VOL 2
ISSUE 1
2024

ISSN 2817-4127 (Print)
ISSN 2817-4135 (Online)

CANADIAN IBD TODAY

Clinical Insights, Perspectives, and Disease Management

TABLE OF CONTENTS

Canadian IBD Today is published 3 times per year in English and French.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadianibdtoday.com

To subscribe to Canadian IBD Today and more open access scientific specialty journals published by Catalytic Health, please visit https://catalytichealth.com/cibdt/

The content in Canadian IBD Today qualifies for Section 2 (self-learning) credits towards the maintenance of certification. For information on how this activity fits in the Royal College Maintenance of Certification (MOC) Program, please visit the Royal College's website (royalcollege.ca/moc). For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

EDITORIAL BOARD

TALAT BESSISSOW, MDCM, MSc, FRCPC

Associate Professor of Medicine, Division of Gastroenterology, McGill University

Attending Staff, McGill University Health Centre & Montreal General Hospital

Vice-President, Canadian IBD Research Consortium

Associate Editor, Journal of the Canadian Association of Gastroenterology

CYNTHIA SEOW, MBBS (HONS), MSc, FRACP

Professor of Medicine, Division of Gastroenterology and Hepatology, University of Calgary

Associate Editor, Alimentary Pharmacology and Therapeutics

Chair, Future Leaders in IBD

JEFFREY MCCURDY, MD, PhD, FRCPC

Assistant Professor of Medicine, University of Ottawa

Clinical Investigator, The Ottawa Hospital Research Institute

Member of The Ottawa Hospital Inflammatory Bowel Disease Centre of Excellence

REMO PANACCIONE, MD, FRCPC

Professor of Medicine & Director of the Inflammatory Bowel Disease Unit & Director of Research, Division of Gastroenterology and Hepatology, University of Calgary

Assistant Dean, MD Admissions, University of Calgary

Crohn's Colitis Canada Endowed Research Chair, Inflammatory Bowel Disease

Pr RINVOQ®
upadacitinib

ONE TABLET, ONCE DAILY*

IS NOW INDICATED IN

CROHN'S DISEASE

The **FIRST & ONLY** JAK inhibitor indicated in adults with moderate to severe Crohn's disease[1,2†]

RINVOQ (upadacitinib) is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional, and/or biologic therapy.[1]

Please consult the Product Monograph at rinvoq.ca/pm for information about contraindications, serious warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling us at 1-888-704-8271.

JAK: Janus kinase.
*For more complete dosage and administration information, please refer to the Product Monograph.
†Comparative clinical significance unknown.
References: 1. RINVOQ Product Monograph. AbbVie Corporation. **2.** Data on File (First & Only). September 28, 2023.

abbvie

CA-RNQG-230076A / NO23

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

ELLEN KUENZIG, PhD

Ellen Kuenzig is a Senior Research Associate at the SickKids IBD Centre at The Hospital for Sick Children and the Child Health Evaluative Sciences program at the SickKids Research Institute. Dr. Kuenzig is an epidemiologist and health services researcher. She is a member of Crohn's and Colitis Canada's Scientific and Medical Advisory Council and the Scientific Committee of the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC), which conducts epidemiology, pharmacoepidemiology, outcomes, and health services research using the health administrative data from multiple provinces.

Affiliations: SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children (SickKids), Toronto, Ontario, Canada
Child Health Evaluative Sciences, SickKids Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada

GILAAD KAPLAN, MD, MPH, FRCPC, CAGF, AGAF, FCAHS

Dr. Kaplan is a Professor in the Cumming School of Medicine at the University of Calgary. Dr. Kaplan is a gastroenterologist who is internationally renowned for studying the global epidemiology of inflammatory bowel disease (IBD). He is an Associate Editor of Gastroenterology. In 2019, Dr. Kaplan was elected to the International Organization of the study of IBD (IOIBD). Clarivate, Web of Science named Dr. Kaplan a Highly Cited Researcher (2020-2023) in recognition of being in the top one percent of cited researchers. In 2021, Dr. Kaplan received Crohn's and Colitis Canada's Research Leader Award and was inducted into the Canadian Academy of Health Sciences. He is a Killam Laureate, receiving the Killam Annual Professor Award in 2022. His research has been widely cited in the news media including Time Magazine, BBC, The New York Times, and Scientific American.

Affiliations: Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

ERIC BENCHIMOL, MD, PhD, FRCPC

Eric Benchimol is the Northbridge Financial Corporation Chair in Inflammatory Bowel Disease (IBD) and a pediatric gastroenterologist at the SickKids IBD Centre at The Hospital for Sick Children in Toronto. He is also a Professor in the Department of Paediatrics and the Institute for Health Policy, Management and Evaluation in the Temerty Faculty of Medicine of University of Toronto. Dr. Benchimol is also a Senior Core Scientist at ICES and Senior Scientist at the SickKids Research Institute. He is an epidemiologist, and chairs the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC), which conducts epidemiology, pharmacoepidemiology, outcomes, and health services research using the health administrative data from multiple provinces.

Affiliations: SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children (SickKids), Toronto, Ontario, Canada
Child Health Evaluative Sciences, SickKids Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada
Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada
ICES, Toronto, Ontario, Canada
Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

THE RISING BURDEN OF INFLAMMATORY BOWEL DISEASE IN CANADA: FINDINGS FROM THE CROHN'S AND COLITIS CANADA 2023 IMPACT OF INFLAMMATORY BOWEL DISEASE IN CANADA REPORT

Introduction

The Impact of Inflammatory Bowel Disease report, produced by the Canadian Gastro-Intestinal Epidemiology Consortium (cangiec.ca) for Crohn's and Colitis Canada is a serial policy report produced every 3–5 years that summarizes the existing literature on the epidemiology, burden, and impact of inflammatory bowel disease (IBD) in Canada and identifies knowledge gaps. Its goal is to inform people living with IBD and their caregivers, donors, physicians, researchers, policy makers, and other stakeholders about the current burden of IBD in Canada. It plays an integral role for Crohn's and Colitis Canada's advocacy efforts. In addition, the report informs the research funding policy of the health charity, which is the second largest non-governmental funder of IBD research in the world.[1] The latest iteration of this report was released on June 1, 2023[2,3] and is available here. This article summarizes the current epidemiology of IBD in Canada and discusses its implications for clinical care in 2024 and beyond.

Incidence of IBD in Canada

The incidence of IBD in Canada in 2023 is estimated at 29.9 per 100,000 people (95% prediction interval [PI] 28.3 to 31.5) and remained stable between 2007 and 2014 (average annual percentage change [AAPC]: 0.4%, 95% confidence interval [CI] -0.05 to 0.7).[4,5] However, in Canada, the trends in IBD incidence vary across provinces **(Figure 1A)**, age groups, and by type of IBD. Incidence rates and trends over time are similar for males and females.

In 2023, the incidence of IBD was predicted to be highest in Newfoundland (52.6 per 100,000 people, 95% PI 41.4 to 63.7) and lowest in Saskatchewan (16.1 per 100,000 people, 95% PI 10.1 to 22.2) **(Figure 1A)**.[4,5] These two provinces also have diverging trends in incidence over time – increasing by 1.4% (95% CI 0.4 to 2.0) per year in Newfoundland and decreasing by 7.7% (95% CI 2.6 to 21.6) per year in Saskatchewan. All other provinces have incidence rates that fall between these two values, increasing in some provinces, decreasing in some provinces, and stable in others.

Nationally, the incidence of pediatric IBD increased by 1.3% (95% CI 0.8 to 1.7) per year between 2005 and 2014.[4,5] The incidence of pediatric IBD was 14.4 (95% CI 13.5 to 15.3) per 100,000 children in 2014, and is estimated to have risen to 16.1 (95% PI 14.9 to 17.2) per 100,000 children in 2023, with a projected to rise to 18.5 (95% PI 16.3 to 20.8) per 100,000 children in 2035. The incidence of pediatric IBD was increasing the fastest among children diagnosed at <6 years of age (7.2% per year, 95% CI 2.8 to 11.6).[6] The incidence of IBD among adults (18 to 64 years) and seniors (≥65 years) has remained stable, with incidence rates of 34.7 (95% CI 31.5 to 37.8) and 28.8 (23.6 to 34.1) per 100,000 people, respectively, in 2023.[4,5]

In 2023, the incidence of Crohn's disease (CD) was 12.7 per 100,000 people and has remained stable in all age groups (overall AAPC -0.52%, 95% CI -1.44 to 0.21).[4,5] In contrast, the incidence of ulcerative colitis (UC) has increased overall (AAPC 1.0%, 95% CI 0.7 to 1.3) and in children (AAPC 2.0%, 95% CI 0.8 to 2.8). The overall incidence of UC was 15.5 per 100,000 people in 2014, estimated to have increased to 17.2 per 100,000 people (95% PI 16.4 to 18.1) in 2023, and is projected to reach 19.3 per 100,000 people (95% PI 17.8 to 20.9) in 2023. The incidence of UC in adults and seniors has remained stable over time.

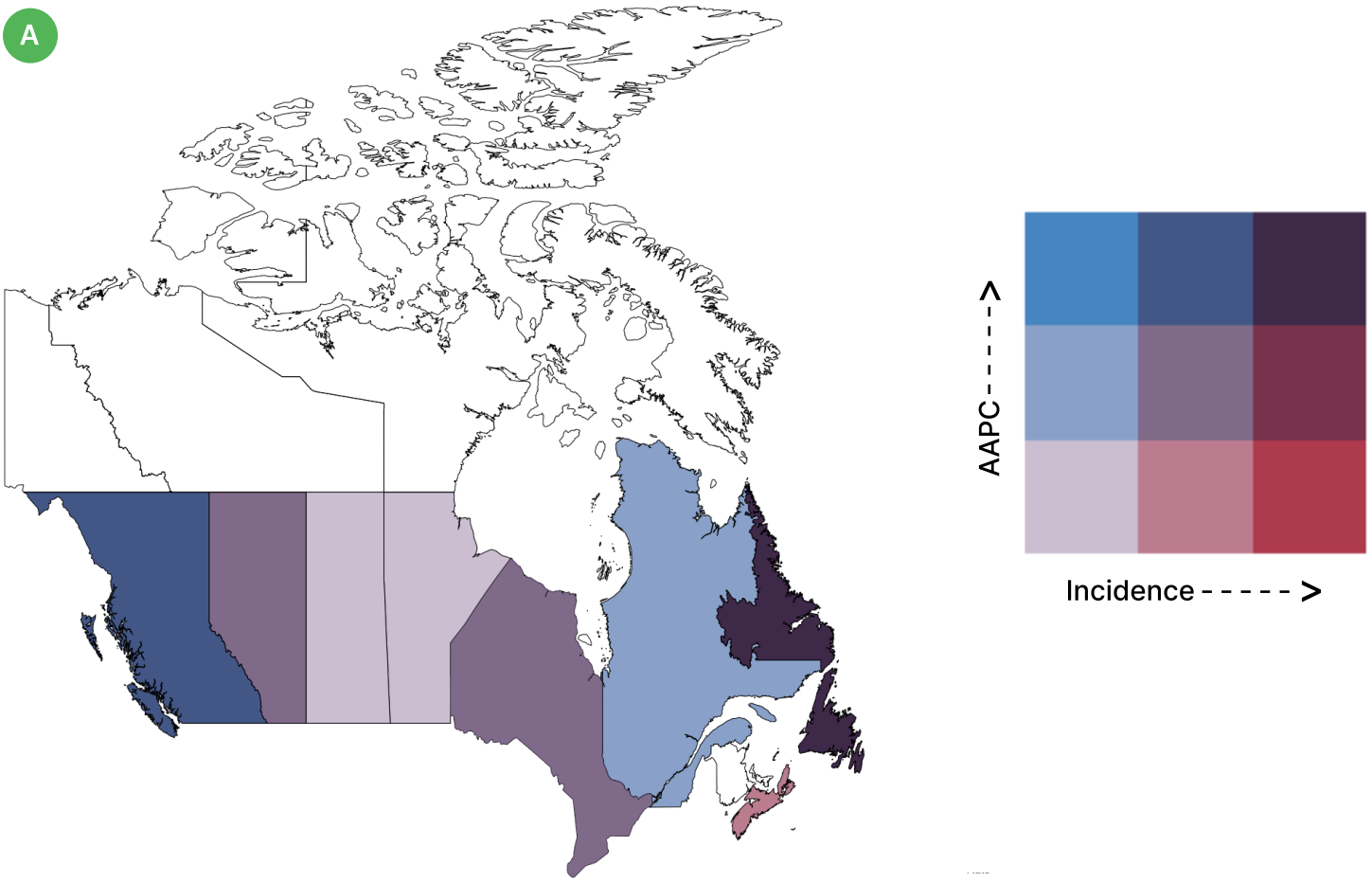
Prevalence of IBD in Canada

The prevalence of IBD is increasing across all provinces, age groups, and types of IBD **(Figure 1B)**.[4,5] In 2023, the estimated prevalence of IBD is reported to be 843 per 100,000 people (95% PI 828 to 859) (i.e. 0.843% of the population) in 2023 and is increasing by 2.4% (95% CI 2.3 to 2.5) per year. The prevalence is highest in Eastern Canada (Newfoundland: 1115 per 100,000 people; Nova Scotia: 1239 per 100,000 people) and lowest in Manitoba (720 per 100,000 people). The prevalence of IBD is increasing fastest among seniors, by 2.78% (95% CI 2.75 to 2.81) per year.[4,5] Seniors also represent the group with the highest prevalence, with an estimated 1174 (95% PI 1164 to 1184) per 100,000 seniors living with IBD in 2023. Based on current trends, we expect the prevalence of IBD to reach 1.1% of the Canadian population by 2035.

Special Populations

IBD is becoming increasingly recognized in populations previously thought to have low rates of IBD.[5] A study from Saskatchewan reported that the prevalence of IBD among First Nations individuals

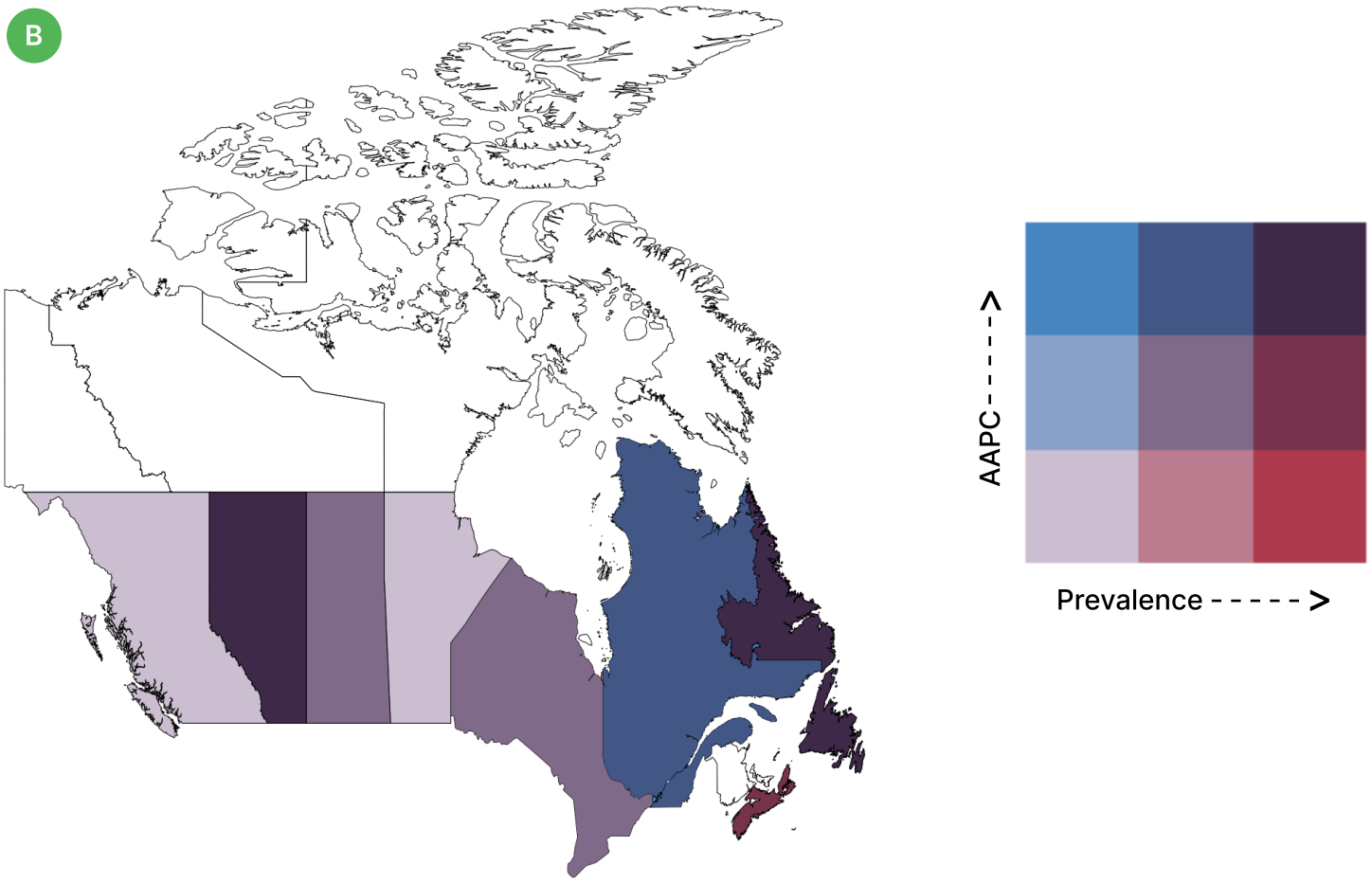
A



	Forecasted AAPC (95% CI)	Forecasted Incidence per 100,000 people in 2023 (95% PI)
Alberta	-0.75 (-2.29, 0.36)	33.6 (29.9, 37.2)
British Columbia	0.71 (0.45, 0.95)	34.6 (32.9, 36.3)
Manitoba	-0.93 (-1.51, -0.47)	24.2 (21.8, 26.7)
Newfoundland	1.35 (0.39, 1.96)	52.6 (41.4, 63.7)
Nova Scotia	-3.86 (-4.86, -3.04)	33.6 (31.2, 36.0)
Quebec	0.58 (0.15, 0.95)	22 (20.5, 23.6)
Ontario	0.83 (-1.55, 2.29)	28.8 (23.0, 34.6)
Saskatchewan	-7.72 (-21.58, -2.56)	16.1 (10.1, 22.2)

Figure 1A. Map describing the incidence of inflammatory bowel disease (IBD) in Canada and the changes over time, stratified by province with available data; Data are derived from Coward et al.[4]
Abbr: AAPC= average annual percentage change

B



	AAPC (95% CI)	Forecasted prevalence per 100,000 people in 2023 (95% PI)
Alberta	2.87 (2.17, 3.46)	951 (889, 1013)
British Columbia	2.02 (1.76, 2.28)	799 (785, 813)
Manitoba	1.84 (1.47, 2.17)	720 (688, 751)
Newfoundland	3 (1.23, 4.21)	1115 (920, 1309)
Nova Scotia	2.26 (1.64, 2.79)	1239 (1182, 1296)
Quebec	3.03 (2.39, 3.55)	810 (730, 891
Ontario	2.22 (2.05, 2.39)	812 (792, 831)
Saskatchewan	2.27 (1.38, 3.00)	811 (758, 864)

Figure 1B. Map describing the prevalence of inflammatory bowel disease (IBD) in Canada and the changes over time, stratified by province with available data; Data are derived from Coward et al.[4]
Abbr: AAPC= average annual percentage change

increased by 4.2% (95% CI 3.2% to 5.2%) per year between 1999 and 2016.[7] UC was more common (2016 prevalence: 87 per 100,000 people, 95% CI 86 to 89) than CD (2016 prevalence: 53 per 100,000 people, 95% CI 52 to 55), with both increasing at similar rates. Incidence rates were stable over time (AAPC -2.7%, 95% CI -6.2 to 0.8). Although the prevalence of IBD among First Nations individuals remains lower than that of the general population, it is increasing faster than in the general population.

