Sunny Singh, MD, FRCPC

Dr. Sunny Singh is a Gastroenterologist at Vancouver General Hospital, where he plays a key role in the Inflammatory Bowel Disease clinic. Now based in Vancouver, Dr. Singh balances clinical excellence with a robust research portfolio. His academic work on inflammatory bowel disease (IBD) surgical outcomes and epidemiology has been featured in premier journals, including *Gastroenterology* and the *American Journal of Gastroenterology*. He remains at the forefront of the field through clinical trials focused on novel biologic therapies and long-term patient safety.

Affiliations: *Clinical Instructor, Department of Medicine, Division of Gastroenterology University of British Columbia, Vancouver General Hospital, Vancouver, BC*

Optimizing the Risk-benefit Conversation with Inflammatory Bowel Disease Patients

Sunny Singh, MD, FRCPC

Key Takeaways:

Contextualize Treatment Options Against the Risk of No Treatment:

A primary driver of therapeutic hesitancy is a disproportionate fear of medication side effects. Clinicians must counter this by clearly articulating the severe and often certain morbidity associated with untreated intestinal inflammation.

Leverage the Safety Profile of Selective Pathways:

The expansion of the therapeutic armamentarium allows for more personalized efficacy and safety considerations. Factor this in when helping patients choose appropriate treatment options (ie. Treatments that will treat extra-intestinal manifestations; treatments with impeccable safety profiles for those patients exceptionally anxious over side effects).

Utilize Structured Communication Models:

Effective communication is the cornerstone of the therapeutic alliance, yet many patients report that treatment discussions are often brief and lack depth. Adopting a structured framework can ensure a collaborative rather than directive process.

Address the Disconnect in Treatment Goals:

There is a significant disconnect between what clinicians measure and what patients experience. While doctors focus on objective markers like fecal calprotectin and endoscopic findings, patients are often most burdened by bowel urgency. Centring the risk-benefit conversation on the restoration of social and professional functioning—rather than just laboratory targets—can meaningfully improve patient satisfaction and long-term treatment adherence.

Introduction

The landscape of inflammatory bowel disease (IBD) management in Canada has undergone a significant transformation over the past decade, transitioning from a reactive approach focused on symptom suppression to a proactive, target-driven paradigm.[1] As of 2026, gastroenterologists are equipped with an unprecedented therapeutic armamentarium. This expansion introduces significant complexity into the shared decision-making process. The challenge lies in articulating the profound clinical benefits of advanced therapies while providing a nuanced, evidence-based contextualization of rare but serious risks. Contemporary IBD care therefore requires clinicians to act not only as prescribers but a sophisticated communicators capable of bridging the gap between objective clinical targets and the subjective priorities of each patient.

Articulating the Risks of Untreated Inflammatory Bowel Disease

A critical component of any risk-benefit discussion of advanced therapies is a clear explanation of the risks associated with untreated IBD. Therapeutic hesitancy, often driven by a patient's disproportionate fear of medication-related side effects, must be countered with an evidence-based discussion of the morbidity associated with uncontrolled intestinal inflammation.[2]

The natural history of Crohn's Disease (CD) indicates that approximately one third of patients' progress from an inflammatory phenotype to stricturing or penetrating complications within 5 years, with nearly half doing so over a 20-year period, based on population-based cohort data. This disease progression can result in bowel obstructions, often necessitating surgical resection. Furthermore, penetrating disease behaviour may lead to the formation of abscesses and fistulas.[3]

The risk of surgery remains a pivotal concern, with approximately 50% of IBD patients requiring at least one surgical intervention over their lifetime.[1] In moderate-to-severe CD, delaying initiation of advanced therapy is associated with significantly increased odds of undergoing surgery.[1] Conversely, early biologic intervention, initiated soon after diagnosis of CD has been shown to modify the disease course for up to 6 years, and can prevent hospitalization, the need for surgery, and disease progression as evidenced by the PROFILE Extend study.[4] Failure to control inflammation can also lead to short bowel syndrome following multiple resections, potentially even requiring long-term parenteral nutrition.

In ulcerative colitis (UC), the risks of untreated disease are often centred on the integrity of the colonic mucosa. Severe, uncontrolled inflammation can lead to opportunistic infections involving *Clostrioides difficile* and cytomegalovirus, or, toxic megacolon, thereby increasing the risk of perforation and sepsis. Patients with extensive, poorly controlled colitis are also at risk for severe rectal bleeding, which can lead to life-threatening anemia and the need for emergency colectomy.[5]

Patients with colonic IBD face an increased risk of colorectal cancer (CRC), which can be as much as fourfold higher than that of the general population if inflammation is not controlled. Achieving mucosal healing is currently recognized as a pivotal strategy for cancer prevention, as the risk of CRC is directly proportional to the duration and severity of the inflammatory burden.[6]

Recent research has illuminated the systemic consequences of chronic intestinal inflammation, including its role in atherosclerosis and increasing cardiovascular risk. IBD patients exhibit a significantly higher incidence of heart failure (37% increase) and atrial fibrillation, particularly during disease flares.[7] Furthermore, untreated disease is associated with metabolic disturbances and bone mineral density loss.

Anti-Tumour Necrosis Factor Therapies: Risks and Benefits

Anti-tumour necrosis factor (TNF) therapies remain among the most widely used advanced treatment options for patients supported by their long-standing record of efficacy and the availability of cost-effective biosimilars.

The primary clinical benefit of anti-TNF therapy is the induction and maintenance of deep remission. In CD, infliximab has demonstrated its ability to maintain clinical remission in 39% of patients with moderate-to-severe disease, compared to 21% in the placebo group, with approximately 50% achieving endoscopic remission by one year versus only 7.1% with placebo.[8] In UC, infliximab has shown a clinical response rate of 69% at week 8, versus 37% in the placebo group, and achieved mucosal healing in approximately 60% of patients during maintenance

therapy, compared to only 30% among placebo-treated patients.[9]

A critical benefit of anti-TNF therapy, specifically infliximab, is its status as the "gold standard" for managing fistulizing CD. Infliximab has shown complete fistula closure in 36% of patients at week 54, compared to 19% in the placebo group.[10] Beyond fistula control, achieving mucosal healing at one year with anti-TNF agents has been shown to be a potent predictor of reduced risks of colectomy and hospitalization in patients with IBD.[11] Lastly, the exceptional safety profile of anti-TNF therapy during pregnancy and breastfeeding supports their use as an attractive option for appropriate patients.[12]

The safety profile of anti-TNF therapies is defined primarily by a moderately increased risk of serious and opportunistic infections. These agents can reactivate latent infections, most notably tuberculosis and hepatitis B. Reports from some cohorts indicate tuberculosis reactivation rates of up to 6.4% among patients receiving anti-TNF therapy, reinforcing the need for screening for latent infections before treatment initiation.[13]

Malignancy risk, particularly lymphoma, remains a prominent concern for patients considering anti-TNF therapy. Current evidence suggests that anti-TNF monotherapy carries a low absolute risk of lymphoma, estimated at 0.41 cases per 1,000 person-years. However, the risk is substantially increased when these agents are used in combination with thiopurines (azathioprine or 6-mercaptopurine), with an adjusted hazard ratio (HR) of 6.11 (95% confidence interval [CI], 3.46–10.8).[14] Patients should also be monitored for non-melanoma skin cancers and for non-malignant complications including drug-induced lupus or demyelinating disease.

Vedolizumab: Risks and Benefits

Vedolizumab represents a significant advancement in therapy by offering a gut-selective mechanism of action, with its clinical utility best demonstrated in UC. In the landmark VARSITY trial, vedolizumab has shown superiority over adalimumab in achieving clinical remission at week 52 (31.3% vs 22.5%; p=0.006). Vedolizumab was also shown to achieve significantly higher rates of endoscopic improvement compared to adalimumab (39.7% vs 27.7%; p=0.0005).[15] These results have positioned vedolizumab as a favourable advanced therapy for moderate-to-severe UC.

In CD, real-world data indicate that vedolizumab is associated with favourable long-term effectiveness and treatment persistence. At one-year, clinical remission rates are approximately 39.4% (95% CI, 33.9–45.1), with mucosal healing rates of 40.6% (95% CI, 34.2–47.3).[16] Vedolizumab has also shown benefit in patients with draining fistulas, providing an alternative for those who fail or cannot tolerate anti-TNF agents.[17]

The gut-selective nature of vedolizumab results in a safety profile that may make it the most favourable among advanced therapies. Data from large-scale studies, including the VARSITY trial, have demonstrated low overall rates of adverse events (AEs) and serious infections, consistent with its minimal impact on systemic immune surveillance.[15]

Common side effects are generally mild and include nasopharyngitis, headache, and arthralgia. Rare reports of hepatic injury have been noted, though they are infrequent and typically reversible upon discontinuation. Infusion-related reactions occur in approximately 4% of patients and are usually manageable with standard infusion protocols.[18]

Ustekinumab: Risks and Benefits

Ustekinumab is a human monoclonal antibody that targets the shared p40 subunit of both interleukin (IL)-12 and IL-23. A distinguishing clinical feature of ustekinumab is its durability and efficacy in treatment-experienced patients. In CD, real-world data indicate that amongst those who have failed anti-TNF therapy, 46% (at 8 week interval dosing of ustekinumab) of patients achieved steroid-free remission at one year.[19] In UC, the pivotal UNIFI trial demonstrated that ustekinumab was significantly more effective than placebo in inducing and maintaining clinical remission and endoscopic healing. Notably, approximately 55% of patients in the UNIFI maintenance study remained in clinical remission through nearly 4 years of therapy.[20]

Ustekinumab is widely regarded as having an exceptional safety profile. Evidence from large-scale clinical trials and real-world cohorts show significantly lower rates of serious infections compared to anti-TNF therapies. Long-term monitoring has also shown no increased risk of lymphoma or other malignancies compared to the general population. Common AEs are typically mild, including nasopharyngitis, upper respiratory

tract infections, headache, and arthralgia.[21] While patients are screened for latent tuberculosis before initiation, the risk of reactivation is considered lower than that observed with anti-TNF agents.

IL-23 Inhibition: Risks and Benefits

Risankizumab, mirikizumab, and guselkumab selectively target the p19 subunit unique to IL-23, thereby blocking the pathogenic Th17 pathway while sparing the IL-12 pathway that contributes to host defence against intracellular pathogens and tumour surveillance.[22]

Emerging evidence suggests that this selective blockade of IL-23—sparing the IL-12 pathway—offers distinct therapeutic advantages in both efficacy and safety.[23] As a therapeutic class, p19 inhibitors have demonstrated robust efficacy to induce and maintain clinical remission, promote deep mucosal healing, and improve patient-reported outcomes while maintaining a favourable safety profile compared to prior biologics and small molecules.[24]

The risankizumab clinical program has established its role in both bio-naive and bio-experienced patients. In the ADVANCE and MOTIVATE Crohn's disease induction trials, risankizumab showed significant superiority over placebo in achieving clinical remission and endoscopic response at week 12. A subsequent meta-analysis of these trials confirms a strong treatment effect, with an odds ratio of 4.11 (95% CI, 2.9–5.9; $p<0.001$) for achieving endoscopic remission, highlighting its potency in inducing mucosal healing.[25]

The VIVID-1 trial evaluated mirikizumab in patients with CD, including a cohort exposed to ustekinumab. Mirikizumab achieved significantly superior clinical remission rates compared to placebo (45.4% vs 19.6%) and achieved endoscopic response rates comparable to ustekinumab in the active-comparator arm. Notably, mirikizumab was associated with a high rate of corticosteroid-free clinical remission, a critical long-term goal for CD management.[26]

Guselkumab demonstrated superiority over ustekinumab in achieving endoscopic remission in patients with CD.[27] More recently, the GRAVITI and ASTRO studies explored a fully subcutaneous induction regimen for guselkumab in IBD, demonstrating that subcutaneous delivery could achieve clinical and endoscopic outcomes comparable to traditional intravenous induction. This flexibility in route of administration represents a significant benefit for patient independence and healthcare resource utilization.[28,29]

In UC, the IL-23 pathway is a central mediator of neutrophilic infiltration and epithelial barrier destruction. Selective p19 inhibitors have shown a unique ability not only to resolve symptoms but also to achieve histologic normalization, a target increasingly linked to reduced risks of hospitalization and colectomy.[30]

As a therapeutic class, IL-23 p19 inhibitors are among the safest advanced therapies currently available for IBD.[31] Their use avoids the potential risks associated with anti-TNF agents (e.g., serious infections, tuberculosis reactivation, and demyelinating disease) and Janus Kinase (JAK) inhibitors (e.g., major adverse cardiovascular events (MACE), venous thromboembolism, and herpes zoster [shingles]).

Across phase 3 trials, the overall incidence of AEs with p19 inhibitors has been comparable to placebo. Serious infections are rare, occurring at rates of approximately 1.1% to 1.5% per 100 patient-years, which is not significantly higher relative to placebo groups. The most common AEs are typically mild and include nasopharyngitis, headache, and injection-site reactions.[32]

Janus Kinase Inhibitors: Risks and Benefits

JAK inhibitors are orally administered small molecule therapies that block intracellular signalling of multiple pro-inflammatory cytokines. Their rapid onset and high efficacy in refractory disease position them as a critical tool, particularly for patients who prefer oral therapy or who have failed multiple advanced therapies.

Tofacitinib provides an exceptionally rapid onset of symptomatic response. It is highly effective in inducing remission among UC patients, even those who are refractory to anti-TNF therapies.[33] A significant side effect is a dose-dependent increase in the risk of herpes zoster, accordingly, vaccination with the recombinant zoster vaccine is highly recommended before starting therapy. Tofacitinib has also been associated with increases in serum lipid levels (low density lipoprotein and high density lipoprotein cholesterol),[33] although this has not been definitively linked to increased cardiovascular events in IBD populations.

Upadacitinib is a preferentially selective JAK1 inhibitor approved for the treatment of both CD

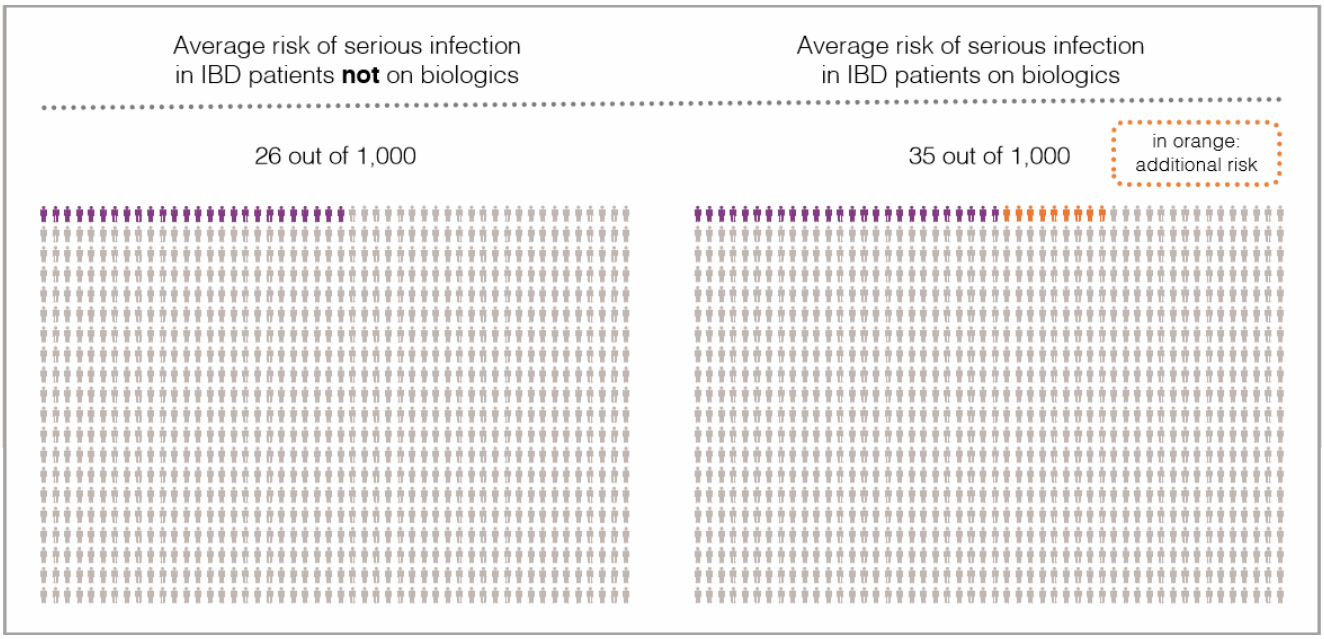


Figure 1. Average risk of serious infection in inflammatory bowel disease (IBD) patients.[43]