Immigrants to Canada and their children represent another group of Canadians with underappreciated rates of IBD. While immigrants have lower rates of IBD relative to individuals born in Canada, individuals who come to Canada as children have a greater risk of developing IBD relative to older immigrants.[8] Furthermore, the Canadian-born children of immigrants from the Middle East, North Africa, and South Asia have a similar risk of developing IBD compared to children of non-immigrants,[8,9] an important finding considering Canada has amongst the highest rates of pediatric IBD in the world. This suggests individuals from these populations exhibit a genetic profile that interacts with Canadian environmental exposures early in life to increase the likelihood that they develop IBD.

Canada in Context

IBD has historically been a disease of the Western world, with the highest rates of IBD observed in Canada, Northwestern Europe, and Scandinavia. The regions that have historically had the highest incidence of IBD are now beginning to observe a stabilization in their incidence rates.[10] At the same time, IBD is becoming increasingly common in newly developed regions in parallel with Westernization.[11]

The shifting landscape of IBD epidemiology may follow four stages: **1.** Emergence; **2.** Acceleration in Incidence; **3.** Compounding Prevalence; and **4.** Prevalence Equilibrium **(Figure 2)**.[12] During the *Emergence stage*, IBD is rare. In the *Acceleration in Incidence stage*, IBD becomes increasingly common owing to accelerating incidence rates. In the *Compounding Prevalence stage*, incidence rates stabilize although the prevalence continues rising rapidly, since most individuals are diagnosed with IBD at a relatively young age and the mortality associated with IBD is low. Canada and other regions with historically high rates of IBD are now in this stage of IBD evolution. No regions have reached the *Prevalence Equilibrium stage*, in which prevalence remains stable because the mortality rates of an aging IBD population approximate the incidence rates.

Mitigating the Rising Burden of IBD

Decreasing the incidence of IBD will be instrumental in stemming the growing burden of IBD in Canada and around the world. In order to prevent IBD, we require additional knowledge about its complex pathogenesis, involving complex interactions between many factors, including the environmental

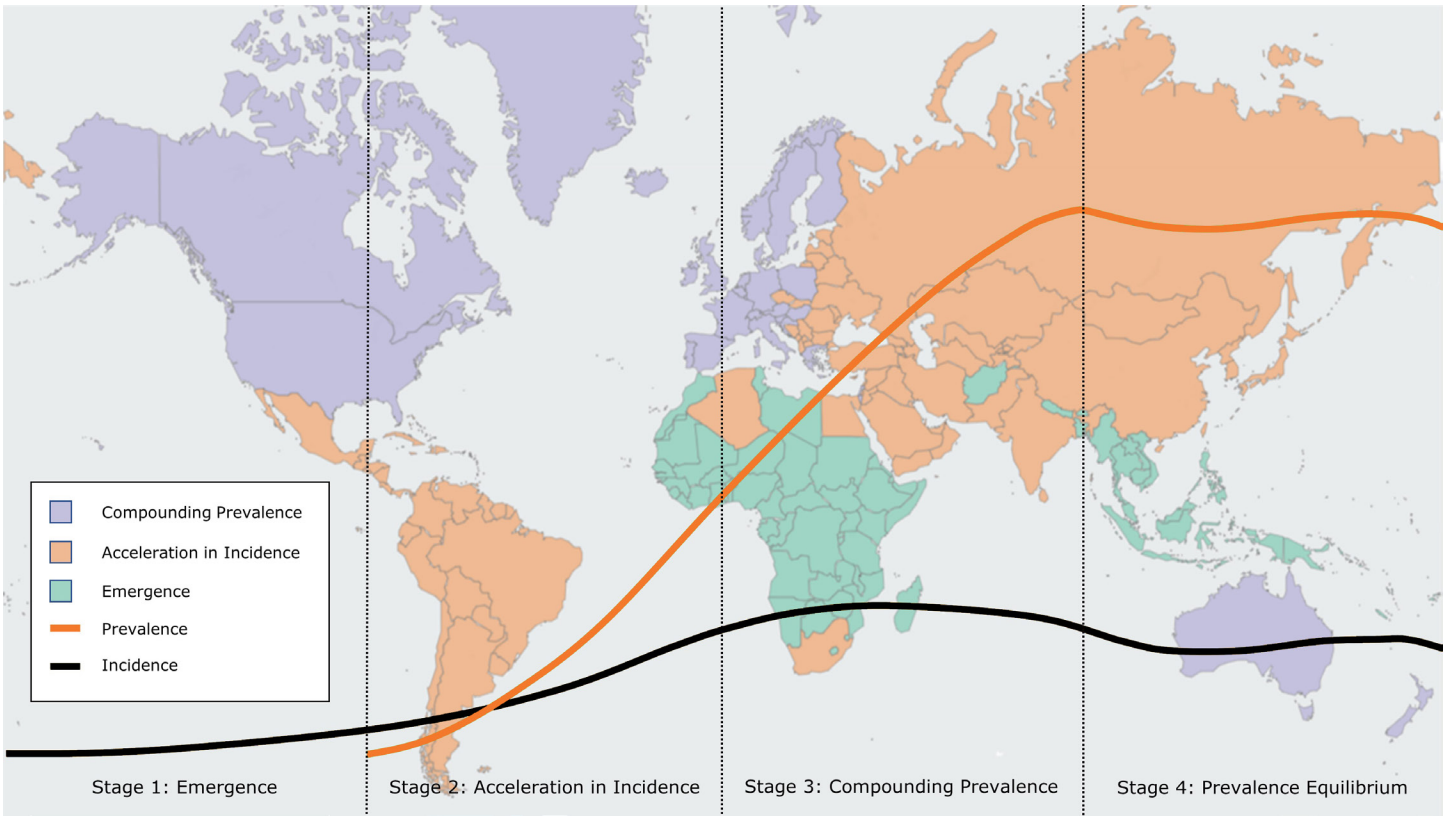


Figure 2. Theoretical description of the evolution of the epidemiology of inflammatory bowel disease (IBD) around the world, including a map of the current evolutionary stage of each nation. Reprinted from Coward et al[5], adapted from Kaplan and Windsor.[12]

exposures and the intestinal microbiome. It is vital that we understand the role of shifting environmental landscapes in regions currently in the *Emergence and Acceleration in Incidence* phases of their epidemiologic evolution. These regions could provide an opportunity to identify important risk factors as their environments are rapidly evolving, often due to policy changes that are made quickly in the face of developing economies. However, countries in the *Compounding Prevalence* phase (i.e., high incidence developed nations such as Canada) could also be highly amenable to environmental policy interventions or public health measures to improve behavioural determinants.[13] This understanding will be critical in any intervention aiming to decrease IBD incidence by minimizing harmful exposures and maximizing beneficial exposures. Preclinical cohorts, such as the Crohn's and Colitis Canada GEM Project, are helping to identify at-risk individuals who are amenable to preventive interventions.[14]

Implications of a Growing and Aging IBD Population

The rapidly rising prevalence of IBD in Canada will drastically increase the number of people requiring care for their IBD – with implications for both health human resources and healthcare spending. Furthermore, the IBD population is aging – the prevalence of IBD is growing faster among seniors than in any other age group.[4,5] This group is comprised both of individuals diagnosed with IBD earlier in life who are aging and individuals newly diagnosed among a rapidly growing Canadian senior population. Although the life expectancy of individuals with IBD is increasing, older adults with IBD are at an increased risk of age-related comorbidities,[15] and have a lower health-related quality of life, resulting in a substantially reduced health-adjusted life expectancy.[16] The combination of managing long-standing IBD and age-related comorbidities implies that the clinical management of people living with IBD will become increasingly complex.

Patients with timely access to gastroenterologist care have better outcomes.[17,18] The ratio of gastroenterologists to the general population in Canada is approximately 2 per 100,000, and this number has remained relatively stable over the past decade[19,20] despite the growing prevalence of IBD. As the prevalence of IBD continues to grow and the IBD population ages, the demands on gastroenterology clinics will only increase and models of care will need to evolve to meet this growing demand.

Furthermore, our healthcare system needs to prepare for the increasing costs of treating people living with IBD. In 2018, the direct healthcare costs of IBD were conservatively estimated at $1.28 billion.[21] Over the past decade, the costs of medical care for IBD have risen rapidly and were estimated to be $3.33 billion in 2023.[22] This substantial increase in healthcare costs is largely driven by the costs of expensive biologic therapies that have not been offset by reductions in costs related to hospitalizations and surgeries. These costs do not account for the substantial indirect and out-of-pocket costs incurred by people living with IBD and their caregivers, which exceeded $2 billion in 2023.[23] Furthermore, indirect costs related to presenteeism (reduced productivity while at work) and absenteeism (time off work) can be reduced by effectively treating a person's IBD. A healthier IBD population will reduce the overall economic burden of IBD. These rising costs are not indefinitely sustainable and need to be addressed without compromising the quality of care provided to people living with IBD.

Conclusions

The number of Canadians living with IBD is rising. Without changes in the approach to how we manage the increasing needs of the growing IBD population, the demand for gastroenterologists and the cost of caring for people living with IBD will exceed our current capacity to provide high quality care to these patients. We need to bring awareness of the growing costs of caring for the growing IBD population to government, policy makers, and other healthcare payers (e.g., the private healthcare insurance industry). Furthermore, it is crucial to understand why IBD is becoming increasingly common in some populations (e.g., First Nations individuals, children, and younger immigrants from certain regions). We will require better research funding to fully understand the environmental factors that are contributing to the rise of IBD in these populations. Only by better understanding the complex etiology of IBD will we be able to develop strategies that will minimize the future burden of IBD in Canada.

Key Takeaways:

1. Trends in IBD incidence in Canada vary across provinces, age groups, and by type of IBD; incidence rates and trends over time are similar for males and females.
2. The incidence of pediatric IBD was increasing the fastest among children diagnosed at <6 years of age. The prevalence of IBD was increasing the fastest among seniors ≥65 years of age.
3. Although the prevalence of IBD among First Nations individuals remains lower than that of the general population, it is increasing faster than in the general population.
4. As the prevalence of IBD continues to grow and the IBD population ages, the demands on gastroenterology clinics will only increase and models of care will need to evolve to meet this growing demand.
5. The rising costs of treating and managing IBD are not sustainable in the long-term and need to be addressed without compromising the quality of care provided to people living with IBD.

Correspondence:

Ellen Kuenzig, PhD
Email: ellen.kuenzig@sickkids.ca

Financial Disclosures:

Ellen Kuenzig: None declared.

Gilaad Kaplan: **Honoraria for Speaking/Consulting:** AbbVie, Amgen, Janssen, Pfizer, Sandoz, and Pendophram; **Research Grants:** Ferring; **Educational Activities:** AbbVie, Bristol Myers Squibb, Ferring, Fresenius- Kabi, Janssen, Pfizer, Takeda; **Shared Patent Ownership:** TREATMENT OF INFLAMMATORY DISORDERS, AUTOIMMUNE DISEASE, AND PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/ CA2018/051098. 7 Sept. 2018.

Eric Benchimol: holds the Northbridge Financial Corporation Chair in Inflammatory Bowel Disease, a joint Hospital-University Chair between the University of Toronto, The Hospital for Sick Children, and the SickKids Foundation. **Consulting:** Dairy Farmers of Ontario, McKesson Canada (unrelated to medications used to treat inflammatory bowel disease), Canadian Agency for Drugs and Technology in Health.

References:

1. Rose KL, Sherman PM, Cooke-Lauder J, Mawani M, Benchimol EI, Kaplan GG, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: IBD Research Landscape in Canada. Journal of the Canadian Association of Gastroenterology. 2018;390(10114):2769 - 11.
2. Windsor JW, Kuenzig ME, Murthy SK, Bitton A, Bernstein CN, Jones JL, et al. The 2023 Impact of Inflammatory Bowel Disease in Canada: Executive Summary. Journal of the Canadian Association of Gastroenterology. 2023;6(Supplement_2):S1-S8.
3. Benchimol EI, Kaplan GG, Bernstein CN, Bitton A, Jones JL, Kuenzig ME, et al. 2023 Impact of Inflammatory Bowel Disease in Canada2023. Available from: https://crohnsandcolitis.ca/Crohns_and_Colitis/documents/reports/2023-IBD-Report-English-LR.pdf?ext=.pdf.
4. Coward S, Benchimol EI, Bernstein CN, Avina-Zubieta A, Bitton A, Carroll MW, et al. Forecasting the incidence and prevalence of inflammatory bowel disease: a Canadian nationwide analysis. Am J Gastroenterol. 2024.
5. Coward S, Benchimol EI, Kuenzig ME, Windsor JW, Bernstein CN, Bitton A, et al. The 2023 Impact of Inflammatory Bowel Disease in Canada: Epidemiology of IBD. Journal of the Canadian Association of Gastroenterology. 2023;6(Supplement_2):S9-S15.
6. Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. The American Journal of Gastroenterology. 2017;112:1120 - 34.
7. Pena-Sanchez JN, Osei JA, Marques Santos JD, Jennings D, Andkhoie M, Brass C, et al. Increasing Prevalence and Stable Incidence Rates of Inflammatory Bowel Disease Among First Nations: Population-Based Evidence From a Western Canadian Province. Inflamm Bowel Dis. 2022;28(4):514-22.
8. Benchimol EI, Mack DR, Guttmann A, Nguyen GC, To T, Mojaverian N, et al. Inflammatory Bowel Disease in Immigrants to Canada And Their Children: A Population-Based Cohort Study. The American Journal of Gastroenterology. 2015;110(4):553 - 63.
9. Dhaliwal J, Tuna M, Shah BR, Murthy S, Herrett E, Griffiths AM, et al. Incidence of Inflammatory Bowel Disease in South Asian and Chinese People: A Population-Based Cohort Study from Ontario, Canada. Clin Epidemiol. 2021;13:1109-18.
10. Hracs L, Windsor J, Gorospe J, Cummings M, Coward S, Buie M, et al. [Pre-print] The global evolution of inflammatory bowel disease across four epidemiologic stages2024 January 30, 2024. Available from: https://www.researchsquare.com/article/rs-3846147/v1.
11. Ng SC, Shi HY, Hamidi N, Underwood FE, Mphil WT, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. The Lancet. 2018;390(10114):2769 - 78.
12. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nature Reviews Gastroenterology & Hepatology. 2021;18(1):56-66.
13. Herauf M, Coward S, Pena-Sanchez JN, Bernstein CN, Benchimol EI, Kaplan GG, et al. Commentary on the Epidemiology of Inflammatory Bowel Disease in Compounding Prevalence Nations: Toward Sustaining Healthcare Delivery. Gastroenterology. 2024.
14. Raygoza Garay JA, Turpin W, Lee SH, Smith MI, Goethel A, Griffiths AM, et al. Gut Microbiome Composition Is Associated With Future Onset of Crohn's Disease in Healthy First-Degree Relatives. Gastroenterology. 2023;165(3):670-81.
15. Shaffer SR, Kuenzig ME, Windsor JW, Bitton A, Jones JL, Lee K, et al. The 2023 Impact of Inflammatory Bowel Disease in Canada: Special Populations—IBD in Seniors. Journal of the Canadian Association of Gastroenterology. 2023;6(Supplement_2):S45-S54.
16. Kuenzig ME, Manuel DG, Donelle J, Benchimol EI. Life expectancy and health-adjusted life expectancy in people with inflammatory bowel disease. Cmaj. 2020;192(45):E1394-E402.
17. Nguyen GC, Bouchard S, Diong C, and PA, Care through Centres of Excellence (PACE) Network. Access to Specialists and Emergency Department Visits in Inflammatory Bowel Disease: A Population-Based Study. J Crohn's Colitis. 2018;13(3):330-6.
18. Kuenzig ME, Stukel TA, Kaplan GG, Murthy SK, Nguyen GC, Talarico R, et al. Variation in care of patients with elderly-onset inflammatory bowel disease in Ontario, Canada: A population-based cohort study. Journal of the Canadian Association of Gastroenterology. 2020;4(2):e16-e30.
19. Leddin D, Carroll M, Gillis C, Cehovin A. Gastroenterology Practitioner and Trainee Numbers in Canada 2018: Annual Report From the Canadian Association of Gastroenterology. J Can Assoc Gastroenterol. 2021;4(2):52-6.
20. Statistics Canada. Table 17-10-0009-01 Population estimates, quarterly. 2023.
21. Kuenzig ME, Benchimol EI, Lee L, Targownik LE, Singh H, Kaplan GG, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Direct Costs and Health Services Utilization. Journal of the Canadian Association of Gastroenterology. 2018;110(9):1324 - 17.
22. Kuenzig ME, Coward S, Targownik LE, Murthy SK, Benchimol EI, Windsor JW, et al. The 2023 Impact of Inflammatory Bowel Disease in Canada: Direct Health System and Medication Costs. Journal of the Canadian Association of Gastroenterology. 2023;6(Supplement_2):S23-S34.
23. Kuenzig ME, Im JHB, Coward S, Windsor JW, Kaplan GG, Murthy SK, et al. The 2023 Impact of Inflammatory Bowel Disease in Canada: Indirect (Individual and Societal) and Direct Out-of-Pocket Costs. Journal of the Canadian Association of Gastroenterology. 2023;6(Supplement_2):S16-S22.

I didn't choose to have Crohn's.
And I didn't choose to stop
responding to immunomodulators.
But together with my doctor,
I ***can*** choose what's next.*

I didn't choose to have UC. And
I didn't choose to respond poorly
to conventional therapy.
But together with my doctor,
I ***can*** choose what's next.*

Talk to your UC or CD patients about the option to **CHOOSE ENTYVIO®**

ENTYVIO® (vedolizumab) is indicated for:

Ulcerative colitis: the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a tumor necrosis factor-alpha (TNFα) antagonist.[1]

Crohn's disease: the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNFα antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids.[1]

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

* Fictitious patients, for illustrative purposes only.
May not be representative of the general population.

Pr Entyvio® vedolizumab

Entyvio®
vedolizumab

The ONLY gut-selective anti-inflammatory biologic indicated in UC and in CD in Canada.[1,2*]

Consult the Product Monograph at www.takeda.com/en-ca/ENTYVIOpm for important information on:

- Contraindications including active severe infection or opportunistic infections
- Warnings and precautions regarding infusion-related reactions (IRR) and hypersensitivity reactions; increased risk of infections or opportunistic infections; the risk of progressive multifocal leukoencephalopathy (PML); caution in patients previously treated with biologic agents other than infliximab; recommendations against concomitant use of ENTYVIO® with biologic immunosuppressants and use in patients with jaundice or other evidence of significant liver injury; recommendations on concurrent administration with live vaccines; use of adequate contraception in women of childbearing potential and caution in use in nursing women.
- Conditions of Clinical Use, Adverse Reactions, Interactions, and Dosage and Administration.

The Product Monograph is also available by calling 1-800-268-2772.

---

* Comparative clinical significance has not been established.

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

Takeda

PRMCDA/CA/ENTY/0325E

REVIEWED BY PAAB

MEMBER OF INNOVATIVE MEDICINES CANADA

BARBARA BIELAWSKA, MD, MSC, FRCPC

Dr. Barbara Bielawska, MD, MSc, FRCPC, Department of Medicine, Division of Gastroenterology, University of Ottawa. Dr. Barbara Bielawska is an Assistant Professor of Medicine at the University of Ottawa and has been working as a clinician investigator at The Ottawa Hospital since 2018, where she is the Medical Lead for Inpatient Nutrition and the Medical Director of the Home TPN program. She trained at Queen's University (MD, Internal Medicine, M.Sc. in Clinical Epidemiology) and the University of Toronto (Gastroenterology and Fellowship in Clinical Nutrition). Dr. Bielawska is a member of the Canadian Malnutrition Taskforce advisory committee. Her clinical and research interests include disease related malnutrition, intestinal failure, sarcopenic obesity and bariatric malnutrition, as well as parenteral and enteral nutrition support for benign and malignant disease.