and UC. Real-world meta-analyses have shown that upadacitinib is effective at achieving clinical remission at week 8 in 69% of patients with highly refractory UC.[34] In addition, observational data in difficult-to-treat CD patients demonstrate clinical remission rates of approximately 50% at week 12.[35]

The safety profile of upadacitinib is consistent with the JAK inhibitor class, with reported increased risks of acne, herpes zoster, and elevated creatine phosphokinase.[36] While it carries the class-wide "Black-Box Warning," recent data suggests its high selectivity may mitigate some off-target risks.[37]

The safety discussion of JAK inhibitors has been shaped by the ORAL Surveillance study, which reported a higher incidence of MACE and venous thromboembolism (VTE) with tofacitinib compared to TNF inhibitors.[38] However, these findings require careful contextualization, as the study population was enriched for rheumatoid arthritis patients and the observed risks have not been consistently replicated in the IBD population. In contrast, a recent systematic review and meta-analysis that included 42 head-to-head studies and over 813,000 patients found no meaningful difference in the risk of MACE, serious infections, or malignancy between JAK inhibitors and anti-TNF therapies across the general population. While a slightly higher risk of VTE was observed (HR 1.26, 95% CI, 1.03–1.54; p=0.03), this was pronounced in rheumatoid arthritis patients, with no significant increase in VTE risk detected among IBD patients compared to those receiving anti-TNF therapies.[39]

Sphingosine 1-Phosphate Receptor Modulators: Risks and Benefits

Sphingosine 1-Phosphate (S1P) receptor modulators offer a novel mechanism for UC by binding to S1P receptors on lymphocytes and preventing their egress from lymph nodes, thereby limiting lymphocyte trafficking to the inflamed gut. Ozanimod and etrasimod have been indicated for use in moderate-to-severe UC.

Ozanimod was the first S1P receptor modulator approved for the treatment of moderate-to-severe UC. In a clinical trial, ozanimod demonstrated higher clinical remission rates at week 52 compared with placebo (37% vs 18.5%).[40] Ozanimod requires a 7-day dose titration to mitigate the risk of transient bradycardia. It has a long half-life, with lymphocyte counts returning to the normal range only 1–3 months after treatment discontinuation. Rare AEs include macular edema and liver enzyme elevations.[40]

Etrasimod is the second selective S1P modulator approved for use in UC and has shown superior clinical remission rates compared to placebo (32% vs 6.7%).[41] Unlike ozanimod,

etrasimod does not require a titration period and has a much shorter half-life, with absolute lymphocyte counts typically recovering within 1–2 weeks of discontinuing therapy. Reported adverse effects include minor transient bradycardia, rare atrioventricular block, and macular edema.

As a therapeutic class, S1P therapies are considered exceptionally safe. A meta-analysis published in late 2025 analyzed data from six phase 3 randomized controlled trials involving 1,744 IBD patients. While overall AEs were slightly higher than placebo (risk ratio 1.18, 95% CI 1.07–1.30; p=0.001), there were no significant differences in the risk of serious infections, cardiac events, or mortality.[42]

Evidence-Based Strategies for Risk and Benefit Communication

Effective communication is the cornerstone of the therapeutic alliance in IBD. It would come as no surprise to many clinicians that many patients report that conversations about treatment are limited in depth and brief. To optimize patient outcomes and adherence, adopting a structured communication framework represents a practical and effective strategy.

Structured Frameworks: The Three-Talk Model and BRAN

1. ***The Three-Talk Model:*** This model ensures the decision is a collaborative process rather than a directive one. The model includes three deliberate stages.
   - **Team Talk:** Establishes that the clinician and patient are working together toward a common goal.
   - **Option Talk:** Compares the benefits and risks of different alternatives using clear, understandable language.
   - **Decision Talk:** Culminates in selecting a treatment choice based on the patient's personal values and preferences.
2. ***The BRAN Framework:*** Provides a simple mnemonic to ensure all critical facets of a treatment discussion are addressed:
   - **B**enefits: What are the specific gains?
   - **R**isks: What are the potential harms, and how rare are they?
   - **A**lternatives: What other medications or surgical options are available?
   - **N**othing: What happens if we do not treat the inflammation?

Visual Communication Strategies

Visual aids are highly effective in facilitating these discussions. Tools such as Paling palettes allow clinicians to visually display the high likelihood of therapeutic success versus the extreme rarity of serious harm. Online tools such as IBD&me[43] provide individualized three-year risk visualizations, which can help patients grasp the long-term impact of their therapeutic choices.

A significant disconnect persists in IBD care: while clinicians focus on objective disease markers such as C-reactive protein and endoscopic findings, patients report that they are burdened by bowel urgency.[44] This urgency leads to significant social withdrawal and embarrassment, yet it is often overlooked during routine appointments. Notably, nearly 40% of patients with moderate-to-severe IBD report wearing protective pads or diapers due to the fear of incontinence. Directly addressing these quality-of-life concerns and centring the benefit-risk conversation on the restoration of social and professional functioning can meaningfully improve patient satisfaction and treatment adherence.

The management of IBD in 2026 demands more than clinical expertise alone; it requires a sustained commitment to evidence-based shared decision-making. By applying structured communication frameworks and clearly conveying the high likelihood of success with contemporary treatments versus the severe, certain risks of uncontrolled inflammation, gastroenterologist can empower patients to regain control of their lives. Ultimately, success is defined by the restoration of quality-of-life, achieved through a robust therapeutic alliance and a shared understanding of the diverse therapeutic landscape.

Correspondence

Sunny Singh, MD, FRCPC
Email: Sunny@westcoastgi.ca

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ABOUT THE AUTHORS



Ali Alharethi, MD, FRCPC

Dr. Ali Alharethi is an Inflammatory Bowel Disease Fellow at McMaster University in Hamilton, Ontario, Canada. He is board certified in Internal Medicine and Gastroenterology and holds the Fellowship of the Royal College of Physicians of Canada (FRCPC).

Affiliations: *Department of Medicine (Division of Gastroenterology), McMaster University*



Abdulmalik Alsabban, MD

Dr. Abdulmalik Alsabban is an Inflammatory Bowel Disease Fellow at McMaster University in Hamilton, Ontario, Canada. He completed prior training in gastrointestinal motility and is board-certified in Internal Medicine and Gastroenterology.

Affiliations: *Department of Medicine (Division of Gastroenterology), McMaster University*



John K. Marshall, MD, MSc, FRCPC

Dr. Marshall is a Professor of Medicine and Director of the Division of Gastroenterology at McMaster University, as well as a consultant gastroenterologist at Hamilton Health Sciences in Hamilton, Ontario. He completed his B.A. and M.D. at Queen's University and then undertook his residency training and M.Sc. in Clinical Epidemiology & Biostatistics at McMaster University. He is a Full Member of the Farncombe Family Digestive Health Research Institute. His publications include over 350 academic papers and book chapters. Dr. Marshall was the founding Editor-in-Chief of the *Journal of the Canadian Association of Gastroenterology (JCAG)*. He is also an Associate Editor of *ACP Journal Club* and an Editorial Board Member for the *Journal of Crohn's and Colitis*.