Affiliations: Department of Medicine, Division of Gastroenterology, University of Ottawa

PERIOPERATIVE NUTRITIONAL CONSIDERATIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Introduction

Despite significant advances in medical therapy for inflammatory bowel disease (IBD) in recent decades, surgical management remains common in the setting of both Crohn's disease (CD) and ulcerative colitis (UC). While the risk of colectomy for UC has declined in the biologic era, most patients with CD will undergo at least one intestinal resection in their lifetime.[1]

Preoperative nutritional status is a well-established determinant of surgical morbidity.[2,3] Surgery elicits a metabolic stress response that is proportional to the extent of surgical injury. Adequate lean body and micronutrient stores are needed for healing of surgical incisions, and the individual must be metabolically capable of anabolism for tissue repair.[2] Deficits at any point in this process may lead to complications including anastomotic failure, surgical site infections, delayed return of gastrointestinal (GI) function, and postoperative physical disability with prolonged length of hospital stay.[3]

Patients with IBD are well known to have a high prevalence of nutritional disorders including protein calorie malnutrition, sarcopenia, obesity, and micronutrient deficiencies.[4-7] Patients with severe active disease unresponsive to medications and those undergoing surgery have the highest malnutrition rates of up to 85%.[6,8,9] Malnutrition in IBD results chiefly from a combination of poor dietary intake and chronic inflammation.[6] Inflammatory cytokines enact systemic metabolic changes, whereby peripheral tissue stores are mobilized to support production of acute phase reactants, and a state of insulin resistance diverts nutrients from non-essential targets including muscle.[2] This produces a catabolic state in which muscle protein degradation exceeds synthesis, leading to net muscle loss roughly proportional to the severity and duration of inflammatory stress.[2] Corticosteroid use and reduced physical activity can further lead to negative changes in body composition.[6]

Nutritionally speaking, the majority of IBD surgeries are indicated at the worst possible time. Patients undergoing colectomy for acute severe UC (ASUC) have severe systemic inflammation and are profoundly catabolic, whereas those who require intestinal resection for CD may have variable inflammatory activity but frequently have had a long period of disease and reduced intake due to strictures and anorexia. Given the combination of reduced nutritional reserves and a chronic inflammatory state that promotes tissue breakdown rather than healing, it is not surprising that malnutrition in IBD is a powerful risk factor for non-elective surgery as well as increased postoperative morbidity and mortality.[6,8] Low body mass index (BMI) at time of surgery is associated with increased risk of anastomotic failure, postoperative infections, need for re-operation, longer hospital length of stay (LOS), and death.[7] Weight loss in excess of 10% in the six months before IBD surgery, which is present in up to 54% of cases,[7] is also a significant negative predictor, particularly in resections for CD. Although malnutrition is overall more prevalent in CD than UC,[6] ASUC is associated with significant catabolism, and sarcopenia is present in up to one third of UC patients with high disease activity.[5] Sarcopenia, the condition of reduced muscle mass and strength, is also present in one quarter of patients with CD at time of surgery and importantly, is independent of BMI, occurring commonly

Malnutrition Universal Screening Tool (MUST)	
	Points
BMI kg/m^2	>20 = 0 18.5-20 = 1 <18.5 = 2
Unplanned weight loss in past 3-6 months (%)	< 5 = 0 5-10 = 1 > 10 =2
Patient is acutely ill and there has been or is likely to be no nutritional intake for >5 days	2
Total score	0 = low risk 1 = medium risk 2+ = high risk

Saskatchewan IBD Nutrition Risk Tool (SaskIBD-NR)	
	Points
Have you experienced nausea, vomiting, diarrhea or poor appetite for greater than two weeks?	No = 0 1-2 symptoms = 1 >3 symptoms = 2
Have you lost weight in the last month without trying?	No = 0 Unsure = 1 Yes = <5lbs = 0 5-10lbs = 1 10-15lbs = 2 >15lbs = 3
Have you been eating poorly because of a decreased appetite?	No = 0 Yes = 2
Have you been restricting any foods or food groups?	No = 0 Yes = 2
Total score	0-2 = low risk 3-4 = medium risk >5 = high risk

Table 1. The Malnutrition Universal Screening Tool (MUST) and the Saskatchewan IBD Nutrition Risk Tool (SaskIBD-NR)(1) are malnutrition screening tools that have been validated in the setting of IBD; adapted from Haskey N, Pena-Sanchez JN, Jones JL, Fowler SA. Development of a screening tool to detect nutrition risk in patients with inflammatory bowel disease. Asia Pac J Clin Nutr. 2018;27(4):756-62

in patients with normal weight and overweight.[7] IBD patients with sarcopenia have an increased risk of needing surgery including higher rates of colectomy in UC.[5] Sarcopenia is also independently associated with an increased risk of major postoperative complications, including infection, critical care unit admission, increased LOS, and venous thromboembolism.[5]

While low BMI is associated with increased risk of many postoperative complications, the evidence for increased risk with obesity is inconclusive with some studies suggesting increased risk and some showing no difference.[7]

With a growing armamentarium of biologic drugs that can instill hesitancy to declare failure of medical

therapy, IBD patients can have long periods of poor nutrition and uncontrolled inflammation preceding an eventual surgical intervention. Healthcare system limitations with reduced availability of surgical resources, exacerbated by the COVID-19 pandemic, have introduced further surgical delays during which nutritional status continues to decline. Given the high prevalence and strong impact of malnutrition on surgical outcomes in IBD, there is a need for a proactive and aggressive nutritional approach in this population.

Preoperative Considerations

Screening and Assessment

All patients with IBD should undergo nutritional evaluation prior to surgery, at minimum with a nutritional screening tool (e.g., MUST, SaskIBD-NR; **Table 1**), followed by formal nutritional assessment by a registered dietitian for those who screen medium to high risk for malnutrition.[6,10] Assessment of weight or BMI alone is insufficient, as there can be profound changes in body composition and hidden sarcopenia in obesity.[6] Albumin should not be used to evaluate nutritional status[7,11] as low albumin levels are caused by inflammation leading to third space redistribution and accelerated albumin breakdown despite normal or even increased albumin synthesis.[2] Albumin is a good indicator of inflammatory stress and has prognostic value for surgical complications, but a preserved albumin level is not uncommon in the presence of severe malnutrition especially when systemic inflammatory burden is low.[2]

Nutritional Intervention

Patients diagnosed with malnutrition or nutritional risk should receive a preoperative nutritional intervention.[6] If severe malnutrition is present and surgery is not emergently required, nutrition society guidelines recommend delaying surgery for 7-14 days during which time there should be aggressive nutritional optimization.[6] These recommendations are based mostly on data from major abdominal cancer surgery, where such optimization results in greatly reduced morbidity and mortality, including seven-fold odds reduction in infectious complications.[3] However, the duration of optimization in the setting of IBD may need to be significantly longer in some cases,[6] particularly in complicated CD with abdominal sepsis and/or strictures where there may be both profound undernutrition and high inflammatory burden.

Most of the evidence for preoperative nutritional intervention in IBD comes from CD literature, whereas there is limited evidence for use of preoperative enteral nutrition (EN) or parenteral nutrition (PN) in UC.[7] Physiologic reasoning supports the notion that the immense inflammatory burden of ASUC cannot be overcome by nutrient delivery and source control (i.e., colectomy is needed to reverse the catabolic state.[2]) Nutrition support modalities outlined below are thus mostly considered for the surgical CD patient, although they may also apply to some UC patients, for whom the nutritional approach should be individualized.[6] In general, the approach is always oral feeding in preference to tube feeding, and parenteral feeding only if the other two modalities fail. Immediately prior to surgery, prolonged fasting (i.e., fasting after midnight) should be avoided in line with Enhanced Recovery After Surgery (ERAS) principles, as this practice exacerbates insulin resistance and increases metabolic stress.

Oral and Enteral Feeding

The preferred method of nutritional intervention in patients who cannot achieve adequate intake with diet alone is the use of oral nutritional supplements (ONS), particularly as this can be done at home.[3,6] ONS can deliver substantial calories and protein, are well tolerated by patients, and when providing up to 600 kcal/d, they do not impair intake of regular food.[6] In some cases, ONS can be used as the exclusive means of nutritional intake, termed exclusive EN (EEN). EEN is an established therapy for treatment of CD in children where it has efficacy similar to corticosteroids, but data have also emerged supporting its use in adults.[12] In the presence of abscess when immune suppressants are contraindicated, EEN not only supports nutrition but can also exert anti-inflammatory effects.[8] If adequate intake cannot be achieved through diet and/or ONS, but there is no contraindication to use of the GI tract for nutrition, a feeding tube for delivery of EN is the next step.[8] Even in the setting of intestinal strictures and partial bowel obstruction where ONS are not tolerated, slow infusion of EN via tube can be successful.[8] Supplemental EN can be used for overnight tube feeding while patients are encouraged to eat during the day. There is no difference in efficacy between EN delivered by tube versus EN consumed orally.[6] Oral EN is feasible and well tolerated in the majority of patients with severe CD who have indications for preoperative EN.[13] Both partial EN and EEN have shown similar benefits.[13] There is insufficient evidence to promote the use of specific products, although typically a polymeric product is preferred.[8]

Retrospective cohorts of EEN before surgery in CD have demonstrated improvement in inflammatory markers and reduced postoperative infectious and anastomotic complications, with up to 25% of patients no longer requiring surgery.[7] Several small prospective trials seem to confirm these benefits.[7,14] Preoperative EN has also shown benefit for reduced major complications in the setting of sarcopenia.[5] Adequate duration of preoperative oral and enteral nutrition interventions has yet to be defined and varies by individuals and likely the type of surgery; however, objective reduction in inflammation has been proposed as a surrogate marker that optimization has been achieved.[15] The time to reach this endpoint appears to be between 2 and 5 weeks in most CD patients.[15] It has been suggested that preoperative EEN should last for no

less than 2 weeks, with preference for 4-6 weeks.[13] In patients with mild-to-moderate malnutrition in whom surgery will not occur for 3 months or more, personalized dietary counselling and the use of ONS have been associated with low risk of postoperative complications and some improvement in body composition before surgery.[14]

Parenteral Nutrition

When there is an indication for preoperative nutrition support but EN is contraindicated or not feasible, PN is required. Typically, this occurs in the setting of bowel obstruction, ileus or a high output fistula.[3] Although a low output distal small bowel or colocutaneous fistula does not require use of PN, a proximal or high output fistula necessitates restriction in oral intake and PN, although maintaining at least partial oral or EN intake is beneficial.[6] PN is also needed in cases of EN failure, which is more likely to occur in patients who require hospital admission preoperatively due to their illness, and those with higher nutritional risk.[13] PN should always be used in conjunction with an oral/EN diet unless those are absolutely contraindicated.[6]

In CD patients with malnutrition, preoperative PN reduces complications and is associated with an approximately 20 cm shorter length of intestinal resection,[7] but potentially at the cost of increased hospital LOS.[11] Benefits are seen with PN duration of at least 5 days and are greater if PN is also continued postoperatively.[7,11] Newer generation lipid emulsions containing fish oil and olive oil may have anti-inflammatory benefits in the setting of surgery that translate to reduced complications, although further study is needed.[11] A concern with the use of PN is often around risk of blood stream infection in the setting of central venous catheter (CVC) use. In cases where PN is needed for less than 10-14 days, the use of peripheral PN should be strongly considered as this therapy can deliver 100% of a patient's protein requirements without the need for a CVC.[8] Even if caloric needs are not met but protein intake can reach 1.5 g/kg/day, there is reduction in postoperative infections in CD.[9]

Postoperative Considerations

Early Postoperative Care

Early (within 24 hours) re-introduction of oral or enteral feeding after surgery for IBD is associated with improved outcomes,[1] including significant reduction in LOS. There is strong evidence that EN within 24 hours of surgery for CD reduces complications and accelerates anastomotic healing.[6] The use of ONS should also be encouraged at this stage if oral intake is inadequate. EN via feeding tube is indicated for patients who cannot initiate nutrition orally or if oral intake will be nil for 5 days or not exceed 50% of requirements for more than a week.[3,6] In patients who are malnourished at the time of surgery, such as when emergency surgery is needed, it is recommended to initiate EN or PN as soon as possible postoperatively.[8] In patients who were receiving PN preoperatively, PN should continue postoperatively until adequate (meeting at least 50-60% of caloric needs) oral or tube feeding is established.[3] Generally, perioperative care of IBD patients should follow ERAS principles including early feeding, early mobilization and maintenance of normoglycemia.[6]

High Output Ileostomy

CD is a strong independent risk factor for development of a high output ileostomy (HOS).[16] Management of HOS requires multiple components of care: expert dietetic advice regarding nutrition and hydration strategies; attention to salt and water repletion to maintain hydration and renal function; pharmacotherapy including anti-motility agents (e.g., loperamide, diphenoxylate-atropine, codeine), and anti-secretory agents (proton pump inhibitors).[17] Anti-motility agents can be used alone, or combined if stronger effect is needed. They should be dosed regularly (as opposed to as needed), and preferably timed 30 minutes before meals in order to counteract the pro-motility effect of eating. If patients cannot maintain urine output above 1.2 L per day, they should be considered for home IV fluids.[17] Provided there is not a concurrent pathology such as obstruction or active IBD, HOS tends to improve over time with bowel adaptation.

Diarrhea

The same medications as those used in HOS can be used to treat malabsorption-related diarrhea after IBD surgery. In the setting of ileal resection for CD, diarrhea may be partly due to bile acid malabsorption; however, bile acid binding medications such as cholestyramine should be used with caution and avoided in patients with extensive (>60-100 cm) ileal resection, as these patients are already bile acid deficient and these drugs will worsen fat malabsorption. Bile acid binders and fibre supplements are to be avoided when there is no colon in continuity (i.e., ileostomy) as they have no physiologic basis for use in this setting and exacerbate nutrient malabsorption.[18]

Short Bowel Syndrome

Patients with CD who undergo extensive or repeated small bowel resections are also at risk of developing short bowel syndrome (SBS), which can lead to intestinal insufficiency or intestinal failure. The risk of SBS should be considered prior to intestinal resection and can be predicted based on the location of intestinal resection and length of remaining small bowel. Jejunal resections are much better tolerated than ileal resections, and preservation of ileocecal valve and/or colon segment in continuity are of great benefit for maintaining intestinal autonomy.[19] Home PN may be required in cases of chronic intestinal failure from SBS.

These patients should be treated by an experienced intestinal failure program for intestinal rehabilitation, as weaning off PN can be accomplished in up to 50% of patients within two years and some patients may benefit from use of gastrointestinal growth factor therapy.[19]

Micronutrients

Because most vitamins and minerals are bound to plasma proteins that are affected by the acute phase response, micronutrient testing should occur following resolution of acute surgical stress when there is no further systemic inflammation related to active IBD.[7,20] Micronutrient deficiencies can be predicted by certain clinical situations. For instance, B12 deficiency can occur with as little as 20 cm resection of distal ileum,[2] while zinc is depleted in the setting of high output ostomy, significant diarrhea, and enterocutaneous fistula.[20] Micronutrient testing should be tailored to patient disease characteristics, anatomy, diet and signs of deficiency (ex. presence of anemia), but should include B12, vitamin D and iron studies as a minimum.[10] Generally, micronutrients should be checked annually when IBD is in remission but patients with a history of upper GI resection or multiple or extensive bowel resections, and those with SBS should receive extra attention to their micronutrient status.[6]

Long-term Outcomes

Patients with UC who undergo colectomy for medically refractory disease typically have good nutritional outcomes. With removal of the inflamed organ, nutritional status improves and sarcopenia will even reverse.[5] In patients with CD, surgery has also been shown to improve lean body mass, although those with sarcopenia are at greater risk of postoperative complications, which can lead to worsening nutritional status in some cases.[5] After IBD surgery, patients need a personalized approach according to their anatomy and disease, ideally including consultation with a skilled registered dietitian. Patients, especially those with sarcopenia, should be advised to do regular resistance exercises, and consume a minimum of 1 g/kg/day of protein in quiescent disease and 1.2-1.5 g/kg/day in active disease.[6] Patients with ileostomy should have regular monitoring of renal function and hydration status.

Conclusions

Surgery remains a mainstay in the treatment of complicated and refractory IBD. These patients have high rates of malnutrition and are at significant risk of surgical complications that directly result from an altered metabolism related to inflammation and malnutrition. Preoperative nutritional screening should be mandatory for all IBD patients who require surgery, and personalized optimization undertaken if malnutrition or high nutritional risk is detected. Nutrition care pre-operatively and post-operatively reduces risk of complications and significantly improves outcomes, and in the setting of refractory inflammation, surgery itself leads to improved nutritional status long term. There is emerging evidence in other fields supporting the use of multi-modal prehabilitation combining nutritional intervention with an exercise program and mental health support. Future studies should evaluate comprehensive prehabilitation in patients with IBD.

Key Takeaways:

1. Patients undergoing surgery for IBD have a high prevalence of malnutrition due to catabolic effects of chronic inflammation coupled with inadequate nutritional intake
2. Malnutrition, especially if there is weight loss exceeding 10% in the prior 6 months, is a strong predictor of adverse surgical outcomes in IBD including infections, anastomotic failure and increased length of stay
3. All patients undergoing surgery for IBD should have a nutritional evaluation prior to surgery using a nutritional risk screening tool followed by nutritional assessment and intervention for those who screen positive
4. If need for surgery is non-emergent and severe malnutrition is present, surgery should be delayed for at least 7-14 days to allow for aggressive nutritional optimization
5. In complicated CD, pre-operative enteral nutrition for at least 2 weeks but preferably 4-6 weeks is demonstrated to reduce post-operative infectious and wound healing complications
6. Successful surgery will improve the nutritional status of IBD patients, but monitoring is required for malabsorptive complications including micronutrient deficiencies, protein calorie malnutrition from SBS, and dehydration in those with an ostomy

Correspondence:

Barbara Bielawska, MD, MSC, FRCPC
Email: bbielawska@toh.ca

Financial Disclosures:

Barbara Bielawska
Speaking Honorarium: Baxter Corporation

References:

1. Barnes EL, Lightner AL, Regueiro M. Perioperative and postoperative management of patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol.* 2020;18(6):1356-66.
2. Sobotka L, Allison SP, European Society for Clinical N, Metabolism. Basics in clinical nutrition. Fifth edition. ed. Prague: Galén; 2019. XXXIV, 676 pages.
3. Weimann A, Braga M, Carli F, et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clin Nutr.* 2021;40(7):4745-61.
4. Gold SL, Raman M. Malnutrition Assessment in patients with inflammatory bowel disease. *Canadian IBD Today.* 2023;1(1):35-42.
5. Ryan E, McNicholas D, Creavin B, et al. Sarcopenia and inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis.* 2019;25(1):67-73.
6. Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on Clinical Nutrition in inflammatory bowel disease. *Clin Nutr.* 2023;42(3):352-79.
7. Adamina M, Gerasimidis K, Sigall-Boneh R, et al. Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis.* 2020;14(4):431-44.
8. Chiu E, Oleynick C, Raman M, et al. Optimizing inpatient nutrition care of adult patients with inflammatory bowel disease in the 21st century. *Nutrients.* 2021;13(5):1581.
9. Yamamoto T, Lightner AL, Spinelli A, et al. Perioperative management of ileocecal Crohn's disease in the current era. *Expert Rev Gastroenterol Hepatol.* 2020;14(9):843-55.
10. Gold SL, Raman M. Editorial: a formula shake each day keeps the complications away - the tolerability and effect of orally-delivered enteral nutrition in improving post-operative outcomes in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2022;56(4):739-40.
11. Schwartz E. Perioperative parenteral nutrition in adults with inflammatory bowel disease: a review of the literature. *Nutr Clin Pract.* 2016;31(2):159-70.
12. Day A, Wood J, Melton S, Bryant RV. Exclusive enteral nutrition: An optimal care pathway for use in adult patients with active Crohn's disease. JGH Open. 2020;4(2):260-6.
13. Meade S, Patel KV, Luber RP, et al. A retrospective cohort study: pre-operative oral enteral nutritional optimisation for Crohn's disease in a UK tertiary IBD centre. *Aliment Pharmacol Ther.* 2022;56(4):646-63.
14. Fiorindi C, Cuffaro F, Piemonte G, et al. Effect of long-lasting nutritional prehabilitation on postoperative outcome in elective surgery for IBD. *Clin Nutr.* 2021;40(3):928-35.
15. Zangenberg MS, Horesh N, Kopylov U, et al. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: a systematic review. *Int J Colorectal Dis.* 2017;32(12):1663-76.
16. Seifarth C, Augustin LN, Lehmann KS, et al. Assessment of risk factors for the occurrence of a high-output ileostomy. *Front Surg.* 2021;8:642288.
17. Bridges M, Nasser R, Parrish C. High output ileostomies: the stakes are higher than the output. *Pract Gastroenterol.* 2019.
18. Bering J, DiBaise JK. Short bowel syndrome: Complications and management. *Nutr Clin Pract.* 2023;38 Suppl 1:S46-S58.
19. Bielawska B, Allard JP. Parenteral nutrition and intestinal failure. *Nutrients.* 2017;9(5):466.
20. Gold SL, Manning L, Kohler D, et al. Micronutrients and their role in inflammatory bowel disease: function, assessment, supplementation, and impact on clinical outcomes including muscle health. *Inflamm Bowel Dis.* 2023;29(3):487-501.

TRUST IN THE POWER OF STELARA®

TO TREAT PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

The image depicted contains models and is being used for illustrative purposes only.

STELARA®/STELARA® I.V. is indicated[1]:

- for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

View STELARA® efficacy data and resources >

Contraindications:

- Patients with known hypersensitivity to any components of STELARA®/STELARA® I.V.
- Severe infections such as sepsis, tuberculosis, and opportunistic infections

Relevant warnings and precautions:

- Potential to increase the risk of infections and reactivate latent infections
- STELARA®/STELARA® I.V. should not be given to patients with any clinically important active infection. Patients should be evaluated for tuberculosis infection prior to therapy and monitored for active tuberculosis during and after treatment
- Potential to increase the risk of malignancy
- All patients, in particular those greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy, or those with a history of PUVA treatment, should be closely monitored for skin cancer
- Hypersensitivity reactions including serious allergic reactions (anaphylaxis and angioedema), allergic alveolitis, and eosinophilic pneumonia
- May cause allergic reactions in individuals sensitive to latex
- Concurrent use with live viral or bacterial vaccines is not recommended
- For infants exposed in utero, use of live vaccinations is not recommended under 6 months of age, unless the benefit of vaccination clearly outweighs the risk
- Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA®/STELARA® I.V.
- May affect allergy immunotherapy
- If reversible posterior leukoencephalopathy syndrome is suspected, administer appropriate treatment and discontinue STELARA®/STELARA® I.V.
- Should be given to a pregnant woman only if the benefit clearly outweighs the risk
- Women of childbearing potential should use contraception and should receive preconception counselling before planning a pregnancy as STELARA®/STELARA® I.V remains in circulation for approximately 15 weeks after treatment

For more information:

Please consult the Product Monograph at www.janssen.com/canada/our-medicines for important information relating to adverse reactions, drug interactions, and dosing that has not been discussed in this piece. The Product Monograph is also available by calling 1-800-567-3331.

Reference:

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

Janssen Inc. | 19 Green Belt Drive | Toronto, Ontario | M3C 1L9 | www.janssen.com/canada

REVIEWED BY PAAB

MEMBER OF INNOVATIVE MEDICINES CANADA

Stelara® ustekinumab | Stelara® I.V. ustekinumab

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

CATHY LU, MD, MSC

Dr. Cathy Lu is a gastroenterologist and Assistant Professor at the University of Calgary. She completed a joint two year advanced IBD fellowship at the University of Alberta and the University of Calgary with specialization in intestinal ultrasound. She is an operational committee board member of the STAR (Stenosis, Therapy, and Anti-Fibrotic Research) Consortium and leads the development of the ultrasound index for Crohn's disease strictures. She has also served as a member of the scientific committee for IBUS (the International Bowel Ultrasound Organization) and the Canadian Association of Gastroenterology. Dr. Lu currently co-chairs the scientific committee of iUS-CAN, the United States and Canada consortium for IUS. Her primary research interests are in fibrostenotic Crohn's disease, intestinal ultrasound, and translational research identifying biomarkers in diagnosis, monitoring, and treatment response in IBD.

Affiliations: Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta

LATEST INTESTINAL ULTRASOUND ADVANCEMENTS IN INFLAMMATORY BOWEL DISEASE

Introduction

Inflammatory bowel disease (IBD) treatment has evolved from monitoring clinical symptoms to targeting objective measurements of mucosal healing with endoscopic and radiologic imaging. It is well known that clinical symptoms do not match disease severity. Frequent evaluation with radiologic imaging is now the standard of care. Although Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) recommendations do not list radiographic targets as an endpoint due to the "limited ability of the currently available treatments to achieve transmural healing," this will likely evolve over time particularly with the rapidly growing uptake of intestinal ultrasound (IUS) in clinical trials.[1] For the time being, imaging is considered as an "adjuvant assessment rather than a formal treatment target."[1]

While endoscopy is the current reference standard technique for examining the bowel in IBD, the feasibility of repeating these invasive examinations for monitoring is limited. One of the greatest limitations of endoscopy in the context of IBD is its inability to evaluate the extent of transmural involvement and peri-enteric disease complications. Furthermore, assessing the proximal disease extent in Crohn's disease (CD) is impossible when there is a failure to intubate a strictured ileum. Consequently, computed tomography (CT), magnetic resonance imaging (MRI), and IUS are all valuable diagnostic imaging modalities for fully monitoring disease extent, severity, and progression. IUS has been shown in reviews and meta-analyses to be equally sensitive and specific as CT and MRI in diagnosing and monitoring CD,[2,3] and has high accuracy for disease activity when compared to endoscopy in diagnosing and monitoring ulcerative colitis (UC).[4,5] IUS is advantageous for its accuracy, non-invasiveness, and easy repeatability due to excellent patient tolerability. Overall, gastroenterologist-performed IUS has revolutionized the ability to visualize inflammation and complications in the bowel. This overview will discuss the availability of IUS, its current use in CD and UC, and future directions.

Current Use of Gastroenterologist-Led IUS in Canada

A. IUS in Canada

The University of Calgary IBD Unit was the first in North America to establish an innovative clinic that uses IUS at the bedside to safely evaluate the bowel. Currently, IUS clinics led by gastroenterologists are present in all but three provinces in Canada. The interest in IUS is experiencing rapid growth globally.

Studies evaluating patient experiences and preferences for disease monitoring in CD has repeatedly shown a desire among patients to have access to IUS for varying reasons, including education of disease severity in real-time and increased engagement.[6,7] Its ease of use for patients by physicians has made IUS a repeatable choice for routine surveillance and urgent imaging. The use of IUS by gastroenterologists for timely decision making has been shown to improve disease control and limit invasive testing.[8]

B. IUS Training

The International Bowel Ultrasound Group (IBUS), based in Germany, has established the only credentialed training program for IBD-focused IUS monitoring in the world. In Canada, the majority of gastroenterologists have either been trained in IUS from radiologists experienced in IUS, or from IBUS. At present, eight IBUS-certified Canadian training centres in pediatric and adult IUS are available (Kelowna, Edmonton [pediatric and adult], Calgary [pediatric and adult], Saskatoon, Hamilton, and Bridgewater). Other centres that are either developing or have established IUS programs include Vancouver, Lethbridge (Alberta), Grand Prairie (Alberta), Winnipeg, Toronto, London, Montreal, Sherbrooke, and Halifax.

Most recently, studies have assessed the accuracy of IUS performed by gastroenterologists by taking into account their abdominal ultrasound experience.[9] IBUS mandates a minimum of 40 observed examinations for a gastroenterologist to be certified for basic competence in IUS. A study by Bezzio et al. observed that trainees with limited abdominal ultrasound experience (<50 exams) required a minimum of 84 exams to achieve concordance with the expert sonographer for detecting findings such as increased bowel wall thickness.[9] To achieve advanced IUS competence, a minimum of 97 examinations is required to obtain concordance with an expert sonographer for identifying intra-abdominal complications.

C. IUS Application in Clinic and Limitations

Hallmark Features of IBD Activity

Four key features on IUS allow for grading of CD and UC activity. These include bowel wall thickness, colour doppler signal (CDS), presence of inflammatory fat, and loss of wall stratification **(Table 1)**. Bowel wall thickness is the most specific objective measure for inflammatory activity with a thickness of > 3mm in the small bowel and colon indicating abnormality.[10] Other adjunct activity parameters include lymphadenopathy. Scoring indices have been devised and the IBUS-SAS (Segmental Activity Score) is one of the most widely used tool that incorporates the four aforementioned parameters.[10] Real-time interpretation of these parameters including complications such as strictures and penetrating disease for CD, and use during UC flares in clinic allows for immediate decision making and reduces reliance on other imaging modalities and endoscopy. Validated scoring indices for CD (Simple Ultrasound Score[11]) and UC (Milan Ultrasound Criteria[12] and UC-Ultrasound Index[4,13]) have been established using endoscopy as the comparator. However, a robustly validated, reliable and responsive index remains unavailable to monitor treatment response.

Obstacles to Implementation

Although IUS offers considerable value, barriers for IUS implementation remain present. Obtaining an IUS machine at a Canadian centre requires a financial investment of typically approximately $100 000 to 150 000 CAD. Additional costs for maintenance and service contracts have to also be factored in. Secondly, physicians interested in obtaining certification from IBUS require the completion of three modules (Module 1; intensive introductory hands-on workshop, Module 2; four-week hands-on training module at a certified IBUS training centre, Module 3; advanced workshop and final exam). This is a competitive process and examinations have been typically only offered annually at ECCO (European Crohn's and Colitis Organization) congress. Most gastroenterologists are unable to leave their practice for 4 weeks at a time, and

Intestinal Ultrasound Parameter*	Cut-Offs
Bowel Wall Thickness	>3mm
Colour Doppler Signal (Hyperemia)**	**Modified Limberg Score** 0 – absent 1 - small spots (single vessels) within the wall 2 - long stretches within the wall 3 - longer stretches within the wall extending into the mesentery.
Inflammatory Fat	Present or Absent
Wall Stratification	Focal loss (<3cm) Extensive loss (>/= 3cm)

Table 1. Four Key Inflammatory Bowel Disease Activity Parameters on Intestinal Ultrasound
Adapted from Novak et al. J Crohns Colitis. 2021 Apr 6;15(4):609–16.
*Other parameters such as motility abnormalities, lymphadenopathy, submucosa echogenicity, stricture measurements, and penetrating complications are also evaluated when evaluating activity, but are not in formal intestinal ultrasound activity scoring.
**Other scoring systems for hyperemia are available: Limberg score and International Bowel Ultrasound Color Doppler Signal score.

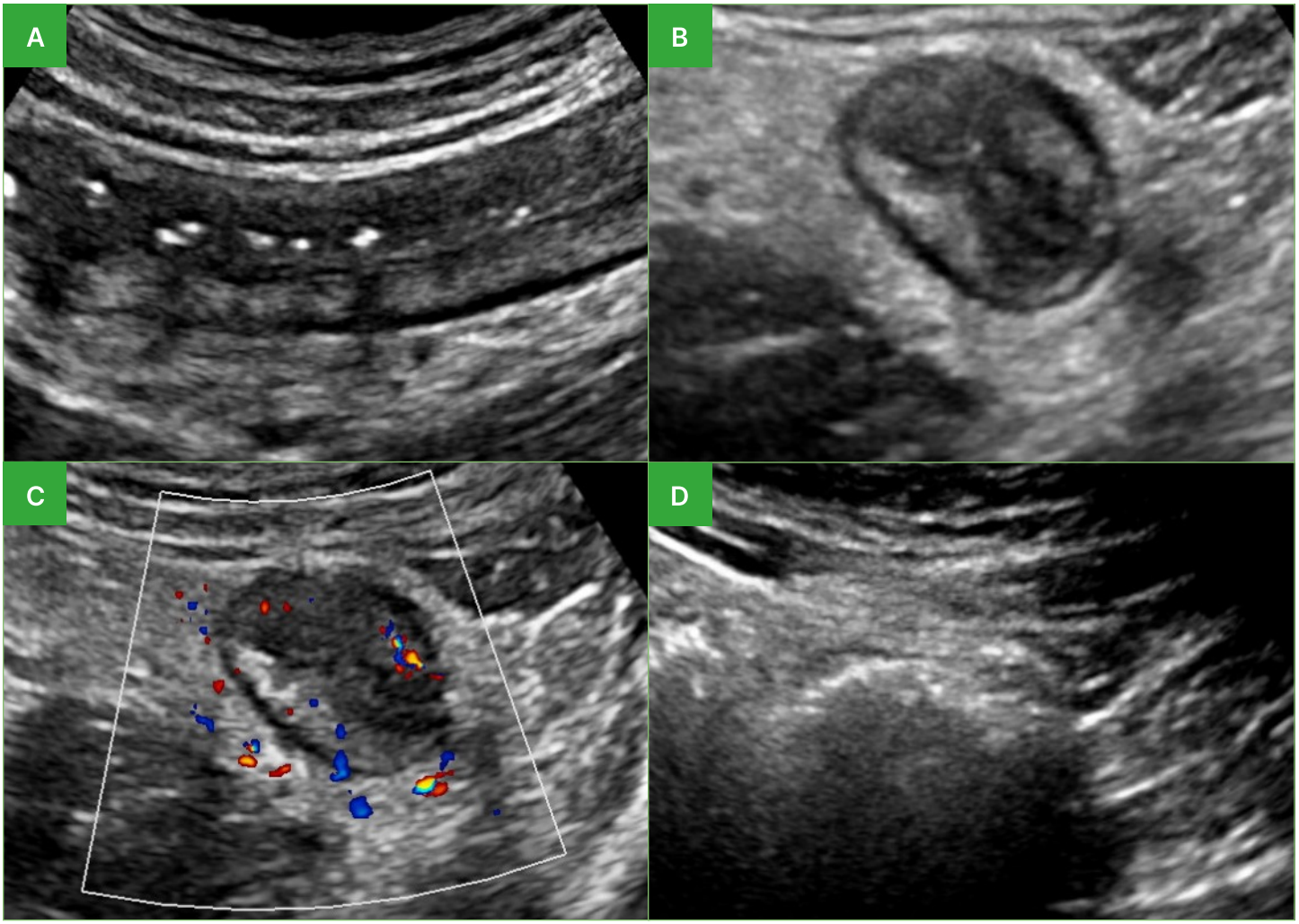


Figure 1. 21 year old male with new diagnosis of left sided ulcerative colitis. Loss of normal descending colon haustration with thickened bowel and loss of stratification in longitudinal view **A**. Ample inflammatory fat seen as echogenic (white) wrapping around descending colon in axial view **B**. Hyperemia graded as modified Limberg 3 with vascular signal in bowel walls and surrounding inflammatory fat **C**. Normal haustration in cross-sectional view of transverse colon unaffected by ulcerative colitis in same patient; *courtesy of Cathy Lu, MD, MSc*

training is typically completed over 1-to-2-week blocks. Training at Canadian centres is organized by IBUS with preference for training of Canadian nationals. Thirdly, gastroenterologist-led IUS during clinic visits generally requires 10 to 15 minutes for straightforward examinations and may take 30 minutes or greater for complex scans such as those with peri-enteric complications, or long segment disease with multi-focal structuring. Allotting time for IUS evaluation, image capture, and documentation may favour academic centres due to the lack of current remuneration and fee codes in the majority of Canadian centres. Achieving competence and maintaining competency in IUS are also areas of current study with comparisons to endoscopy and echocardiography frequently cited.[14,15]

Limitations of IUS include its inability along with CT and MR to detect mild mucosal disease such as a simple endoscopic score of 3 in the ileum or colonic segment. Proctitis is often also difficult to evaluate as examination of the rectum using transabdominal IUS may be limited visually; the transperineal approach is typically favoured in this situation. Similarly, very deep structures of bowel may be missed. Detection of proximal CD such as in the duodenum may also be limited. Abdominal obesity is reported as a limitation of IUS. However, bowel visualization may actually be minimally hampered by central adiposity and body habitus does not predict failure of ultrasound.[16] A criticism of ultrasound is that accuracy is dependent on examining experience of the sonographer. Good reproducibility of assessing bowel thickness and complications has been described between gastroentoerlogists alone, and between gastroenterologists and radiologists from six IBD referral centres.[17,18]

Efficacy of IUS and Comparison with Other Imaging Modalities

IUS is comparable to MR enterography (MRE) in diagnosing CD with a sensitivity of 94%, a specificity of 97%, a positive-predictive value of 97% and a negative predictive value of 94%.[19] Regarding the diagnostic performance of IUS for CD, the ileum, sigmoid, and descending colon have the highest diagnostic performance; however, a lower predictive accuracy has

been reported for the duodenum, proximal jejunum and rectum.[20]

A landmark prospective, multicentre trial, MR Enterography or ulTRasound In Crohn's disease, (METRIC), was conducted in the United Kingdom. The trial evaluated the diagnostic accuracy of MRE and IUS for the extent and activity of newly diagnosed and relapsed CD. This trial's findings have confirmed that both MRE and IUS are accurate and have a high sensitivity for detecting terminal ileal CD, with a sensitivity of 97% (95% confidence interval (CI) 91–99) for MRE, and a sensitivity of 91% (95% CI 79–97), for IUS.[21] This trial has observed that detecting colonic disease on cross-sectional imaging is more challenging. There were no significant differences in detecting colonic disease, with an MRE sensitivity of 64%, and an IUS sensitivity of 73%.[21] Overall, IUS is comparable to MRE and CT enterography (CTE) in identifying the location and activity of IBD.

Post-operative recurrence of CD can be confidently predicted when combining IUS with fecal calprotectin levels.[22] The role of IUS in diagnosing post-operative recurrence of CD has been evaluated in multiple studies.[23–27] More specifically, a recent prospective study has shown that bowel wall thickening of >3 mm and the presence of lymphadenopathy with a fecal calprotectin level of >50 mcg/g is reliable at predicting endoscopic disease recurrence, with less than 5% of patients being falsely classified.[22] Overall, non-invasive techniques such as IUS and fecal calprotectin levels allow for adequate CD evaluation post-surgery, although future studies are necessary to determine whether the changes that can be made to medical therapy without the requirement for endoscopy are appropriate.

Transmural Healing and Response; Definitions on CT, MR, and IUS

Concepts such as transmural healing, transmural remission, and transmural response are evolving and are currently based on expert consensus. However, ongoing studies are working on a prospective validation of these terms. Research has shown that achieving deeper control, particularly in CD, is associated with better long-term outcomes, specifically, with lower rates of surgery, hospitalization, and therapy escalation.[28,29]

Transmural healing refers to the healing of all layers of the bowel in both CD and UC, recognizing that UC does involve layers beyond the mucosal surface **(Figure 1)**. Proposed definitions of transmural response and remission have been described for CT, MRI, and IUS **(Table 1)**.[30] In a systematic review by Geyl et al, transmural remission for any modality was proposed as the improvement of bowel wall thickness to <3 mm for the small bowel and <4 mm for the colon.[30] The authors suggest that the definition of transmural remission should consider both imaging for full thickness assessment and endoscopic evaluation in order to confirm the achievement of transmural remission. Furthermore, the optimal timing for evaluating transmural healing has been found to be at week 26 or 52 for CD, and at week 12 or 14 for UC, also recognizing that some patients will obtain a much quicker response.