Affiliations: *Department of Medicine (Division of Gastroenterology), McMaster University*
Farncombe Family Digestive Health Research Institute, McMaster University

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2025: The Inflammatory Bowel Disease (IBD) Year in Review

Ali Alharethi, MD, FRCPC
Abdulmalik Alsabban, MD
John K. Marshall, MD, MSc, FRCPC

Whole Food Diet Induces Remission in Children and Young Adults with Mild to Moderate Crohn's Disease and Is More Tolerable Than Exclusive Enteral Nutrition: A Randomized Controlled Trial. Aharoni-Frutkoff Y, et al. Gastroenterology. 2025;169(7):1462–1474.

Effective and well-tolerated dietary therapies for Crohn's disease have long been sought by both patients and providers. In pediatric inflammatory bowel disease (IBD), exclusive enteral nutrition (EEN) has gained traction and is recommended by treatment guidelines.[1,2] However, it has not been broadly implemented in adults due to poor tolerability, social constraints, and challenges with long-term adherence.[3,4] Consequently, there is a growing interest in dietary interventions that offer efficacy while imposing a lower burden on patients.

TASTI-MM is the first randomized controlled trial to provide evidence supporting an exclusive whole-food dietary strategy to treat active Crohn's disease.[5] Previous evidence for whole-food approaches was limited to observational cohorts.[6-9] This trial sought to determine whether a whole food diet could enhance compliance in comparison with EEN, improve disease activity, and modify the microbiome with the goal of sustained disease control.[10]

TASTI-MM employed an open-label design with blinded outcome assessment. Biologic-naive children and young adults (age 6–25 years) with mild-to-moderate Crohn's disease were randomized to either the Tasty & Healthy diet or EEN for an 8-week induction period. The Tasty & Health diet excludes gluten, animal fat (i.e. red meat and dairy, except plain yogourt) and processed foods. All participants received structured weekly dietary support to promote adherence and monitoring. The primary endpoint was tolerability, while secondary endpoints included symptoms, biochemical markers, and changes in the gut microbiome.

The key finding of the TASTI-MM trial was that the whole-food dietary intervention was significantly more tolerable than EEN, with tolerability rates of 88% versus 52%, respectively ($p<0.001$) with no significant differences in symptomatic remission rates or objective markers of inflammation. This suggests that improved tolerability was not accompanied by reduced clinical effectiveness. While EEN led to a reduction in microbiome alpha-diversity, the whole-food diet led to enrichment of commensal microbial taxa and a reduction in species associated with gut inflammation. Taken together, these observations suggest that whole-food dietary therapy may achieve remission as effectively as EEN, while improving adherence and creating a healthier gut microbiome environment.

Although TASTI-MM was generally well designed, several limitations warrant consideration. The trial did not assess endoscopic endpoints, enrolled only patients with mild-to-moderate uncomplicated disease, and evaluated induction rather than long-term maintenance of remission. Furthermore, successful implementation of any dietary regimen requires intense dietetic education and support, which can vary in feasibility across healthcare settings. Despite these concerns, TASTI-MM represents a significant advance in nutritional therapy for Crohn's disease, offers an alternative for patients who are either unwilling or unable to follow enteral feeding protocols, and should encourage multidisciplinary care with a renewed interest in nutritional stewardship.

Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials. Colombel JF, et al. Clinical Gastroenterology and Hepatology. 2025;23(6):1019–1029.

Fistulas are among the most challenging clinical manifestations of Crohn's disease, affecting up to half of patients throughout the course of their disease and exerting a substantial impact on their quality-of-life.[11-13] Current approaches combine medical therapy with surgical interventions such as seton placement or fistula repair.[14] Among medical therapies, only infliximab has demonstrated efficacy in controlled clinical trials for fistulizing disease.[15,16] Responses to treatment are often incomplete, creating a significant unmet need.[17,18]

Upadacitinib, a selective Janus kinase 1 (JAK1) inhibitor, has demonstrated efficacy across both clinical and endoscopic outcomes in moderate-to-severe luminal Crohn's disease.[19] Colombel et al conducted a post hoc analysis of the U-EXCEL and U-ENDURE trials, in which adults with moderately-to-severely active Crohn's disease were randomized to either receive once-daily upadacitinib 45 mg or placebo for a 12-week induction period.[20] Those who achieved a clinical response were subsequently re-randomized to either placebo, upadacitinib 15 mg, or upadacitinib 30 mg daily for 52 weeks of maintenance therapy. This post hoc analysis examined fistula-related outcomes among the subset of patients with penetrating disease at baseline.

Among 1,021 patients enrolled in the induction trials, 143 had active fistulas at baseline, the majority of which were perianal. Over the 12-week induction period, cessation of perianal fistula drainage was achieved in 44.7% of patients with upadacitinib versus 5.6% with placebo (p=0.003). Similarly, closure of external fistula orifices in 22.1% of patients in the upadacitinib group versus 4.8% of those receiving placebo (p=0.013). These efficacy signals were similar across fistula locations. Maintenance therapy with upadacitinib showed a sustained effect through week 52 with respect to drainage resolution and fistula closure. The safety profile of upadacitinib was consistent with prior trials, with comparable rates of serious adverse events and no new safety signals identified.

Of note, the effect sizes for fistula outcomes in the induction phase of this trial are broadly comparable to those reported in the original infliximab trials.[15,16] The maintenance outcomes are more difficult to assess, as re-randomization was driven by luminal rather than fistula response. Nonetheless, these data support upadacitinib as an effective option for patients with perianal fistulizing Crohn's disease, particularly those who fail or do not tolerate anti-tumour necrosis factor (TNF) therapies.

Efficacy and Safety of Guselkumab Subcutaneous Induction and Maintenance in Participants with Moderately to Severely Active Crohn's Disease: Results from the Phase 3 GRAVITI Study. Hart A, et al. Gastroenterology. 2025;169(2):308–325.

The GALAXI trials established the efficacy of the interleukin (IL)-23 inhibitor guselkumab for the treatment of moderate-to-severe Crohn's disease.[21,22] The study protocol employed a regimen of intravenous induction dosing followed by subcutaneous maintenance dosing. While intravenous induction dosing of advanced therapy has long been popular among clinicians for its perceived potency, some patients prefer subcutaneous delivery, and access to infusion services can be limited in certain healthcare settings.

GRAVITI was a randomized, double-blind, placebo-controlled, multicentre trial designed to evaluate the efficacy and safety of subcutaneous guselkumab for both induction and maintenance therapy in moderately-to-severely active Crohn's disease. The study used a treat-through design, which has been argued to more closely reflect real-life clinical decision-making. Participants were randomized in a 1:1:1 ratio to receive one of two guselkumab dosing regimens or placebo. The guselkumab regimens were 400 mg administered every 4 weeks for a 12-week induction period, followed by maintenance dosing of either 100 mg every 8 weeks or 200 mg every 4 weeks. Corticosteroid tapering was permitted after week 12. The two co-primary endpoints were clinical remission and endoscopic response at week 12, in alignment with the STRIDE consensus.[23] Multiplicity-controlled secondary endpoints included clinical remission and endoscopic response at week 48.

Subcutaneous guselkumab achieved clinical remission in 56.1% of patients, versus 21.4% on placebo (p<0.001), as well as superior endoscopic response in 41.3% versus 21.4% on placebo (p<0.001). These efficacy benefits extended through week 48, with clinical remission achieved in 60.0% of patients receiving 100 mg every 8 weeks and 66.1% of those receiving 200 mg every 4 weeks, versus 17.1% on placebo (both p<0.001). Endoscopic response at week 48 was achieved by 44.3% in the lower maintenance dose group and 51.3% in the higher dose group, versus 6.8% with placebo (both p<0.001). Efficacy was maintained across subgroups stratified by prior biologic exposure; however, those with prior biologic exposure were more likely to achieve endoscopic outcomes at week 48 with the higher maintenance dose. The overall safety profile was excellent, with no meaningful differences in adverse outcomes between guselkumab treatment and placebo, consistent with the established safety profile of IL-23 inhibitors across all indications.

The GRAVITI trial further confirms the efficacy of guselkumab for the treatment of Crohn's disease with clinically meaningful gains in both clinical and endoscopic outcomes compared with placebo. Although cross-trial comparisons should be interpreted with caution, the outcome rates observed in GRAVITI are broadly comparable to those reported using intravenous guselkumab induction in the GALAXI trial.[21,22] Avoidance of intravenous dosing may better align with some patients' preferences and may facilitate access in many healthcare settings. GRAVITI also demonstrated efficacy of two maintenance dosing strategies, with one providing four-fold higher drug exposure. How clinicians and patients will decide between intravenous and subcutaneous induction, and between two doses for maintenance therapy, remains an important question for real-world practice.

Collectively, the GRAVITI and GALAXI trials provide helpful insights into the use of guselkumab in the treatment of Crohn's disease; however, results from other trials of this agent are eagerly awaited. These include DUET-CD, which evaluates the efficacy and safety of guselkumab in combination with the TNF antagonist golimumab,[24] and a planned head-to-head comparison of guselkumab and risankizumab, another inhibitor of IL-23.

Vedolizumab to Prevent Postoperative Recurrence of Crohn's Disease (REPREVIO): A Multicentre, Double-Blind, Randomised, Placebo-Controlled Trial. D'Haens G, et al. Lancet Gastroenterology and Hepatology. 2025;10(1):26–33.

Although overall rates of surgery for Crohn's disease have declined over time,[25] resection is still required for patients with refractory or complicated disease. Furthermore, emerging data support early ileocolic resection as an effective first-line strategy for patients with limited ileal disease.[26,27] A major and persisting challenge after resection and reanastomosis is the high rate of disease recurrence. Without therapy, approximately 80% of patients experience endoscopic recurrence, 50% experience symptomatic recurrence, and up to 20% will require a second surgery.[28] Consequently, both clinicians and patients must consider strategies to reduce these risks in the post-operative setting.

The REPREVIO trial assessed the efficacy and safety of vedolizumab, a monoclonal antibody targeting the α4β7 integrin, as secondary prophylaxis in patients undergoing ileocolic resection for Crohn's disease.[29] Adults at increased risk of recurrence (e.g., active smokers, penetrating disease phenotype, prior exposure to TNF antagonists, or more than one previous resection) were randomized within 4 weeks of ileocolonic resection to receive either intravenous vedolizumab (300 mg every 8 weeks without loading doses) or placebo. Ileocolonoscopy was performed after 26 weeks to assess endoscopic recurrence according to the modified Rutgeerts score. The primary endpoint compared the distribution of Rutgeerts scores between treatment groups using non-parametric analysis, while the first-ranked secondary endpoint was the proportion of patients with severe endoscopic recurrence, defined as a modified Rutgeerts score ≥i2b.

Both the primary endpoint and the first-ranked secondary endpoint significantly favoured vedolizumab. Importantly, severe endoscopic recurrence occurred in only 23.3% of patients receiving vedolizumab versus 62.2% assigned to placebo (p=0.0004). Interestingly, rates of clinical recurrence (defined as an increase in the Crohn's Disease Activity Index score of more than 70 points) were similar between the treatment arms, occurring

in 20.9% with vedolizumab versus 21.6% with placebo (p=0.94). No concerning safety signals were observed.

REPREVIO is the first major trial of biologic therapy for post-surgical prophylaxis in Crohn's disease to meet its primary endpoint, representing a major advance in this setting. However, it is worth noting that its findings align well with those of the PREVENT trial.[30] Although PREVENT did not demonstrate improvement in clinical outcomes (its primary endpoint) it did show a clinically and statistically significant reduction in endoscopic recurrence.

The post-operative setting is arguably the best human model of early Crohn's disease, a setting in which most advanced therapies would likely show benefit. Although the strongest evidence now favours vedolizumab, selection of therapy should also consider patient preferences and prior treatment exposures. It should also be noted that REPREVIO enrolled only patients at increased risk of recurrence, and those at low-risk may reasonably elect not to start any therapy after surgery. Regardless of the initial management strategy, the POCER trial demonstrated the importance of scheduled endoscopic surveillance to assess for recurrence and inform treatment intensification.[31] These approaches are supported by recent clinical practice guidelines from the American College of Gastroenterology.[32]

Mucosal Healing with Vedolizumab in Patients with Chronic Pouchitis: EARNEST, a Randomized, Double-Blind, Placebo-Controlled Trial. Jairath V, et al. Clinical Gastroenterology and Hepatology. 2025;23(2):321–330.

Chronic pouchitis is one of the most difficult long-term complications following restorative proctocolectomy with ileal pouch-anal anastomosis among patients with ulcerative colitis. Although this procedure improves quality-of-life for many patients with medically refractory disease, most patients will experience at least one episode of pouchitis and a significant minority will develop chronic and disabling antibiotic-refractory or antibiotic-dependent pouchitis.[33] Historically, high-quality evidence to guide treatment for these patients has been lacking.[34]

EARNEST evaluated vedolizumab for the treatment of chronic pouchitis. Its primary efficacy results have shown that vedolizumab was more likely than placebo to induce remission according to the modified Pouchitis Disease Activity Index (mPDAI) (31.4% vs. 9.8%; p=0.01), with this benefit appearing to extend to week 34.[35] These findings led to the approval of vedolizumab for the treatment of pouchitis in many jurisdictions.

The additional analyses reported by Jairath et al examined the endoscopic and histologic outcomes in the EARNEST study cohort. All participants underwent pouchoscopy with biopsy at baseline and at weeks 14 and 34. In the absence of a validated endoscopic scoring for pouchitis, the authors used a modified version of the Simple Endoscopic Score for Crohn's Disease (SES-CD),[36] with endoscopic healing defined as a segmental score of 0. Histologic activity was assessed using the histologic component of the mPDAI,[37,38] with healing defined as a score of 0 or 1 (no or mild polymorphonuclear leukocyte infiltrate without ulceration). The outcome of mucosal healing required fulfillment of both endoscopic and histologic criteria.

The study population consisted of adults with a baseline mPDAI score of at least 5 and an endoscopic subscore of at least 2. Participants were randomized to receive either intravenous vedolizumab (300 mg at weeks 0, 2, and 6, followed by dosing every 8 weeks) or placebo. Both endoscopic and histologic outcomes were read centrally at weeks 14 and 34. Additional outcomes included patient-reported quality-of-life measured using the Inflammatory Bowel Disease Questionnaire, and biomarkers such as fecal calprotectin.

Both endoscopic and histologic outcomes favoured vedolizumab therapy over placebo. Remission according to the SES-CD was achieved in 23.8% of those receiving vedolizumab versus 7.5% with placebo, while mucosal healing was achieved in 16.7% versus 2.5%, respectively. A range of other endoscopic outcomes including the number of ulcers, absence of ulceration, and the proportion of mucosal surface with ulceration also favoured vedolizumab therapy. Of note, patients who achieved mucosal healing at week 14 had subsequently lower disease activity and improved quality-of-life scores compared with those who did not.