Treatment response has been evaluated and in CD it is described as a reduction in bowel wall thickness by >25%, or >2.0 mm, or >1.0 mm, along with one reduction in the colour Doppler signal grade.[31] Transmural remission is defined as normalization of bowel wall thickness, and normalization of all IUS parameters (increased blood flow, loss of bowel wall stratification, and inflammatory mesenteric fat).[32]

For UC, definitions of transmural remission utilized a bowel wall thickness cut off of <3 mm for the colon and an absent colour Doppler signal.[31] Transmural healing data is evolving in UC, particularly as it is being recognized that wall layers other than the inner mucosa are involved. Colectomy for refractory UC is associated with thickening of the muscularis mucosae and increased fibrosis, while submucosal fibrosis is related to the severity of intestinal inflammation.[33] Given that endoscopic biopsies of the mucosa are unable to predict the quantity of fibrosis or muscularis mucosae thickening,[33] IUS is an excellent modality to further understand the composition of the colon, and to study the definitions of transmural remission. IUS is the only imaging modality that is able to detect the five distinct layers of the bowel **(Figure 2)**. Therefore, IUS offers sizable advantages over CT and MR for both clinical evaluation and research.

Current Evidence for Therapies Achieving Transmural Healing on IUS

Emerging data suggests that successful therapies should be able to achieve endoscopic remission and achieve transmural improvement. STARDUST, a randomized controlled trial evaluating a treat-to-target approach for ustekinumab in CD, has utilized IUS to assess the efficacy of treatment.[32] The trial has shown that a transmural response was present as early as week 4 after treatment initiation, and that 46.3% of patients had a progressive IUS response, and 24.1% had achieved transmural remission at week 48.[32]

A prospective study using IUS at baseline and at 6 months, with at least 12 months of follow up after starting a new medication, has shown that transmural healing can predict more favourable long-term outcomes than those of mucosal healing in CD.[34] Furthermore, 32% patients achieved transmural healing (bowel wall thickness <3 mm with normalization of stratification, absent hypervascularization, inflammatory fat, and abscesses/fistula) while 40% achieved mucosal healing; notably, both parameters showed poor correlation with each other (Cohen's $\kappa = 0.387$; $p<0.05$).[34] Transmural healing was an independent predictor of being steroid-free, requiring less drug escalation, and fewer hospitalizations.[34]

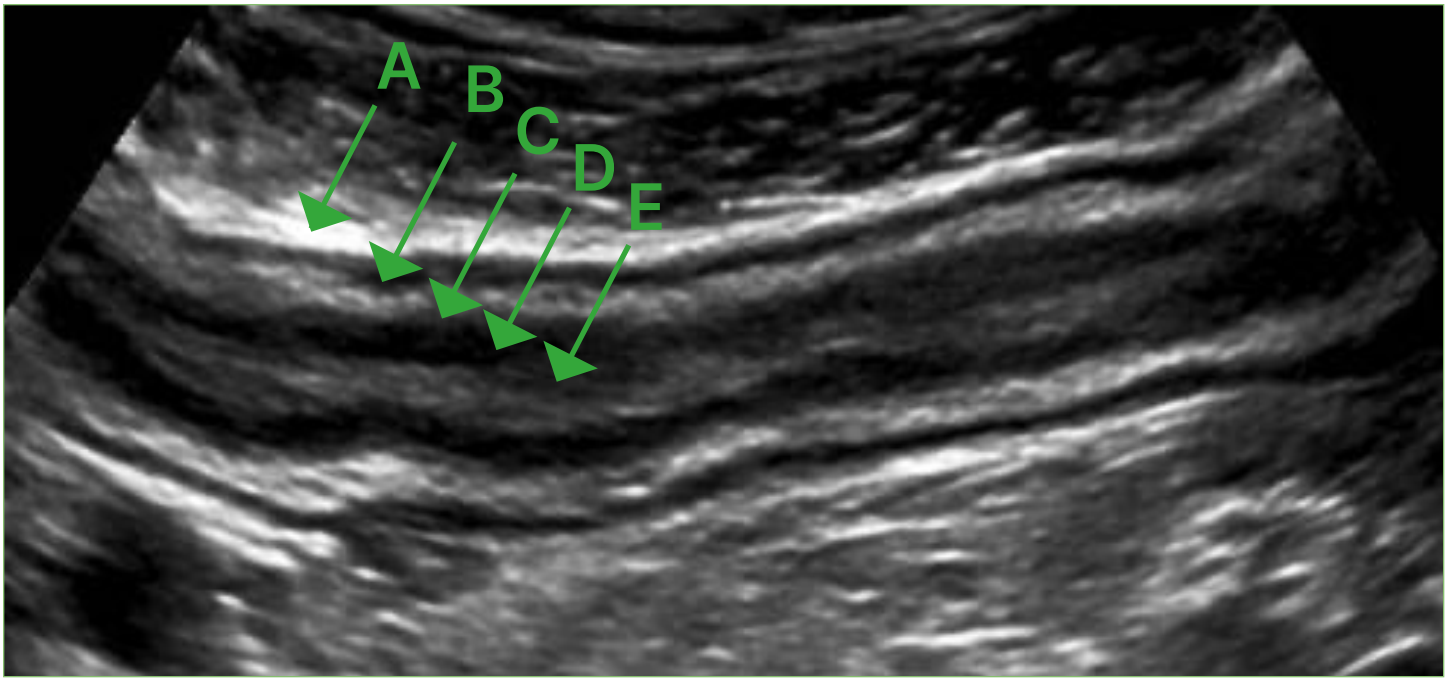


Figure 2. Normal terminal ileum with five wall layers in longitudinal view. Layers alternate in echogenicity. **A.** serosa, **B.** muscularis propria (hypoechoic), **C.** submucosa (echogenic), **D.** muscularis mucosa (hypoechoic), and **E.** mucosa interface; *courtesy of Cathy Lu, MD, MSc*

In UC, a recent prospective cohort study conducted in 2022 has demonstrated that IUS is accurate for determining endoscopic response and remission in patients with moderate-to-severe UC who started treatment with tofacitinib.[5] Patients received IUS and endoscopy at baseline and at week 8. A bowel wall thickness of 2.8 mm (area under curve [AUC] of 0.87) matched endoscopic remission (endoscopic mayo score and Robarts Histopathologic Index), and a decrease of 32% (AUC of 0.87) was able to detect an endoscopic response.[5]

A recent study conducted in 2022 was the first to predict disease progression in UC using the Milan Ultrasound Criteria (MUC), which is a validated transmural IUS score. The study findings suggest that a baseline transmural assessment using MUC could predict a negative disease course, hospitalization, and colectomy.[35]

Although a deeper level of disease control in the form of transmural healing may be optimal, questions remain regarding the following: the appropriate timing of transmural healing; acceptable ranges of healing, with some patients experiencing slower healing; whether an overall improvement in bowel wall thickness along with residual thickness of certain layers, such as the submucosae is meaningful; and whether transmural healing of the small bowel and colon are different. Furthermore, whether strictures can achieve remodelling and transmural healing is an area of interest. Notably, the first anti-fibrotic agent, Agomab-129, is currently available in Canada for Crohn's Disease, and is being evaluated in a phase 2a global clinical trial. Overall, bowel wall thickness is the most frequently described parameter for assessing transmural healing. Future research is required to develop standardized and validated definitions of transmural healing in diagnostic imaging to gain an understanding of the true impact on patient disease control.

Future Frontiers of IUS

A. Artificial Intelligence

The field of artificial intelligence is rapidly growing across all types of cross-sectional imaging. In IUS, machine-learning models have been validated to distinguish between IUS images of normal bowel wall and bowel wall thickening, which is the best surrogate for active disease and inflammation.[36] This machine learning module was trained on a dataset of 1008 images (50% abnormal images, 50% normal images). The model demonstrated high accuracy, sensitivity, and specificity for detection of bowel wall thickening at 90.1%, 86.4%, and 94%, respectively. In addition, the network exhibited an average area under the receiver operating characteristic curve of 0.9777.[36]

B. Future Directions and IUS Advancements in CD Complications

IUS easily detects the morphologic alterations of CD strictures **(Figure 3)**. An expert consensus panel has provided definitions, diagnosis, and treatment targets for anti-fibrotic stricture therapies in CD using CTE and MRE.[37] The three key parameters for small bowel strictures on CT and MR are bowel wall thickness, luminal apposition, and pre-stenotic diameter. Recently, these same parameters for IUS have been evaluated in an international consensus using a modified RAND/University of California Los Angeles process led by the Stenosis Therapy and Anti-Fibrotic Therapy (STAR) consortium. These statements

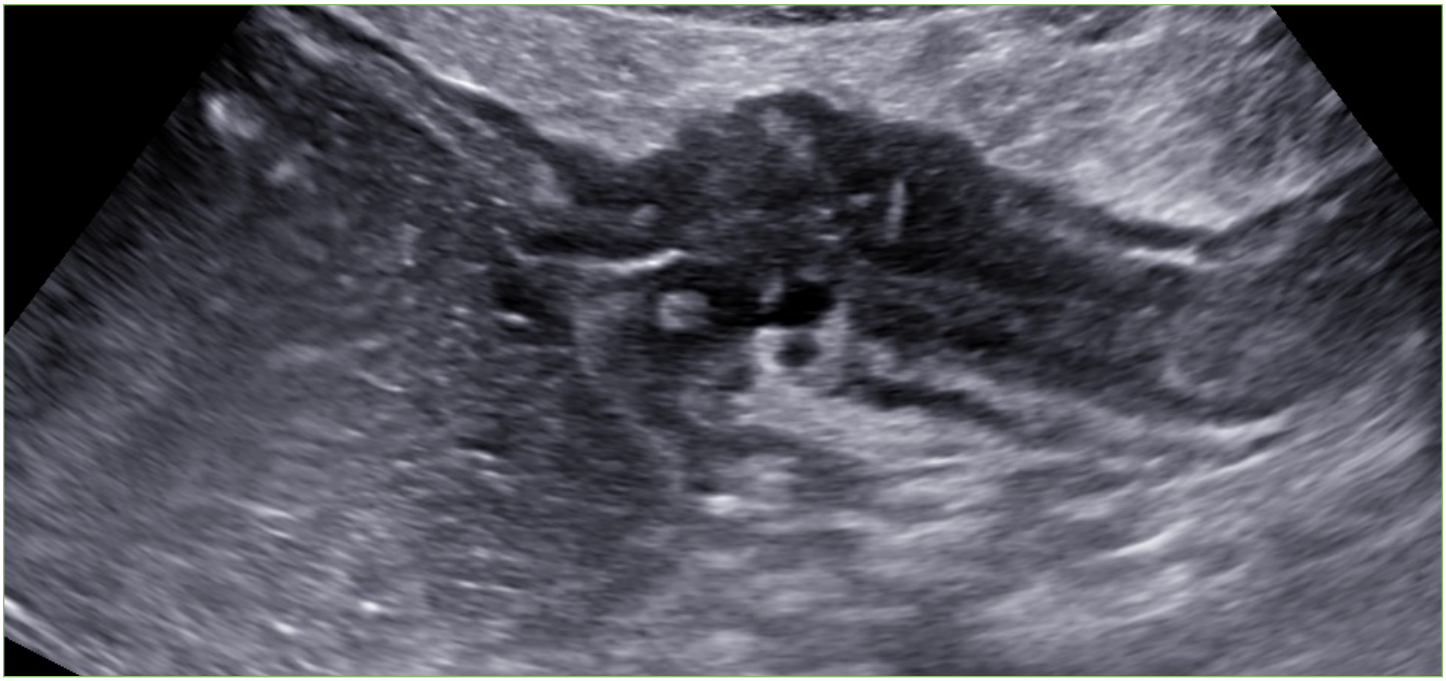


Figure 3. Longitudinal view of neo-terminal ileal stricture with bowel wall thickness 8.9mm, luminal apposition of 1.1mm, and pre-stenotic dilation of 4.5cm; *courtesy of Cathy Lu, MD, MSc*

will lead to the formation of an imminent IUS index for validation and use in clinical trials.

An emerging area of interest in fibrostenotic CD is the relationship of IUS parameters and each individual bowel layer in comparison with histopathology obtained from small bowel resection samples.[38,39] Considering that strictures contain varying degrees of inflammation and fibrosis, understanding the imaging correlates with stricture composition may be of use to assess who can benefit most when considering resection. Studies have shown that distinct IUS findings such as the submucosal layer brightness/echogenicity,[39] mucosal layer thickness,[39] and submucosa spiculates extending toward the mesentery are associated with fibrosis in small bowel CD strictures.[38]

Regarding peri-enteric complications, a recent systematic review, which analyzed 60 of 1498 identified studies, demonstrated that IUS is accurate for diagnosing inflammatory masses and fistulas, with a sensitivity of 0.90 and 0.87, respectively and a specificity of 0.67 and 0.95, respectively.[40]

Conclusions

Timely and accurate measures of inflammation in IBD during routine follow-up are essential to inform clinical decision-making to ensure patients reach therapeutic targets. IUS offers physicians timely information on the structure and function of the bowel including bowel motility, while for the patient, it offers a patient-centred, safe, alternative means of routine monitoring in the clinic. The progress of IUS is rapidly advancing in several areas. These include the development of validated indices, understanding its use in transmural healing and response to therapy, its correlation with histopathology, its integration with artificial intelligence, and its expanding role in training and education. IUS is currently playing a prominent role and is being interpreted centrally, similar to endoscopy, in multi-centre international studies involving both approved and anticipated biologic therapies, and small molecules. This points to a future for IUS that is both exciting and incredibly bright.

Key Takeaways:

1. Gastroenterologist-led intestinal ultrasound improves patients' knowledge of their disease and provides accurate real-time measures of activity in IBD.
2. Validated intestinal ultrasound scoring systems in both UC and CD are available.
3. Intestinal ultrasound utilization is rapidly growing in Canada and the United States, as more gastroenterologists are training and becoming certified in the skill.
4. As intestinal ultrasound provides reproducible and repeatable point-of-care assessment of IBD activity and response to therapy, its use has expanded into clinical trials.

Correspondence:

Cathy Lu, MD, MSc
Email: luc@ucalgary.ca

Financial Disclosures:

Cathy Lu: Speaker fees: Abbvie, Janssen, and Fresenius Kabi. **Advisory board fees:** AbbVie, Celltrion, Janssen, Lilly, Pfizer, Takeda, Fresenius Kabi, Pendopharm, and Ferring.

References:

1. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021 Apr 1;160(5):1570–83.
2. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. Radiology. 2008 Apr;247(1):64–79.
3. Panés J, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34(2):125–45.
4. Bots S, Nylund K, Löwenberg M, Gecse K, D'Haens G. Intestinal Ultrasound to Assess Disease Activity in Ulcerative Colitis: Development of a novel UC-Ultrasound Index. J Crohns Colitis. 2021 Jan 7;15(8):1264–71.
5. de Voogd F, van Wassenaer EA, Mookhoek A, Bots S, van Gennep S, Löwenberg M, et al. Intestinal Ultrasound Is Accurate to Determine Endoscopic Response and Remission in Patients With Moderate to Severe Ulcerative Colitis: A Longitudinal Prospective Cohort Study. Gastroenterology. 2022 Dec 1;163(6):1569–81.
6. Miles A, Bhatnagar G, Halligan S, Gupta A, Tolan D, Zealley I, et al. Magnetic resonance enterography, small bowel ultrasound and colonoscopy to diagnose and stage Crohn's disease: patient acceptability and perceived burden. Eur Radiol. 2019 Mar;29(3):1083–93.
7. Rohatinsky N, Zelinsky S, Dolinger M, Christensen B, Wilkens R, Radford S, et al. Crohn's Disease Patient Experiences and Preferences With Disease Monitoring: An International Qualitative Study. Crohns Colitis 360. 2023 Apr 1;5(2):otad012.
8. St-Pierre J, Delisle M, Kheirkhahrahimabadi H, Goodsall TM, Bryant RV, Christensen B, et al. Bedside Intestinal Ultrasound Performed in an Inflammatory Bowel Disease Urgent Assessment Clinic Improves Clinical Decision-Making and Resource Utilization. Crohns Colitis 360. 2023 Oct 1;5(4):otad050.
9. Bezzio C, Saibeni S, Vernero M, Furfaro F, Monteleone M, Ribaldone D, et al. The learning curve for using intestinal ultrasonography. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2024 Feb 5;S1590-8658(24)00222-6.
10. Novak KL, Nylund K, Maaser C, Petersen F, Kucharzik T, Lu C, et al. Expert Consensus on Optimal Acquisition and Development of the International Bowel Ultrasound Segmental Activity Score [IBUS-SAS]: A Reliability and Inter-rater Variability Study on Intestinal Ultrasonography in Crohn's Disease. J Crohns Colitis. 2021 Apr 6;15(4):609–16.
11. Ripollés T, Poza J, Suarez Ferrer C, Martínez-Pérez MJ, Martín-Algíbez A, de Las Heras Paez B. Evaluation of Crohn's Disease Activity: Development of an Ultrasound Score in a Multicenter Study. Inflamm Bowel Dis. 2021 Jan 1;27(1):145–54.
12. Allocca M, Fiorino G, Bonovas S, Furfaro F, Gilardi D, Argollo M, et al. Accuracy of Humanitas Ultrasound Criteria in Assessing Disease Activity and Severity in Ulcerative Colitis: A Prospective Study. J Crohns Colitis. 2018 Nov 28;12(12):1385–91.
13. Sævik F, Eriksen R, Eide GE, Gilja OH, Nylund K. Development and Validation of a Simple Ultrasound Activity Score for Crohn's Disease. J Crohns Colitis. 2021 Jan 13;15(1):115–24.
14. Dubé C, Rostom A. Acquiring and maintaining competency in gastrointestinal endoscopy. Best Pract Res Clin Gastroenterol. 2016 Jun;30(3):339–47.
15. Burwash IG, Basmadjian A, Bewick D, Choy JB, Cujec B, Jassal DS, et al. 2010 Canadian Cardiovascular Society/Canadian Society of Echocardiography Guidelines for Training and Maintenance of Competency in Adult Echocardiography. Can J Cardiol. 2011;27(6):862–4.
16. Novak KL, Wilson SR. Sonography for surveillance of patients with Crohn disease. J Ultrasound Med Off J Am Inst Ultrasound Med. 2012 Aug;31(8):1147–52.
17. Fraquelli M, Sarno A, Girelli C, Laudi C, Buscarini E, Villa C, et al. Reproducibility of bowel ultrasonography in the evaluation of Crohn's disease. Dig Liver Dis. 2008 Nov;40(11):860–6.
18. Calabrese E, Kucharzik T, Maaser C, Maconi G, Strobel D, Wilson SR, et al. Real-time Interobserver Agreement in Bowel Ultrasonography for Diagnostic Assessment in Patients With Crohn's Disease: An International Multicenter Study. Inflamm Bowel Dis. 2018;24(9 PG-2001–2006):2001–6.
19. Castiglione F, Mainenti PP, De Palma GD, Testa A, Bucci L, Pesce G, et al. Noninvasive diagnosis of small bowel Crohn's disease: direct comparison of bowel sonography and magnetic resonance enterography. Inflamm Bowel Dis. 2013 Apr;19(5):991–8.
20. Parente F, Greco S, Molteni M, Cucino C, Maconi G, Sampietro GM, et al. Role of early ultrasound in detecting inflammatory intestinal disorders and identifying their anatomical location within the bowel. Aliment Pharmacol Ther. 2003 Nov 15;18(10):1009–16.
21. Taylor SA, Mallett S, Bhatnagar G, Baldwin-Cleland R, Bloom S, Gupta A, et al. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. Lancet Gastroenterol Hepatol. 2018 Aug;3(8):548–58.
22. Furfaro F, D'Amico F, Zilli A, Craviotto V, Aratari A, Bezzio C, et al. Noninvasive Assessment of Postoperative Disease Recurrence in Crohn's Disease: A Multicenter, Prospective Cohort Study on Behalf of the Italian Group for Inflammatory Bowel Disease. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2023 Nov;21(12):3143–51.
23. Yung DE, Har-Noy O, Tham YS, Ben-Horin S, Eliakim R, Koulaouzidis A, et al. Capsule Endoscopy, Magnetic Resonance Enterography, and Small Bowel Ultrasound for Evaluation of Postoperative Recurrence in Crohn's Disease: Systematic Review and Meta-Analysis. Inflamm Bowel Dis. 2018 Jan 1;24(1):93–100.
24. Andreoli A, Cerro P, Falasco G, Giglio LA, Prantera C. Role of ultrasonography in the diagnosis of postsurgical recurrence of Crohn's disease. Am J Gastroenterol. 1998 Jul;93(7):1117–21.
25. Rispo A, Bucci L, Pesce G, Sabbatini F, de Palma GD, Grassia R, et al. Bowel sonography for the diagnosis and grading of postsurgical recurrence of Crohn's disease. Inflamm Bowel Dis. 2006 Jun 1;12(6):486–90.
26. Parente F, Sampietro GM, Molteni M, Greco S, Anderloni A, Sposito C, et al. Behaviour of the bowel wall during the first year after surgery is a strong predictor of symptomatic recurrence of Crohn's disease: a prospective study. Aliment Pharmacol Ther. 2004 Nov 1;20(9):959–68.
27. Maconi G, Sampietro GM, Cristaldi M, Danelli PG, Russo A, Bianchi Porro G, et al. Preoperative characteristics and postoperative behavior of bowel wall on risk of recurrence after conservative surgery in Crohn's disease: a prospective study. Ann Surg. 2001 Mar;233(3):345–52.
28. Fernandes SR, Rodrigues RV, Bernardo S, Cortez-Pinto J, Rosa I, da Silva JP, et al. Transmural Healing Is Associated with Improved Long-term Outcomes of Patients with Crohn's Disease. Inflamm Bowel Dis. 2017 Aug;23(8):1403–9.
29. Fernandes SR, Serrazina J, Botto IA, Leal T, Guimarães A, Garcia JL, et al. Transmural remission improves clinical outcomes up to 5 years in Crohn's disease. United Eur Gastroenterol J. 2022 Dec 27;11(1):51–9.
30. Geyl S, Guillo L, Laurent V, D'Amico F, Danese S, Peyrin-Biroulet L. Transmural healing as a therapeutic goal in Crohn's disease: a systematic review. Lancet Gastroenterol Hepatol. 2021 Aug 1;6(8):659–67.
31. Ilvemark JFKF, Hansen T, Goodsall TM, Seidelin JB, Al-Farhan H, Allocca M, et al. Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement. J Crohns Colitis. 2022 May 10;16(4):554–80.
32. Kucharzik T, Wilkens R, D'Agostino MA, Maconi G, Le Bars M, Lahaye M, et al. Early Ultrasound Response and Progressive Transmural Remission After Treatment With Ustekinumab in Crohn's Disease. Clin Gastroenterol Hepatol. 2023 Jan 1;21(1):153-163.e12.
33. Gordon IO, Agrawal N, Willis E, Goldblum JR, Lopez R, Allende D, et al. Fibrosis in Ulcerative Colitis is Directly Linked to Severity and Chronicity of Mucosal Inflammation. Aliment Pharmacol Ther. 2018 Apr;47(7):922–39.
34. Ma L, Li W, Zhuang N, Yang H, Liu W, Zhou W, et al. Comparison of transmural healing and mucosal healing as predictors of positive long-term outcomes in Crohn's disease. Ther Adv Gastroenterol. 2021;14:1–11.
35. Allocca M, Dell'Avalle C, Craviotto V, Furfaro F, Zilli A, D'Amico F, et al. Predictive value of Milan ultrasound criteria in ulcerative colitis: A prospective observational cohort study. United Eur Gastroenterol J. 2022 Mar;10(2):190–7.
36. Carter D, Albshesh A, Shimon C, Segal B, Yershov A, Kopylov U, et al. Automatized Detection of Crohn's Disease in Intestinal Ultrasound Using Convolutional Neural Network. Inflamm Bowel Dis. 2023 Dec 1;29(12):1901–6.
37. Rieder F, Bettenworth D, Ma C, Parker CE, Williamson LA, Nelson SA, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. Aliment Pharmacol Ther. 2018 Aug;48(3):347–57.
38. Allocca M, Dal Buono A, D'Alessio S, Spaggiari P, Garlatti V, Spinelli A, et al. Relationships Between Intestinal Ultrasound Parameters and Histopathologic Findings in a Prospective Cohort of Patients With Crohn's Disease Undergoing Surgery. J Ultrasound Med Off J Am Inst Ultrasound Med. 2023 Aug;42(8):1717–28.
39. Bhatnagar G, Rodriguez-Justo M, Higginson A, Bassett P, Windsor A, Cohen R, et al. Inflammation and fibrosis in Crohn's disease: location-matched histological correlation of small bowel ultrasound features. Abdom Radiol N Y. 2021 Jan;46(1):144–55.
40. Pruijt MJ, de Voogd FAE, Montazeri NSM, van Etten-Jamaludin FS, D'Haens GR, Gecse KB. Diagnostic Accuracy of Intestinal Ultrasound in the Detection of Intra-Abdominal Complications in Crohn's Disease: A Systematic Review and Meta-Analysis. J Crohns Colitis. 2024 Jan 4;jjad215.

Pr RINVOQ® upadacitinib

IS NOW AVAILABLE FOR USE IN

ULCERATIVE COLITIS

A ONCE-DAILY ORAL JAK INHIBITOR[1]*

RINVOQ (upadacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional, and/or biologic therapy.[1]

Please consult the Product Monograph at rinvoq.ca/pm for information about contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling us at 1-888-704-8271.

JAK: Janus kinase.
*Refer to the Product Monograph for complete dosing and administration information.

Reference: 1. RINVOQ Product Monograph. AbbVie Corporation.

abbvie

CA-RNQG-230032A / SE23

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

abbvie.ca
1-888-703-3006

Pr RINVOQ® upadacitinib

LAURA TARGOWNIK, MD

Dr. Laura Targownik is a clinical researcher at Mount Sinai Hospital with a focus of epidemiology of IBD, and is the Departmental Division Director of the University of Toronto Division of Gastroenterology and Hepatology.

Affiliations: Zane Cohen Centre for Digestive Diseases, Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
Division of Gastroenterology & Hepatology, University of Toronto Temerty Faculty of Medicine, Toronto, Ontario, Canada

PABLO OLIVERA, MD

Dr. Olivera is an Advanced IBD Fellow at Mount Sinai Hospital. Concurrently, he is pursuing a Master of Science degree in the Clinical Epidemiology & Health Care Research program at the Institute of Health Policy, Management and Evaluation, University of Toronto. His current research focuses on elucidating the myriad comorbidities that afflict older adults living with IBD. Specifically, he focuses on understanding the effect of disease course and treatment interventions on comorbid conditions and their outcomes in this subpopulation.

Affiliations: Zane Cohen Centre for Digestive Diseases, Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
Division of Gastroenterology & Hepatology, University of Toronto Temerty Faculty of Medicine, Toronto, Ontario, Canada

BONE HEALTH IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): AN OVERVIEW OF THE EPIDEMIOLOGY, PATHOGENESIS, AND MANAGEMENT

Introduction

Metabolic bone disease is prevalent in persons with immune-mediated inflammatory diseases, including inflammatory bowel disease (IBD). Within these conditions the most common are osteoporosis and reduced bone mineral density (BMD), often termed osteopenia in adult patients, and refer to a decreased mineralization of the bone matrix. This decreased mineralization weakens the resistance of the bone to external forces, thus increasing the risk of fractures when external compressive or deforming forces are applied.[1] Osteoporosis is asymptomatic in the absence of a fracture, and diagnosis generally occurs through the use of programmatic screening (most commonly dual energy x-ray absorption [DEXA]) or incidentally following the occurrence of a fracture. Osteoporosis is defined as a DEXA-measured BMD at the lumbar spine or proximal femur which falls more than 2.5 standard deviations below the mean value for healthy young adults (known as a T-score). BMD decreases of a lesser degree (a T-score falling between -1 and -2.5) are referred to as osteopenia.[2] Osteoporosis is a major public health concern, owing to the significant morbidity and mortality that is attributed to fractures. While fractures may represent a time-limited hardship among persons in otherwise good health and function, major osteoporosis-related fractures, especially those of the femur and spine, can lead to permanent disability and premature mortality. In Canada, approximately 150 people per 100,000 suffer a hip fracture per year,[3] which confers a 3-fold higher risk of mortality.[4]

There are several reasons why persons with IBD may be at increased risk of osteoporosis, and why IBD-clinicians should be concerned about metabolic

bone disease. Osteoporosis is most common in post-menopausal women and in men over the age of 50 years. Additionally, the prevalence of IBD is rising more quickly among persons over the age of 60 years. Osteoporosis is also more common among persons with low body mass, which can result from the inflammatory pro-catabolic state seen in active IBD, and systemic inflammation itself could lead to an increase in bone turnover. Also, corticosteroid use, which remains common in IBD despite the more widespread use of steroid-sparing therapies, is a significant accelerant of the loss of BMD. Moreover, absorption of the necessary nutrients, vitamins, and minerals necessary to maintain bone health (calcium, magnesium, vitamin D) may be affected by small intestinal involvement in IBD; consequently, persons living with IBD may have insufficient intake of the dietary components which contain the essential elements for bone health. Finally, especially in the elderly, persons living with IBD may experience increases in frailty and reduced mobility, which may increase their risk of injurious falls. As such, it is important that physicians who are tasked with the care of persons living with IBD be cognizant of these bone-related comorbidities.

This review aims to provide an overview of the pathophysiology and epidemiology of bone health disorders in persons with IBD, and to provide guidance to the IBD clinician on prevention and management.

Epidemiology of Osteoporosis and Osteoporosis-Related Fractures in IBD

The prevalence of metabolic bone disorders among individuals living with IBD exhibits considerable variability across studies, with estimates ranging from 4.4% to 77%.[11] This broad range is attributable to differences in study designs, sampling frames (e.g., tertiary centre studies versus population-based studies), and outcome definitions (i.e., osteoporosis or reduced BMD). Notably, the variability in the reported prevalence may be influenced by ascertainment bias, given that BMD screening is not universally conducted among persons at risk; consequently, the prevalence may be overestimated in tertiary care populations and underestimated in regions with limited access to DEXA scans.

In a 2020 systematic review, Karnsund et al. investigated the prevalence of osteoporosis and low BMD in population-based studies.[12] The prevalence of osteoporosis demonstrated considerable heterogeneity, ranging from 4% to 9% in studies involving the overall IBD population, while varying from 2% to 9% in studies focusing on patients with ulcerative colitis (UC), and ranging between 7% and 15% in studies specifically addressing patients with CD. They found that a diagnosis of CD, low BMI, and low body weight were risk factors associated with osteoporosis or low BMD.[12]

A population-based study conducted in Manitoba reported that after adjusting for age, sex, BMI, corticosteroid use, estrogen replacement therapy, and osteoprotective medications, IBD was not associated with an increased risk of osteoporosis at the different measurement sites. The study also observed that IBD had only a marginal effect on lower T-scores. CD was associated with lower T-scores at all of the measurement sites except the lumbar spine and was associated with an increased risk of osteoporosis at all of the measurement sites except the total hip. Within individuals with IBD, advancing age and decreasing BMI consistently emerged as factors associated with lower T-scores and a heightened risk of osteoporosis.[13]

In addition to the increased risk of osteoporosis, an IBD diagnosis has been linked to an increased risk of osteoporotic fractures. In a population-based study from Sweden, Ludvigsson et al. found an association between IBD diagnosis and time to hip fracture (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.36–1.48), which was stronger in individuals diagnosed with CD compared to those diagnosed with UC ($p<0.001$). Interestingly, the association between IBD and hip fracture lacked statistical significance among individuals without a history of corticosteroid treatment (HR 1.11; 95% CI 0.86–1.44), with an excess risk of hip fracture predominantly observed among elderly patients with IBD who were exposed to corticosteroids.[14]

Another population-based study from Manitoba found that IBD diagnosis was not associated with an increased hazard of major osteoporotic fractures even after adjusting for the World Health Organization Fracture Risk Assessment tool (FRAX), which integrates BMD and clinical risk factors to predict the person's 10-year fracture risk.[15]

These findings suggest that while individuals living with IBD face an increased risk of osteoporosis and osteoporosis-related fractures, this heightened risk appears to be influenced by factors such as changes in anthropometric measurements and the use of corticosteroids rather than solely being attributed to IBD itself. Considering that these risk factors may be more prevalent among persons with IBD than in the general population, this may explain the increased risk of fracture among persons with IBD.

Pathogenesis of Reduced BMD in Patients with IBD

Normal Bone Homeostasis:

Bone homeostasis is a complex and dynamic process that involves the coordinated and opposed work of osteoblasts, which are responsible for bone deposition, while osteoclasts participate in bone resorption. The combined activity of these cells leads to bone remodelling.[5] A key regulatory pathway of the relative activity of osteoblasts and osteoclasts is the receptor activator of NF-κB (RANK)-RANK ligand (RANKL)-osteoprotegerin (OPG) system **(Figure 1)**. The RANKL is produced by osteoblasts and bone marrow

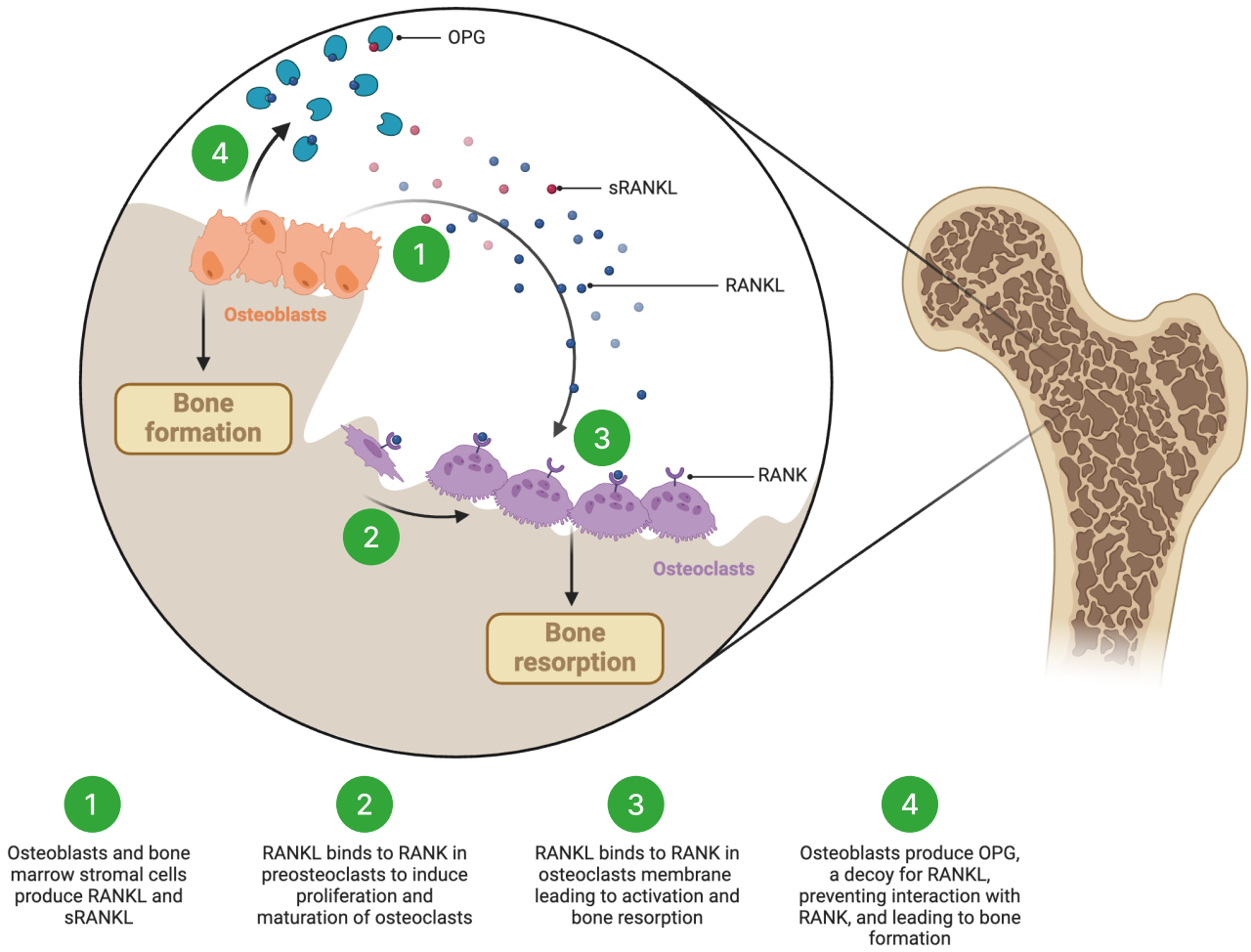


Figure 1: Normal bone homeostasis. RANK: receptor activator of nuclear factor-kB; RANKL: RANK ligand; sRANKL: soluble RANK ligand; OPG: osteoprotegerin. Created in BioRender.com

stromal cells, while the soluble sRANKL is secreted by osteoblasts and activated T-cells. Engaging RANKL with RANK, leads to the activation of osteoclasts and subsequent bone loss. Osteoblasts also produce OPG, which is a decoy receptor for RANKL, and its role is to prevent the interaction between RANK and RANKL. By doing so, OPG inhibits osteoclast differentiation and activation, thus tilting the balance toward bone formation.[6]

Bone Metabolism Derangements in IBD:

In the setting of systemic inflammation, as is observed with IBD, several cytokines are upregulated, such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, and interferon-γ.These pro-inflammatory cytokines increase the secretion of RANKL, leading to accelerated bone resorption. Interestingly, it appears that the inflammatory milieu, rather than individual cytokines, determines the shift to a bone resorption state. An in-vitro study exposed osteoblast models to the following cytokines, IL-6, IL-1β, and TNF-α, individually and in combination, at concentrations observed in patients with active Crohn's disease (CD). They found that none of the individually applied cytokines affected RANKL or OPG expression. However, when applied in combination, these cytokines shifted the RANKL/OPG ratio toward bone resorption. Moreover, when dexamethasone was added, this shift was further increased.[7] Despite these observations, the direct impact of systemic inflammation on the risk of osteoporosis is not definitively established, and the clinical significance of this effect remains to be fully characterized.