EARNEST is the only trial of advanced therapy to show benefit in the treatment of pouchitis and has established vedolizumab as the preferred treatment option for patients with antibiotic failure or antibiotic dependence. This trial addresses an important evidence gap in an

understudied population. An enduring challenge in the management of pouchitis is the frequent disconnect between symptoms, endoscopic findings, and histologic activity, with the natural history and long-term sequelae of endoscopic ulceration within the pouch remaining poorly understood. EARNEST makes an important contribution by demonstrating that both endoscopic and histologic activity can respond to medical therapy, and by showing that early endoscopic response predicts a more favourable subsequent clinical course. Nevertheless, further validation of endoscopic and histologic indices is still needed, and long-term data from this and other clinical cohorts will be essential to better define the long-term trajectory of refractory pouchitis.

Correspondence

John K. Marshall, MD, MSc, FRCPC
Email: marshllj@mcmaster.ca

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ABOUT THE AUTHORS



Ashvin Varadharajan, MD

Dr. Ashvin Varadharajan is a fellow in the Division of Gastroenterology in the Department of Medicine at Washington University in St. Louis, St. Louis, Missouri. He holds a medical degree from Armed Forces Medical College in India, and his research interests include therapeutic outcomes and risk stratification in patients with inflammatory bowel disease, as well as the application of advanced imaging techniques for disease phenotyping in IBD.

Affiliations: *Division of Gastroenterology, Washington University School of Medicine, Saint Louis, Missouri, USA.*



Parakkal Deepak, MD, MS, FACG

Dr. Parakkal Deepak is currently a physician-scientist in the Inflammatory Bowel Disease (IBD) Center in the Division of Gastroenterology at the Washington University School of Medicine (WUSM) in St. Louis, Missouri where he is a Professor of Medicine, Co-Director of the IBD center and Director of Clinical and Translation research for the Division of Gastroenterology. His research focus is cardiometabolic syndrome in IBD where his group has made novel observations in prevalence of MASLD, risk of cirrhosis, performance of current ASCVD prediction tools and is investigating the impact of GLP1RAs in patients with IBD through a prospective study funded by Helmsley Trust.

Affiliations: *Division of Gastroenterology, Washington University School of Medicine, Saint Louis, Missouri, USA.*

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The Risk of Cardiovascular Complications in Patients with Inflammatory Bowel Disease

Ashvin Varadharajan, MD
Parakkal Deepak, MD, MS, FACG

Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis (UC), is a chronic, relapsing-remitting inflammatory condition of the gastrointestinal tract. Beyond intestinal involvement, IBD commonly affects diverse organ systems in the body, making it a 'systemic disease with intestinal predominance'.

While extraintestinal manifestations are primarily due to immune-mediated involvement of organ systems, IBD also exerts systemic effects on the cardiovascular system. Emerging data suggests an association between IBD and myocardial infarction (MI), ischemic heart disease, cerebrovascular accidents, and other major adverse cardiovascular events (MACE).[1] As a result, the pathophysiological basis of cardiovascular complications in IBD has been a subject of growing investigation.

Pathophysiological Basis of Cardiovascular Risk in IBD

The inherent risk of cardiovascular complications in IBD stems from the effects of chronic systemic inflammation on the endothelium and coagulation pathways (**Figure 1**).

Endothelial Dysfunction

The chronic inflammatory state characteristic of IBD leads to persistently increased levels of proinflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. These mediators induce endothelial activation and increased vascular permeability, thereby contributing to the development and progression of atherosclerotic plaque. In parallel, elevated reactive oxygen species levels lead to the formation of oxidated lipoproteins, upregulation of metallic metalloproteinases, and foam cell formation, collectively accelerating atherogenesis and impaired plaque stability.[2]

Hypercoagulable and Prothrombotic State

Elevated levels of proinflammatory cytokines upregulate procoagulant factors, such as fibrinogen, coagulation factors V, VIII and IX, while downregulating anticoagulant proteins (antithrombin-III, protein-S), leading to an increased risk of venous thrombotic events. Endothelial injury and dysfunction promote platelet activation and aggregation, resulting in the formation of microthrombi. Additionally, cytokine-mediated inhibition of the enzyme arginase inhibit leads to a decrease in production of endothelial nitric oxide (NO). Given NO's protective role in inhibiting platelet aggregation and leukocyte adhesion, this decrease corresponds to a worsening prothrombotic state.[3]

Gut Barrier Dysfunction

Chronic inflammation in IBD leads to a decrease in beneficial gut bacterial groups such as *Firmicutes, Bacteroidetes*, and *Bifidobacterium*, alongside an increase in detrimental groups, such as *Enterobacteriaceae, Bacteroides fragilis*, and *Escherichia coli*. This imbalance results in gut barrier dysfunction and facilitates translocation of bacterial lipopolysaccharides and trimethylamine N-oxide, which promote atherosclerosis and worsen cardiac health. Genetic susceptibility may further potentiate these effects. Mutations in *NOD2*, an intracellular sensor of bacterial peptidoglycan, can lead to impaired mucosal integrity and promote gut barrier dysfunction.[4]

A meta-analysis revealed that patients with IBD have a higher risk of developing cardiovascular

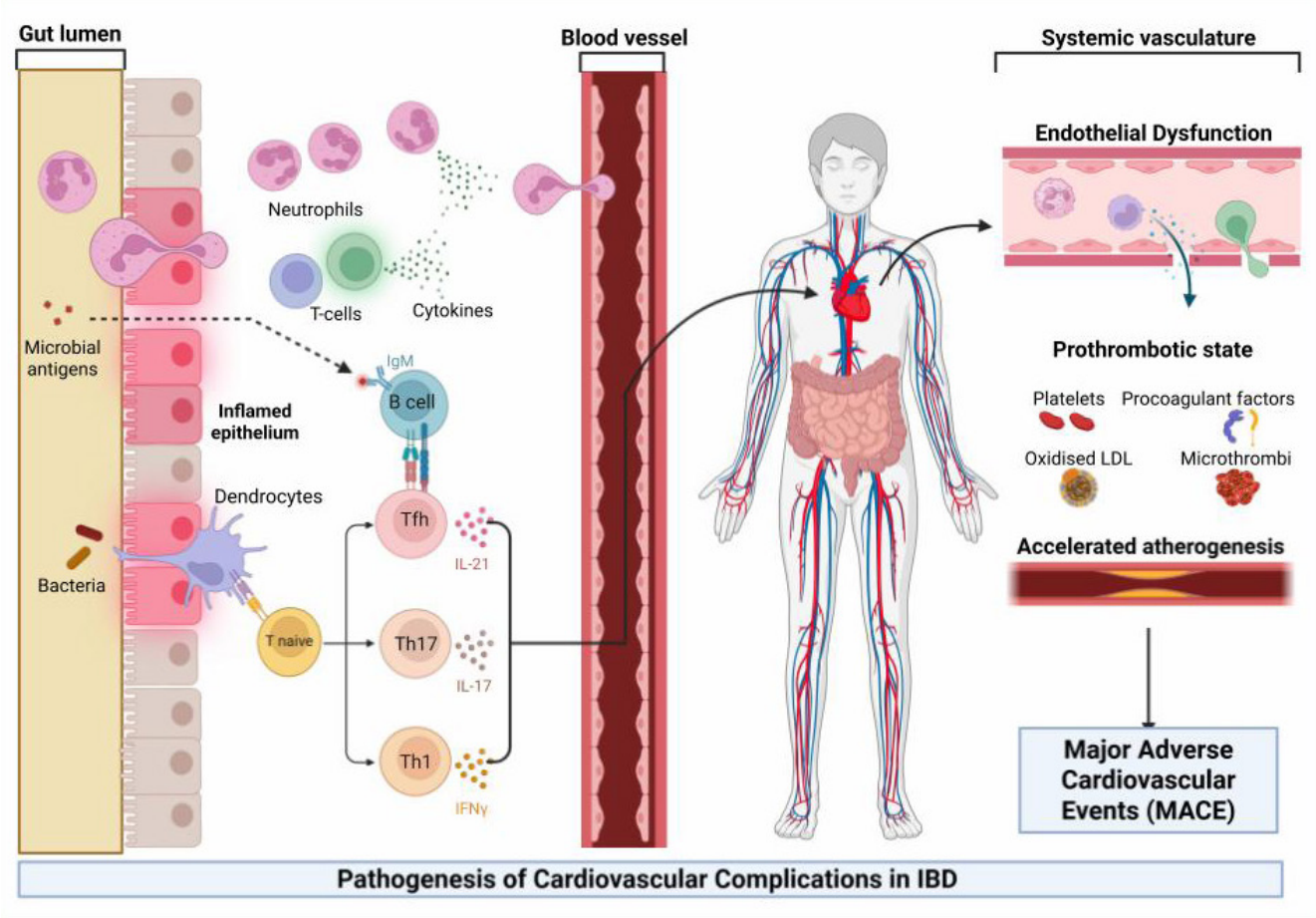


Figure 1. Pathogenesis of Cardiovascular Complications in IBD; *created in BioRender*.