Impact of IBD on Nutrition and Body Habitus:

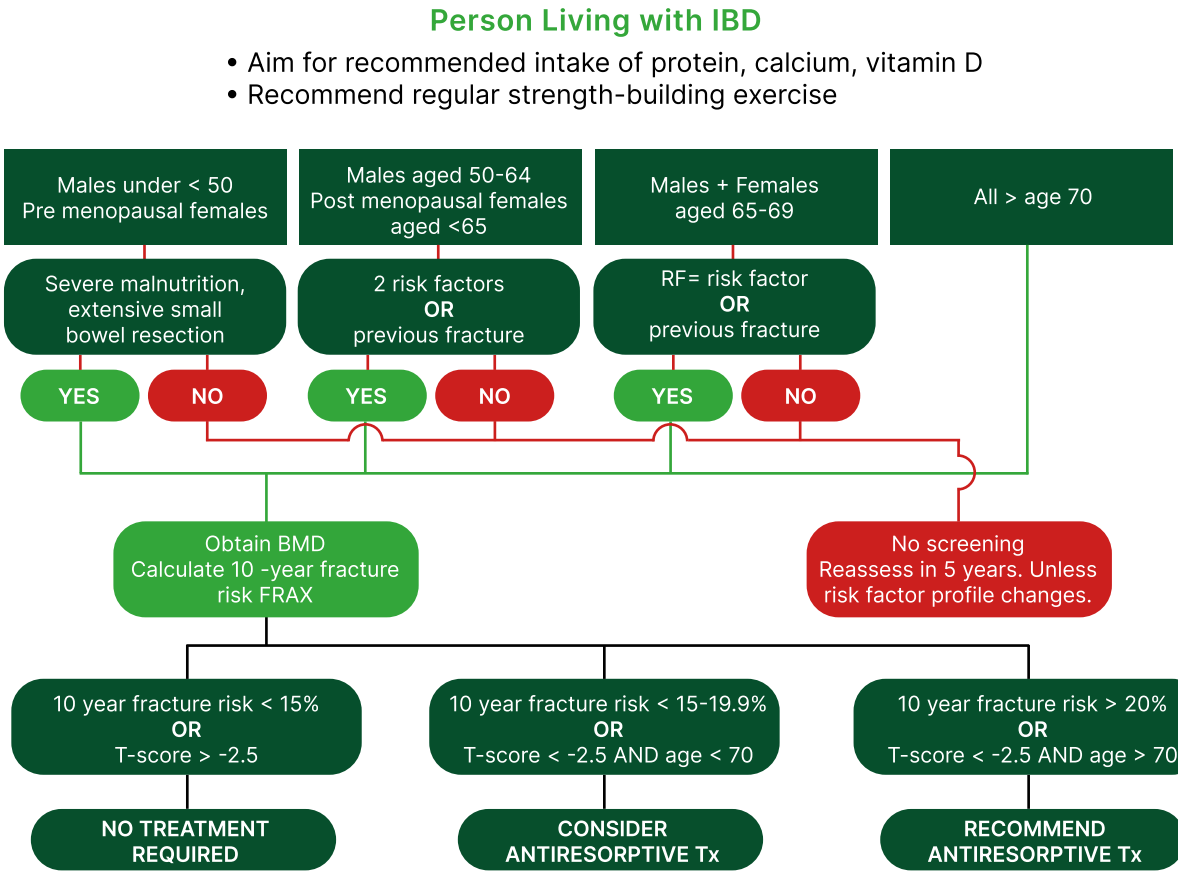
Nutritional factors are also believed to play a role in the development of reduced BMD in individuals with IBD. A decrease in body mass index (BMI) has been associated with a decrease in BMD in patients with IBD.[8] Nonetheless, given that fat mass does not reliably predict bone health, sarcopenia may be more strongly correlated with osteoporosis than BMI. A cross-sectional study of 137 patients with IBD has observed that both low lean mass and sarcopenia were independently associated with reduced BMD, while neither BMI nor fat mass showed such an association.[9] Key components for maintaining bone homeostasis, such as calcium and vitamin D, may be deficient in those with IBD.[10] This deficiency can result from reduced intake due to avoidance behaviours

driven by concerns about triggering symptoms or poor absorption following bowel resections or extensive areas of active disease. Additionally, inadequate exposure to sunlight may contribute to vitamin D deficiency in individuals with IBD.

Prevention and screening for osteoporosis in IBD

Given that the risk of fractures in patients living with IBD is primarily driven by traditional risk factors for osteoporosis, we suggest that prevention and screening for osteoporosis should largely follow the recommendations for screening in the general population **(Figure 2.)** IBD clinicians, however, should be mindful of the increased prevalence of risk factors for osteoporosis in persons with IBD, including the impact of chronic systemic inflammation, a higher prevalence of vitamin D deficiency, low BMI, and a history of corticosteroid use. Consequently, persons with IBD who are younger than the age of 50 and/or pre-menopausal may be at increased risk of osteoporosis and may be candidates for screening. In addition, the risk of fracture at a given BMD may be higher for patients with IBD because of the presence of concomitant risk factors for falls and/or injury following a fall.

The 2023 Osteoporosis Canada Guidelines recommend screening for osteoporosis with BMD testing along with DEXA in all persons aged 70 or over, in persons aged 64–69 with one risk factor, in men over the age of 50, and in post-menopausal women with 2 or more fracture risk factors.[3] These guidelines consider IBD to be a fracture risk factor, although realistically IBD only independently contributes if there is significant ongoing or recent inflammatory activity. In addition, it is recommended that all persons at risk for osteoporosis engage in balance and muscle-strengthening exercises at least twice weekly, obtain the recommended daily allowance of protein (>0.8 mg/kg/day, 1.2 mg/kg/day for active IBD), calcium (500 mg elemental calcium) and vitamin D (400 IU daily, 1000-2000 IU/day if deficient)



Risk Factors (RF) Include

- ACTIVE IBD in last year
- Previous low-trauma fracture before age 40
- CS exposure >3 months in the previous year
- Recurrent falls or known gait issues
- Family history of hip fracture
- Low body mass index or sarcopenia
- Current smoking
- >3 alcoholic drinks/day
- Hypogonadism or premature menopause

Figure 2: Schema for Evaluation of Osteoporosis and Fracture Risk in Persons with IBD; *adapted from Morin SN, et al., 2023*
Abbr.: IBD: inflammatory bowel disease; CS: corticosteroids.

either from dietary or supplemental sources. Calcium and vitamin D supplementation may specifically lower the risk of fracture in persons who have been using corticosteroids at a dose of >10 mg for three months or greater. The FRAX risk stratification tool here is recommended to determine a patient's 10-year estimated risk of fracture, and anti-resorptive therapies are recommended for those with a 10-year fracture risk of 15% or greater. It is recommended that persons with IBD who require anti-resorptive therapy have their bone health managed by an osteoporosis specialist. The FRAX tool has been shown to be predictive of fracture risk in persons with IBD, though it is not widely utilized by IBD specialists. Bisphosphonates are recommended as first-line therapy for persons at increased risk for fracture. A network meta-analysis that assessed the efficacy and safety of therapeutic interventions for low BMD in patients with CD observed that zoledronate ranked highest for increasing spinal BMD, while risedronate was noted for its favourable safety profile.[16] There may be some unique considerations regarding osteoporosis screening and surveillance that apply for persons with IBD. The American College of Gastroenterology provided a conditional recommendation to screen for osteoporosis with BMD testing at the time of IBD diagnosis and periodically thereafter in patients with conventional risk factors for abnormal BMD, though this recommendation is based on a very low level of evidence.[17] Similarly, the European Crohn's and Colitis Organisation recommends screening for osteoporosis in high-risk patients with IBD using DEXA scans, though the term high risk is not well defined. There are no clear recommendations for BMD screening in persons with IBD who are under the age of 50 or who are pre-menopausal, and baseline fracture rates in this population are very low. BMD testing still might be considered in IBD patients who either have had or anticipate having >3 months of continuous corticosteroid use, those with a BMI <20 and those with evidence of malnutrition, extensive small bowel disease, or with extensive small bowel resections.[18] There are no specific guidelines on how often persons with IBD should undergo repeat BMD testing, though the Canadian guidelines suggest those with a 10-year risk of fracture that is under 15% should be re-evaluated at 5 years unless there are incident risk factors for osteoporosis, or a new fracture is diagnosed.[3]

Conclusions

In the chronic and often unpredictable disease course of IBD, several factors might produce imbalances in bone hemostasis, namely repeated bouts of inflammation, cumulative exposure to steroids, and nutritional deficiencies. It is paramount for clinicians to be aware of the risk of metabolic bone disorders, especially given that these conditions are often asymptomatic and may only become apparent with the occurrence of an osteoporotic fracture, which itself can be asymptomatic. In the context of the increasingly complex management of IBD, the assessment of osteoporosis risk and the implementation of preventive and therapeutic measures for bone health and other aspects of health maintenance are sometimes overlooked. However, physicians should aim to incorporate these assessments regularly into the management of IBD to ensure comprehensive care for their patients.

Key Takeaways:

1. Metabolic bone disease is prevalent in persons with immune-mediated inflammatory diseases, including IBD. Within these conditions the most common are osteoporosis and reduced bonemineral density BMD.
2. The prevalence of metabolic bone disorders among persons living with IBD exhibits considerable variability owing to ascertainment bias. As a result, the prevalence may be overestimated in tertiary care populations and underestimated in regions with limited access to DEXA scans.
3. During the disease course of IBD, several factors might produce imbalances in bone hemostasis (e.g. repeated flares-ups of inflammation, cumulative exposure to steroids, and nutritional deficiencies).
4. Prevention and screening for osteoporosis should largely follow the recommendations for screening in the general population. However, clinicians should recognize that persons living with IBD have an increased prevalence of risk factors of metabolic bone disorders and adjust screening and prevention strategy accordingly.

Correspondence:

Laura Targownik, MD
Email: Laura.Targownik@sinaihealth.ca

Financial Disclosures:

Pablo Olivera: None declared.
Laura Targownik: **Investigator-initiated funding:** Janssen Canada, **Advisory boards:** AbbVie Canada, Sandoz Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Canada, Fresenius Kabi Canada, Biocon Canada, BMS Canada and Lilly Canada; **Grant support:** Janssen Canada; **Infrastructure support:** Abbvie Canada, Amgen Canada, Pfizer Canada, Takeda Canada and Sandoz Canada.

NOW AVAILABLE

Pr Velsipity™

etrasimod tablets

PP-V1A-CAN-0035-EN

References:

1. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-2381. doi:10.1007/s00198-014-2794-2
2. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int. 2014;25(5):1439-1443. doi:10.1007/s00198-014-2655-z
3. Morin SN, Feldman S, Funnell L, Giangregorio L, Kim S, McDonald-Blumer H, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. Cmaj. 2023;195(39):E1333-e1348. doi:10.1503/cmaj.221647
4. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. Cmaj. 2009;181(5):265-271. doi:10.1503/cmaj.081720
5. Bravenboer N, Oostlander AE, van Bodegraven AA. Bone loss in patients with inflammatory bowel disease: cause, detection and treatment. Curr Opin Gastroenterol. 2021;37(2):128-134. doi:10.1097/mog.0000000000000710
6. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008;473(2):139-146. doi:10.1016/j.abb.2008.03.018
7. Blaschke M, Koepp R, Cortis J, Komrakova M, Schieker M, Hempel U, et al. IL-6, IL-1β, and TNF-α only in combination influence the osteoporotic phenotype in Crohn's patients via bone formation and bone resorption. Adv Clin Exp Med. 2018;27(1):45-56. doi:10.17219/acem/67561
8. Targownik LE, Leslie WD, Carr R, Clara I, Miller N, Rogala L, et al. Longitudinal change in bone mineral density in a population-based cohort of patients with inflammatory bowel disease. Calcif Tissue Int. 2012;91(5):356-363. doi:10.1007/s00223-012-9650-1
9. Bryant RV, Ooi S, Schultz CG, Goess C, Grafton R, Hughes J, et al. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41(9):895-906. doi:10.1111/apt.13156
10. Iijima H, Shinzaki S, Takehara T. The importance of vitamins D and K for the bone health and immune function in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2012;15(6):635-640. doi:10.1097/MCO.0b013e328357f623
11. Wei H, Zhao Y, Xiang L. Bone health in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2023;17(9):921-935. doi:10.1080/17474124.2023.2248874
12. Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. World J Gastroenterol. 2020;26(35):5362-5374. doi:10.3748/wjg.v26.i35.5362
13. Targownik LE, Bernstein CN, Nugent Z, Leslie WD. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clin Gastroenterol Hepatol. 2013;11(3):278-285. doi:10.1016/j.cgh.2012.10.022
14. Ludvigsson JF, Mahl M, Sachs MC, Björk J, Michaelsson K, Ekbom A, et al. Fracture risk in patients with iInflammatory bowel disease: a nationwide population-based cohort study from 1964 to 2014. Am J Gastroenterol. 2019;114(2):291-304. doi:10.14309/ajg.0000000000000062
15. Targownik LE, Bernstein CN, Nugent Z, Johansson H, Oden A, McCloskey E, et al. Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013;28(5):1007-1013. doi:10.1002/jbmr.1848
16. Zhao X, Zhou C, Chen H, Ma J, Zhu Y, Wang P, et al. Efficacy and safety of medical therapy for low bone mineral density in patients with Crohn disease: A systematic review with network meta-analysis. Medicine (Baltimore). 2017;96(11):e6378. doi:10.1097/md.0000000000006378
17. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol. 2017;112(2):241-258. doi:10.1038/ajg.2016.537
18. Gordon H, Burisch J, Ellul P, Karmiris K, Katsanos K, Allocca M, et al. ECCO Guidelines on extraintestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2024;18(1):1-37. doi:10.1093/ecco-jcc/jjad108

abbvie care™ with you™
Support Program

1 program. promise.

Trust in AbbVie Care for a committed partnership built on our promise of seamless and continuous patient support across our portfolio.

18 years of learning
from
over 300,000 patients
across former and current AbbVie programs[1]

Pr Skyrizi® (risankizumab) injection

Pr HUMIRA® adalimumab injection

Pr RINVOQ® upadacitinib

Pr MAVIRET® glecaprevir/pibrentasvir tablets

Reference: 1. AbbVie Corporation. Data on file.

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

abbvie.ca
1-888-703-3006

abbvie

NICHOLAS CARMAN, MBBS, FRACP

Dr. Carman is currently an Assistant Professor at the University of Toronto and Paediatric Gastroenterologist at the IBD Centre at the Hospital for Sick Children in Toronto. He completed his medical training in Australia and moved to Canada to undertake an IBD fellowship in 2014, and has remained to continue working in the IBD field in Canada. He is currently the Associate Director of Endoscopy and lead of the Intestinal Ultrasound Program at SickKids, and the chair of the Endoscopy and Imaging Committee for the national Canadian Children IBD Network.

Affiliations: SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children (SickKids), Toronto, Ontario

UPDATES IN THE MANAGEMENT OF PEDIATRIC INFLAMMATORY BOWEL DISEASE

Introduction

Canada has one of the highest rates of childhood-onset inflammatory bowel disease (IBD) in the world, with the recent Crohn's and Colitis Canada's 2023 Impact of Inflammatory Bowel Disease in Canada Report[1] demonstrating that approximately 6,158 children and youth under 18 years are living with IBD, along with 600-650 new diagnoses under age 16 per year. This number is expected to rise to 8,079 by 2035.[2] This represents approximately 10-20% of newly diagnosed patients.[3] Concerningly, although still relatively uncommon compared with adolescent onset IBD, the incidence has increased most significantly in children under 5 years old. Recent health administrative data demonstrated the national incidence of IBD, overall, to be 29.9 per 100,000 (95%CI: 28.3, 31.5) in 2023, with increasing incidence in pediatrics (AAPC:1.27%; 95%CI:0.82, 1.67), despite stable incidence in adults (AAPC:0.26%; 95%CI: -0.42, 0.82).[4] **Figure 1** demonstrates that this increase in pediatric incidence is a worldwide phenomenon. Current IBD care in pediatrics is moving toward a precision medicine approach, with unique and standardized approaches to genetics, risk stratification and disease phenotype, nutritional and advanced therapies, and specialized multidisciplinary clinics with knowledge of the unique challenges pediatric patients and their families face with a diagnosis of IBD.[5]

Pediatric Inflammatory Bowel Disease is Becoming Increasingly Common Around the World

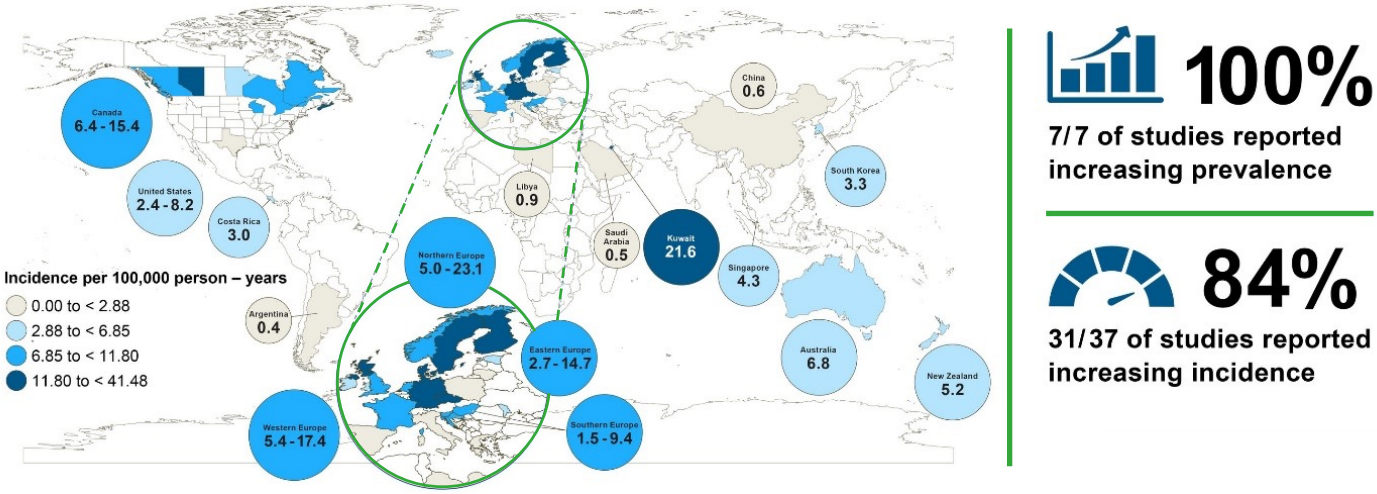


Figure 1. Map depicting global increasing incidence of pediatric IBD; Adapted from - Kuenzig ME, Fung SG, Marderfeld L, et al; InsightScope Pediatric IBD Epidemiology Group; Benchimol EI. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. Gastroenterology. 2022 Apr;162(4):1147-1159.e4

Genetics

Genetic factors, microbial dysbiosis and aberrant immune responses associated with environmental factors are thought to be the main influencing factors in the development of IBD,[6] with likely varying contributions of these depending on age. With advances in next generation DNA sequencing, it is possible to genetically diagnose children with IBD or IBD-like disease, labelled 'monogenic IBD'. These patients typically are rare, severe and refractory to conventional therapies.[7] These were recently examined in a systematic review of monogenic IBD to collect established cases,[8] where the most commonly reported monogenic defect was interleukin (IL)-10-signalling colitis, followed by chronic granulomatous colitis (CGD), and X-linked inhibitor of apoptosis (XIAP) deficiency. **Figure 2a** shows the commonly seen genetic mutations,

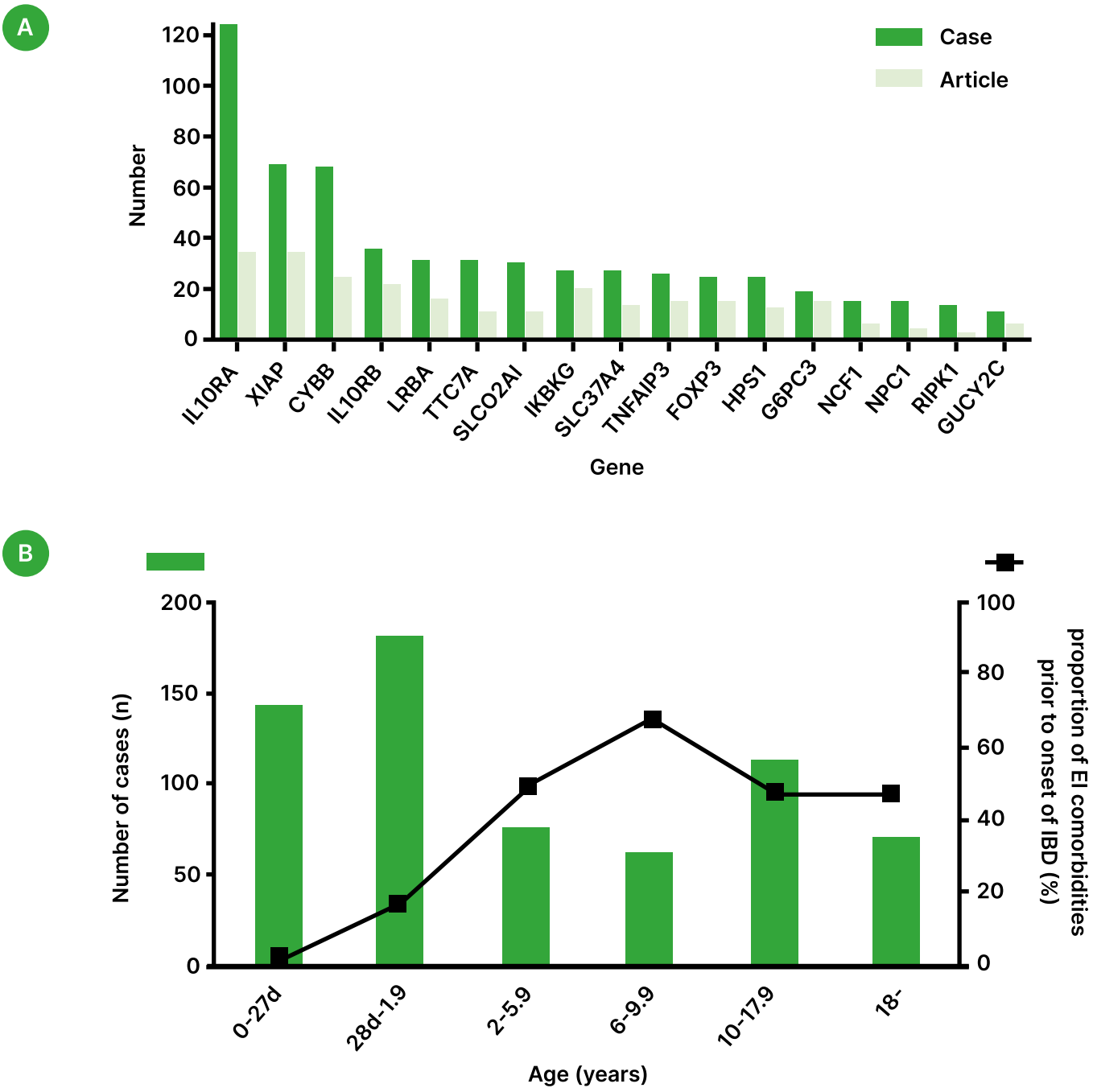


Figure 2. Common genes and age at onset of monogenic inflammatory bowel disease (IBD). **A** - Number of reported monogenic IBD cases and articles stratified by gene. Only genes that have 10 or more cases are listed. Dark orange bars, number of cases; light orange bars, number of articles. **B** - Distribution of IBD onset age. Orange bar (left y-axis) is the number of cases in each age group. The line graph (right y-axis) is the proportion of patients with extraintestinal (EI) manifestations before onset of IBD.
Image adapted from - Nambu R, Warner N, Mulder DJ, et al. A systematic review of monogenic inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022 Apr;20(4):e653-e663.

and **Figure 2b** shows distribution by age, where more than 10% of cases were identified in adult age groups. Seventy-six percent of patients developed at least one extraintestinal issue during their disease course, with treatments including surgery (27.1%), hematopoietic stem cell transplantation (23.1%) and biological therapies (32.9%). These data highlight the diverse nature of monogenic disease, and it should be considered in all patients if there is an unusual phenotype, significant extraintestinal disease, or they are refractory to therapy.

Diet and Nutritional Therapies

Diet has been implicated in both the pathogenesis and relapsing/remitting nature of IBD, with a wealth of past and ongoing research into diet and its role in IBD. Numerous studies of nutritional epidemiology research demonstrating harmful associations with western diet and protective benefits from a Mediterranean diet and animal studies implicating ultra-processed and industrialized food in the development of inflammation have been examined for many years. There have also been small clinical trials showing degrees of benefit utilizing exclusive enteral nutrition and other dietary interventions.[9] Diet research has, however, been slow to progress, with mechanistic relationships difficult to understand, and diet interventions complicated and restrictive. The mainstay of nutritional therapy in pediatric IBD has been exclusive enteral nutrition (EEN) for Crohn's disease (CD), and it is the primary induction agent in many countries around the world for mild-to-moderate disease.[10] In Canada, rates of EEN use are similar to that of corticosteroids for induction according to data from the Canadian Children IBD Network (CIDsCaNN). EEN has demonstrated efficacy across a number of studies to induce remission and mucosal healing, and for nutritional rehabilitation.[11] It also has demonstrated adjunct benefit in children with stricturing/penetrating disease or with inflammatory masses.[11] Patient selection remains important for EEN success, and is best served when supported by a dietitian in an IBD centre with EEN experience and adequate follow-up. Data evaluating disease severity and phenotype as predictors of success are conflicting, but those with predominantly distal ileal disease and mild-to-moderate disease severity have been shown to be more likely to be responsive.[13,14] Exploration of microbiome signatures[15] and genetic markers[16] related to EEN success are ongoing.

There have been multiple dietary therapies proposed as IBD 'treatment diets', with a recent literature review suggesting more than 24 identified in the management of IBD.[17] These have had varying methodologies and outcome assessments, with no convincing evidence to support the use of a single diet over another. The most robustly assessed is the Crohn's Disease Exclusion Diet (CDED),[18] which combined a restricted diet with partial enteral nutrition (PEN) across several phases of decreasing restriction. Diet restrictions were based on animal data where food products impacted inflammation, dysbiosis or intestinal permeability. This combination was similar to EEN in inducing remission at week 6 (75% in the CDED plus PEN group vs 59% in the EEN group; P = 0.38), but has had limited success in patients with severe disease, or in the setting of loss of response to biologics.[19] Across Canadian pediatric centres there remains significant variation in standard diet recommendations and uptake of diet therapies until more robust data on therapeutic diets emerge, which continues to be a source of frustration for patients and families.

Drug Therapies

The number of approved available drug therapies for IBD in adult patients has increased rapidly over recent years. However, the unavailability of these drugs for children has been an increasing problem for pediatric IBD practitioners. There is a significant lag time prior to pediatric randomized controlled trial completion and regulatory approval, leading to prolonged off-label use of new therapies. Traditional induction therapies like corticosteroids and EEN have continued to be used, but the use of immunomodulators as maintenance monotherapy, especially in CD, has decreased significantly as we move to a focus on 'early effective therapies' as part of our treat-to-target approach, especially as most pediatric patients present with moderate-to-severe and extensive disease. In ulcerative colitis (UC), the PROTECT study demonstrated a reasonable proportion of steroid responsive children respond to standard 5-ASA therapies, but at 52 weeks, only 40% of patients were able to maintain 5-ASA therapy without requiring escalation.[20] Anti-tumour necrosis factor (TNF) therapies continue to be the most utilized maintenance therapies in pediatrics given their prolonged period of availability and ongoing effectiveness, with infliximab and adalimumab the only licensed biologics for children. However, approximately one-third of IBD patients are non-responders to anti-TNF therapy,[21] and another 20-30% will develop secondary loss of response, with or without development of anti-drug antibodies. The use of body surface area (BSA)-based dosing for young children[22] and proactive therapeutic drug monitoring[23] has shown some benefit in children compared to adults, potentially related to differences in drug clearance and body composition, as well as a non-linear relationship between body weight and BSA in young/light children. The latter point makes it such that the youngest/lightest children require the most drug per kilogram to achieve comparable drug exposure to older children/adults. Regardless, a significant proportion of children will lose response to first line anti-TNF therapy. Therefore, readily available alternatives are of the utmost importance.

In 2014 vedolizumab became the first anti-integrin designed specifically for gastrointestinal disease in adults, targeting α4β7; it was established

through the GEMINI program.[24] It has been used off label in pediatrics, initially in anti-TNF refractory patients, but more recently in bio-naïve patients, especially in UC. There are multiple pediatric observational studies demonstrating its safety and efficacy, the largest of which is the VEDOKIDS study[25] demonstrating 42% steroid-free remission rates at Week 14 in UC and 32% in CD, with some benefit in bio-naïve patients. Durability data are sparse, with small series demonstrating some benefit with early dose optimization and proactive therapeutic drug monitoring.[26] To this point safety data are excellent, which make this drug an attractive therapy for pediatric patients. Additional studies are needed to explore the role of other anti-integrin therapies in pediatrics.

Ustekinumab, a monoclonal antibody that binds to the p40 sub-unit of IL-12 and IL-23, is approved in adults, with established efficacy through the UNITI and UNIFI trials.[27,28] The drug has been used off-label in Canada since 2016 in children, again initially in anti-TNF refractory patients. CIDsCaNN published the early Canadian experience in anti-TNF refractory UC,[29] demonstrating 44% steroid-free remission at Week 52. In CD, Canadian data by Chavannes et al[30] demonstrated 38.6% of patients achieving clinical remission at Week 52. Both studies reported good safety profiles. Data regarding the utility of proactive therapeutic drug monitoring and dose optimization are sparse in pediatrics, so far only presented in abstract form, demonstrating some association between higher proactively measured week 8 ustekinumab levels and favourable clinical outcomes.[31] Recently, newer molecules targeting p19 found only on IL-23, including risankizumab, mirikizumab and guselkumab, have been undergoing clinical trials in adult patients demonstrating efficacy with encouraging data. Pediatric clinical trials are ongoing. Early off-label use for risankizumab was recently made available, but published data of the pediatric experience are not yet available.

JAK-STAT inhibitors, which inhibit the activity of one or more JAK enzymes interrupting intracellular STAT pathway phosphorylation, were the first family of targeted small molecules utilized in IBD, with tofacitinib the first licensed for use in adults. The OCTAVE clinical trials demonstrated safety and efficacy in adults for UC,[32] and there is currently an active clinical trial in pediatric patients with moderate-to-severe UC in both bio-naïve and anti-TNF failed patients. Pediatric off-label use has been available, predominantly for anti-TNF failed patients, with published series demonstrating efficacy and early safety data. Up to 41.2% of patients had clinical response and steroid-free remission at 52 weeks.[33] A second small study showed improvements in colectomy rates in hospitalized patients who were steroid and anti-TNF refractory.[34] Upadacitinib, an oral selective JAK1 inhibitor, is undergoing a Phase 3 clinical trial in moderate-to-severe pediatric UC in both bio-naïve and experienced patients, and has had encouraging off-label use to date presented in abstract form.[35] Other JAK inhibitors are currently under investigation. Most intriguing to this group of drugs is rapidity of onset, which in future could potentially obviate the need for corticosteroids in select patient; therefore, more robust safety and efficacy data are eagerly awaited.

Finally, sphingosine-1-phophate (S1P) receptor modulators bind to, and indirectly antagonize, the S1P receptors on lymphocytes trapping them within lymph nodes, reducing immune response. Multiple S1P receptors are undergoing clinical trials in IBD (ozanimod, fingolimod and etrasimod), with ozanimod currently undergoing a clinical trial in pediatric CD, with off-label use recently available.

With a number of new drugs and pathways available, pediatric IBD specialists will have more treatments available for our patients. Data regarding sequencing and positioning will become of paramount importance. In addition, data evaluating safety and efficacy of so called 'multi-modal' therapy combining dual biologics or biologics and small molecules are starting to emerge for refractory pediatric patients,[36-38] expanding our treatment armamentarium for patients with difficult to control disease.

Conclusions

Goals of care in pediatric IBD are initially similar to those of adults. These include achieving long-term, steroid-free clinical remission and achieving mucosal healing, to prevent long-term disease-related complications. Children have unique additional goals, including optimizing physical, pubertal and psychological growth, maintaining nutrition and quality of life through school and adolescence, and consideration of the potential treatment toxicities given extended periods of time on medications. This is especially true as our patient population at disease onset continues to get younger and treatments more complicated. Given this, it is increasingly recognized that children with IBD should be treated in specialized, multidisciplinary centres with access to physicians, specialized nurses, dietitians, and mental health professionals with expertise in IBD[1] to try and enable children and families to access the highest quality care for their IBD.

Correspondence:

Nicholas Carman, MBBS, FRACP
Email: nicholas.carman@sickkids.ca

Financial Disclosures:

Nicholas Carman
Honoraria: Sanofi

References:

1. El-Matary W, Carroll MW, Deslandres C, et al. The 2023 impact of inflammatory bowel disease in Canada: special populations-children and adolescents with IBD. *J Can*

Think RENFLEXIS®

The #1 Biosimilar to Remicade* Dispensed by Canadian Pediatricians†‡[1]

Discover RENFLEXIS®, Available for use in adults and children 6 years of age and up.[2]

Patient Support Program

Harmony By ORGANON

Supporting RENFLEXIS® Canadian patients **since 2018**§¶

SCAN HERE

Visit harmonyorganon.ca to learn more

Indications have been granted on the basis of similarity between RENFLEXIS® and the reference biologic drug, Remicade*.
RENFLEXIS® (infliximab for injection) is indicated for:[2]

- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. RENFLEXIS® can be used alone or in combination with conventional therapy.
- reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of RENFLEXIS® is not established in patients less than 9 years of age.
- treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
- reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of RENFLEXIS® have not been established in patients less than 6 years of age.

Consult the Product Monograph at **https://www.organon.com/canada-en/renflexis-pm_e** for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The product monograph is also available by calling 1-844-820-5468.

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

† Comparative clinical significance unknown.
‡ IQVIA data from February 2023 to March 2024.
§The program was initially operated by Merck Canada Inc. under the name MERCK HARMONY. In June 2021, it transitioned to Organon Canada Inc. and is now operating under the name HARMONY BY ORGANON™.
¶Clinical significance is unknown.

ORGANON

CA-SBT-110271

REVIEWED BY PAAB

RENFLEXIS® infliximab for injection

Assoc Gastroenterol. 2023;6(Suppl 2):S35-s44.
2. Benchimol EI, Bernstein CN, Bitton A, C, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol.* 2017;112(7):1120-34.
3. Benchimol EI, Manuel DG, Guttmann A, et al. Changing age demographics of inflammatory bowel disease in Ontario, Canada: a population-based cohort study of epidemiology trends. *Inflamm Bowel Dis.* 2014;20(10):1761-9.
4. Coward S, Benchimol EI, Bernstein CN, et al. Forecasting the incidence and prevalence of inflammatory bowel disease: A Canadian nationwide analysis. *Am J Gastroenterol.* 2024.
5. Uhlig HH, Booth C, Cho J, et al. Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards. *Nat Rev Gastroenterol Hepatol.* 2023;20(12):810-28.
6. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol.* 2006;3(7):390-407.
7. Muise AM, Snapper SB, Kugathasan S. The age of gene discovery in very early onset inflammatory bowel disease. *Gastroenterology.* 2012;143(2):285-8.
8. Nambu R, Warner N, Mulder DJ, et al. A systematic review of monogenic inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2022;20(4):e653-e63.
9. Gerasimidis K, Russell RK, Giachero F, et al. Precision nutrition in pediatric IBD: A position paper from the ESPGHAN special interest group for basic science and translational research, the IBD Porto group, and allied health professionals. *JPGN.* 2024;78(2):428-45.
10. van Rheenen PF, Aloi M, Assa A, et al. The medical management of paediatric Crohn's disease: an ECCO-ESPGHAN Guideline update. *J Crohn's Colitis.* 2020 Oct 7:jjaa161.
11. Swaminath A, Feathers A, Ananthakrishnan AN, et al. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in pediatric Crohn's disease. *AP & T.* 2017;46(7):645-56.
12. Hu D, Ren J, Wang G, et al. Exclusive enteral nutritional therapy can relieve inflammatory bowel stricture in Crohn's disease. *J Clin Gastroenterol.* 2014;48(9):790-5.
13. Afzal NA, Davies S, Paintin M, et al. Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci.* 2005;50(8):1471-5.
14. Moriczi M, Pujol-Muncunill G, Martín-Masot R, et al. Predictors of response to exclusive enteral nutrition in newly diagnosed Crohn´s disease in children: PRESENCE Study from SEGHNP. *Nutrients.* 2020;12(4).
15. Jones CMA, Connors J, Dunn KA, et al. Bacterial taxa and functions are predictive of sustained remission following exclusive enteral nutrition in pediatric Crohn's disease. *Inflamm Bowel Dis.* 2020;26(7):1026-37.
16. Frivolt K, Schwerd T, Werkstetter KJ, et al. Repeated exclusive enteral nutrition in the treatment of pediatric Crohn's disease: predictors of efficacy and outcome. *AP & T.* 2014;39(12):1398-407.
17. Gerasimidis K, Godny L, Sigall-Boneh R, et al. Current recommendations on the role of diet in the aetiology and management of IBD. *Frontline gastroenterology.* 2022;13(2):160-7.
18. Levine A, Wine E, Assa A, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterol.* 2019;157(2):440-50.e8.
19. Sigall Boneh R, Sarbagili Shabat C, Yanai H, et al. Dietary therapy with the Crohn's disease exclusion diet is a successful strategy for induction of remission in children and adults failing biological therapy. *J Crohn's Colitis.* 2017;11(10):1205-12.
20. Hyams JS, Davis Thomas S, Gotman N, et al. Clinical and biological predictors of response to standardised paediatric colitis therapy (PROTECT): a multicentre inception cohort study. *The Lancet.* 2019;393(10182):1708-20.
21. Gisbert JP, Marín AC, McNicholl AG, et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *AP & T.* 2015;41(7):613-23.
22. Stallard L, Frost K, Frost N, et al. Body surface area-based dosing of infliximab is superior to standard weight-based dosing in children with very early onset inflammatory bowel disease. *Gastro Hep Advances.* 2024;3(2):215-20.
23. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated withincreased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology.* 2019;157(4):985-96.e2.
24. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710.
25. Atia O, Shavit-Brunschwig Z, Mould DR, et al. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet Gastroenterol Hepatol.* 2023;8(1):31-42.
26. Rowland P, McNicol M, Kiel A, et al. Proactive therapeutic drug monitoring and vedolizumab dose optimization in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2024 Jan. 25.
27. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2019;381(13):1201-14.
28. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2016;375(20):1946-60.
29. Dhaliwal J, McKay HE, Deslandres C, et al. One-year outcomes with ustekinumab therapy in infliximab-refractory paediatric ulcerative colitis: a multicentre prospective study. *AP & T.* 2021;53(12):1300-8.
30. Chavannes M, Martinez-Vinson C, Hart L, Ket al. Management of paediatric patients with medically refractory Crohn's disease using ustekinumab: a multi-centred cohort study. *J Crohn's Colitis.* 2019;13(5):578-84.
31. Ricciuto A, McKay H, deBruyn J, et al. P512 Early proactive therapeutic drug monitoring with ustekinumab therapy in pediatric Crohn's Disease. *J Crohn's Colitis.* 2024;18(Supplement_1):i1012-i3.
32. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2017;376(18):1723-36.
33. Moore H, Dubes L, Fusillo S, et al. Tofacitinib therapy in children and young adults with pediatric-onset medically refractory inflammatory bowel disease. J *Pediatr Gastroenterol Nutr.* 2021;73(3):e57-e62.
34. Constant BD, Baldassano R, Kirsch J, et al. Tofacitinib salvage therapy for children hospitalized for corticosteroid- and biologic-refractory ulcerative colities. *J Pediatr Gastroenterol Nutr.* 2022;75(6):724-30.
35. Spencer EA, Bergstein S, Dolinger M, et al. Single center experience with upadacitinib for refractory adolescent inflammatory bowel disease. NASPGHAN, San Diego 2023.
36. Dolinger MT, Spencer EA, Lai J, et al. Dual biologic and small molecule therapy for the treatment of refractory pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2021;27(8):1210-4.
37. Penagini F, Lonoce L, Abbattista L, et al. Dual biological therapy and small molecules in pediatric inflammatory bowel disease. *Pharmacol Res.* 2023;196:106935.
38. Yerushalmy-Feler A, Olbjorn C, Kolho KL, et al. Dual biologic or small molecule therapy in refractory pediatric inflammatory bowel disease (DOUBLE-PIBD): A multicenter study from the pediatric IBD Porto Group of ESPGHAN. *Inflamm Bowel Dis.* 2024;30(2):159-66.

Medical minds gather here.

As the largest independent medical publisher in Canada, our peer-reviewed open access scientific journals are a practical resource for Canadian healthcare practitioners. We currently publish specialty journals in the areas of allergy & immunology, dermatology, hematology, ophthalmology, diabetes & endocrinology, gastroenterology, primary care, women's health, rheumatology, oncology and our press is constantly growing with new titles planned for 2025.

catalytic health
communications • advertising • strategy

15 years

VOL 2
ISSUE 1
2024

Register for future digital and print issues by visiting us at catalytichealth.com/cibdt

Looking for more?
All back issues are available online at canadianibdtoday.com