disease despite a lower prevalence of traditional risk factors such as diabetes and hypertension, suggesting that IBD is, in itself, an inherent risk factor for cardiovascular disease.[5]

Cardiovascular Risk in Treatment Modalities

Given that chronic inflammation appears to be central to cardiovascular disease in IBD, effective suppression of disease activity may reduce cardiovascular risk. However, the varied mechanisms of action across different treatment classes necessitates a closer examination of the effects of specific treatment modalities on cardiovascular health (**Figure 2**).

Corticosteroids

Corticosteroids are primarily used to induce clinical remission during acute IBD flares, and guidelines recommend minimizing their use for maintenance therapy.[6] Corticosteroid exposure has shown a clear dose-dependent increase in the risk of cardiovascular disease. A longitudinal study on immune-mediated diseases including IBD revealed an increase in cumulative risk from 1.5% to 3.8% over one year among individuals receiving a daily prednisolone-equivalent dose of <5 mg, which increased to 9.1% with doses of >25 mg/day.[7] A meta-analysis revealed a two-fold increase in the rate of venous thromboembolism with corticosteroid use, especially during IBD flares, due to underlying inflammation.[8] Corticosteroids are well-recognized for contributing to hypertension, insulin resistance, and dyslipidemia, which potentiate the inherent risk of endothelial dysfunction and atherosclerosis in IBD. In addition, the relative risk of heart failure and acute MI are increased among IBD patients receiving corticosteroids, warranting the need for careful use in patients with cardiovascular comorbidities.[9]

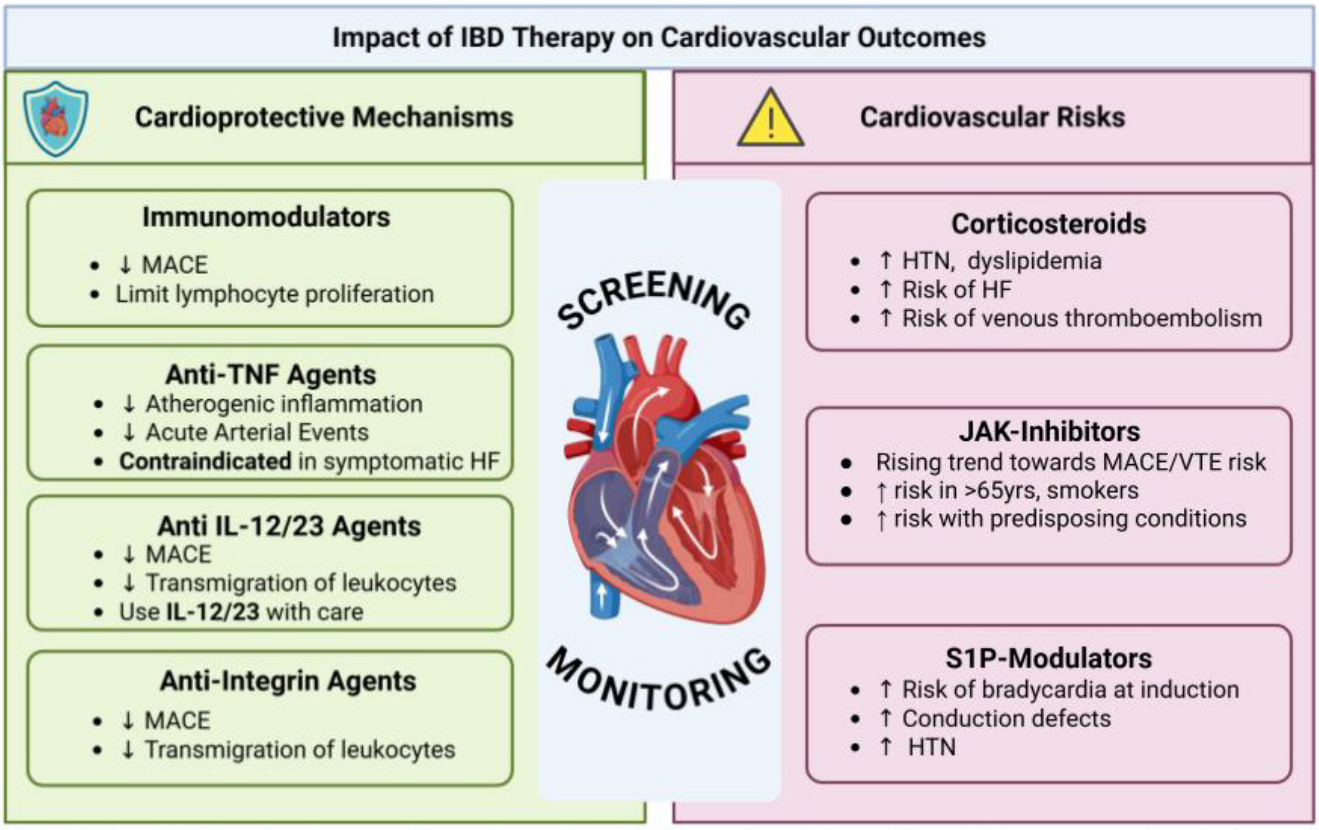


Figure 2. Impact of IBD Therapy on Cardiovascular Outcomes; *created in BioRender*.

TNF-α Inhibitors

TNF-α inhibitors or anti-TNF agents act by binding to TNF-α, a key proinflammatory cytokine that is overexpressed in the intestinal mucosa and promotes leukocyte recruitment and activation, increases epithelial permeability, and contributes to barrier disruption. Large nationwide cohort studies indicate that anti-TNF agents reduce the risk of acute arterial events by reducing atherogenic chronic inflammation in the body.[10,11] Another study reports that anti-TNF agents confer a greater reduction in the risk of MACE than other conventional non-biologic therapies.[12]

Despite these benefits, anti-TNF agents carry a U.S. Food and Drug Administration (FDA) label warning for cardiovascular side effects. The use of infliximab >5 mg/kg is contraindicated in moderate-to-severe symptomatic heart failure (HF) of (New York Heart Association [NYHA] class III/IV), based on the findings of the Anti-TNF Alpha Therapy Against Congestive Heart Failure (ATTACH) trial, which evaluated patients with reduced ejection fraction (EF) of <35%.[13] A case report described an IBD patient with cardiovascular risk factors and probable structural heart disease who developed decompensated HF following exposure to high-dose infliximab.[15] In a nationwide study, IBD patients receiving anti-TNF agents showed a higher risk of atrial fibrillation,[15] while a separate study in patients with ankylosing spondylitis demonstrated a reduction in QT interval with infliximab, indicating the lack of consensus on this matter.[16] Overall, the use of anti-TNF agents is associated with a reduced risk of MACE events, but should be used with caution in patients with moderate-to-severe HF (EF ≤40%).

IL-12/23 and IL-23 Inhibitors

The IL-12/23 pathway contributes to the proinflammatory state by promoting differentiation and maintenance of inflammatory T-cells. Medications such as ustekinumab act on the p-40 subunit of IL-12 and IL-23. In contrast, other therapeutics such as risankizumab, guselkumab, and mirikizumab specifically inhibit the p19 subunit of IL-23. Compared with anti-TNF therapies, these biologics have fewer systemic side effects and

are increasingly finding utility for IBD patients who have not responded to conventional therapy.

Cardiovascular side effects data from IBD cohorts are generally reassuring for therapeutic modalities targeting the IL-12/23 pathway. Clinical trials and real-world cohort studies have not reported cases of HF among IBD patients using these agents. Moreover, an analysis of a TriNetX IBD cohort showed a lower risk of atherosclerotic disease with IL-12/23 inhibitors than with other biologics.[17] On the other hand, a meta-analysis examining the risk of MACE across immune-mediated inflammatory disorders reported an increased risk with IL-12/23 inhibitors compared with placebo, but not with IL-23 specific inhibitors.[18] A study comparing biologic therapies in psoriasis noted an increased risk of MACE with IL-12/23 inhibitors compared with TNF inhibitors.[19] Additionally analyses of U.S. FDA adverse effects reporting data have identified a statistically significant signal for atrial fibrillation and coronary artery disease associated with risankizumab, a finding not observed with guselkumab.[20] Thus, while IL-12/23 inhibitors may reduce the risk of adverse cardiovascular outcomes in IBD patients, monitoring for any new onset MACE or atrial fibrillation is suggested.

Anti-integrin Agents

Anti-integrin monoclonal antibodies, such as vedolizumab and natalizumab, bind to adhesion molecules on the vascular endothelium, and exert their effects by blocking the transmigration of leukocytes from the bloodstream into bowel tissue. This targeted blockade reduces immune-mediated inflammation while avoiding broad immunosuppression.

Analysis of a TriNetX IBD cohort showed a reduction in the risk of MACE among patients treated with anti-integrin agents.[17] Data from the GEMINI trials and the real-world ENEIDA registry have not indicated increased risks of HF, acute coronary syndrome, or arrhythmias associated with these therapies.[21] Meta-analyses that examined the comparative risk of MACE with anti-integrin agents have similarly reported no increased risk of MACE with these therapies versus placebo. However, data from one study noted more instances of MACE with vedolizumab versus anti-TNF agents, a finding that may reflect differences in disease control.[22]

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors such as tofacitinib, upadacitinib, and filgotinib, act on the intracellular JAK-signal transducers and activators of transcription (STAT) signalling pathway by blocking kinase activity and preventing STAT phosphorylation.

Cardiovascular safety concerns with oral JAK inhibitor surveillance have been most clearly identified in older, high-risk populations, particularly from the Oral Rheumatoid Arthritis (ORAL) Surveillance trial. This randomized trial evaluated MACE in patients with rheumatoid arthritis who were 50 years of age or older with at least one cardiovascular risk factor (approximately half were ever-smokers),comparing tofacitinib 10 mg and 5 mg twice daily with TNF inhibitors. Tofacitinib failed to demonstrate non-inferiority for the composite cardiovascular endpoint, indicating an increased risk of MACE relative to TNF inhibitors. Subgroup analysis revealed a higher incidence of MACE among patients aged 65 years or older compared to younger patients.[23] As a result, JAK-inhibitors (tofacitinib, and upadacitinib) carry a U.S. FDA black-box warning for MACE and thrombotic events.

A network meta-analysis assessing the risk of MACE, venous thromboembolism, and cardiovascular events reported no significant increase in risk associated with JAK-inhibitors overall, although a rising trend was noted for tofacitinib and upadacitinib.[24] Consistent with these findings, a recent study based on a real-world cohort compared the cardiovascular safety of JAK-inhibitors and anti-TNF agents reported no difference between the two treatment classes.[25,26] In contrast, a study based on an analysis of the U.S. FDA Adverse Event Reporting System (FAERS) data identified a potential association between JAK inhibitor use and cardiovascular adverse events in older patients (72% aged above 50 years and 39% aged above 65 years) and those with pre-existing cardiovascular risk factors.[27] Accordingly, cautious use of these drugs is recommended in patients ≥65 years of age with pre-existing risk factors for cardiovascular disease.

Sphingosine-1-phosphate Modulators

Sphingosine-1-phosphate (S1P)-receptor modulators such as ozanimod and etrasimod act by binding to the S1P-receptor and preventing

it from sensing S1P levels, thereby inhibiting lymphocyte egress from lymphoid tissue. These agents have the potential to cause cardiac conduction-related abnormalities in patients. Clinical trial data for ozanimod in patients with UC indicate a risk of bradycardia in the induction phase, with a subset of patients also developing mild atrioventricular conduction block.[28] Mild-to-moderate hypertension has also been noted as a treatment-emergent adverse effect in patients on etrasimod.[29] Given the consistent observation of bradycardia, hypertension, and conduction defects, it is advisable to perform a baseline electrocardiographic assessment and careful dose titration to help reduce the risk of cardiovascular adverse effects. S1P receptor modulators are contraindicated in patients with a history of MACE, unstable angina, transient ischemic attack, decompensated HF, or NYHA class III/IV HF within the preceding 6 months, as well as in those with advanced heart block or sick sinus syndrome unless a functioning pacemaker is present.

Immunomodulators

Traditional immunomodulators in IBD, which include azathioprine, 6-mercaptopurine and methotrexate are frequently used in combination with biologic therapies to enhance efficacy and reduce immunogenicity. In select cases, particularly in UC, they may be used as monotherapy for maintenance of remission. Studies of IBD cohorts have noted the cardioprotective effect of thiopurines, with associations to reduced incidence of HF, MI, and stroke. These benefits have been observed despite thiopurines often being introduced in patients with refractory disease and considerable underlying inflammation, indicating the strong immunomodulatory and antithrombotic effect of these therapies.[1,11] Although cardiovascular outcomes data from IBD cohorts are limited for methotrexate, data from other immune-mediated diseases has shown that methotrexate use is associated with reductions in MACE and cardiovascular mortality.[30]

5-Aminosalicylic Acid Agents

5-Aminosalicylic acid (5-ASA) agents exert their anti-inflammatory effects on the intestinal mucosa, by inhibiting cyclooxygenase and lipoxygenase pathways, reducing production of proinflammatory cytokines, and scavenging reactive oxygen species.

Evidence on the effect of 5-ASA agents on cardiovascular outcomes is inconclusive. While a Danish study reported coronary artery disease risk reduction, a study from the UK showed a higher risk of cardiovascular disease among treated patients. Other investigations have shown increased aortic stiffness with 5-ASA therapy, a finding that can contribute to hypertension and adverse cardiovascular outcomes. In addition, rare cases of myocarditis and pericarditis have also been observed in patients using 5-ASA, likely representing an idiosyncratic hypersensitivity reaction.[31] Taken together, the presence of conflicting data suggests that these agents should be used with caution in individuals with pre-existing cardiovascular disease.

Conclusion

Patients with IBD are at increased risk of cardiovascular morbidity, largely driven by chronic systemic inflammation. While many IBD therapies reduce inflammation and improve cardiovascular outcomes, the magnitude and consistency of these benefits vary across drug classes. Agents such as corticosteroids, anti-TNF therapies, anti-IL12/23 and anti-IL23 inhibitors, small molecule therapies, and 5-ASA, while generally beneficial, have the potential to produce class-specific cardiovascular adverse effects that must be considered when making decisions regarding treatment plans.

Additionally, clinicians should proactively screen for traditional risk factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking, as these factors can predispose patients with IBD to cardiovascular events. Establishing a baseline cardiovascular assessment in patients prior to starting IBD therapy can help detect and possibly mitigate the risk of cardiovascular morbidity. Implementation of class-specific measures such as cardiovascular risk stratification and regular monitoring of lipid profiles for patients receiving JAK-inhibitors, as well as baseline electrocardiographic assessment for those treated with S1P-modulators, can meaningfully improve long-term cardiovascular outcomes in patients with IBD.

Correspondence

Parakkal Deepak, MD, MS, FACG
Email: deepak.parakkal@wustl.edu

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