

**VOL 1
ISSUE 2
2023**

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

CANADIAN IBD TODAY

Clinical Insights, Perspectives
and Disease Management

SURGICAL APPROACHES TO PERIANAL CROHN'S DISEASE

Anthony de Buck van Overstraeten, MD, MSc

CUTANEOUS MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: CLINICAL PEARLS FOR GASTROENTEROLOGISTS

Jennifer Lipson, MD

VACCINE PREVENTABLE DISEASE IN IBD: RELEVANCE, GUIDELINES AND CONSIDERATIONS FOR IMPLEMENTATION

Felix Zhou, Kyle Kilby, Jennifer Jones

ADVANCED COMBINATION THERAPY IN IBD: CAN IT BE ACHIEVED WITH SUCCESS?

Virginia Solitano, MD, Vipul Jairath, MD

POST-OPERATIVE CROHN'S DISEASE: CURRENT AND EMERGING MANAGEMENT TECHNIQUES

Maxime Delisle, MD, FRCPC

TABLE OF CONTENTS

5

SURGICAL APPROACHES TO PERIANAL CROHN'S DISEASE

Anthony de Buck van Overstraeten, MD, MSc

9

ADVANCED COMBINATION THERAPY IN IBD: CAN IT BE ACHIEVED WITH SUCCESS?

Virginia Solitano, MD, Vipul Jairath, MD

13

CUTANEOUS MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: CLINICAL PEARLS FOR GASTROENTEROLOGISTS

Jennifer Lipson, MD

20

POST-OPERATIVE CROHN'S DISEASE: CURRENT AND EMERGING MANAGEMENT TECHNIQUES

Maxime Delisle, MD, FRCPC

25

VACCINE PREVENTABLE DISEASE IN IBD: RELEVANCE, GUIDELINES AND CONSIDERATIONS FOR IMPLEMENTATION

Felix Zhou, Kyle Kilby, Jennifer Jones

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.

Canadian IBD Today is an open access journal, which means all its content is freely available without charge. Users are permitted to copy and redistribute the material in any medium or format for any noncommercial purpose, provided they cite the source.

© 2023 *Canadian IBD Today*. Licensed under CC BY-NC-ND 4.0.

To learn more about our policies please visit <http://canadianibdtoday.com/cibdt>

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



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, respirology and our press is constantly growing with new titles planned.



ANTHONY DE BUCK VAN OVERSTRAETEN MD, MSc



Dr. Anthony de Buck MD, MSc, is a colorectal surgeon practicing at Mount Sinai Hospital in Toronto and serving as an Associate Professor at the University of Toronto. With a strong background in surgical and colorectal training, Dr. de Buck has made significant contributions to the field of colorectal surgery and clinical outcome research in inflammatory bowel disease (IBD).

Dr. de Buck earned his medical degree at the University of Leuven. To further enhance his knowledge and skills, Dr. de Buck pursued a colorectal fellowship at the University of Toronto in 2013. Additionally, he obtained a Master's Degree in Clinical Epidemiology from the University of Toronto, equipping him with advanced research skills to investigate clinical outcomes in IBD.

Dr. de Buck's scientific work is primarily focused on clinical outcome research in IBD, with a specific emphasis on functional and quality of life outcomes in patients with this chronic condition. His dedication to improving patient outcomes has led him to conduct numerous studies and secure several peer-reviewed grants to support his research endeavors. As a leading researcher, he is actively involved in multi-institutional studies, including randomized controlled trials (RCTs), that aim to advance our understanding of IBD and its impact on patients' lives. In addition to his research pursuits, Dr. de Buck is deeply committed to educating the next generation of medical professionals. As an Associate Professor at the University of Toronto, he plays an important role in teaching and mentoring students, residents, and fellows, imparting his knowledge and expertise to shape the future of colorectal surgery and IBD research.

Affiliations:

Department of Surgery, Sinai Health System, University of Toronto, Toronto, Ontario

SURGICAL APPROACHES TO PERIANAL CROHN'S DISEASE

Introduction

Virtually one-third of patients with Crohn's disease (CD) develop anal symptoms.^{1,2} In addition to the typical skin tags and chronic fissures, 50% of these patients develop perianal abscesses and fistulas, which are among the most challenging CD phenotypes to treat. They can significantly affect patients' quality of life (QOL) and result in a significant amount of lost days at school or work, as they often occur in a young, active population.^{3,4}

Pharmacologic Therapy

Pharmacologic therapy is the cornerstone of the treatment of anal CD, although none of the currently

available treatments have demonstrated high success rates. The surgeon also plays an important role in the management of anal CD. In fact, anal CD requires the highest level of interaction between multiple disciplines, including the gastroenterologist, the surgeon and the radiologist. Close collaboration and transition of care between these disciplines, along with allied healthcare specialists, has a beneficial impact on patient outcome by providing integrated care and optimal patient follow-up.

Surgical Measures

Remission of anal CD is extremely challenging to achieve. Therefore, the initial treatment goal is to control

sepsis, which should be accomplished prior to initiating immunomodulatory therapy. Abscesses require drainage performed by a surgeon. The presence of an abscess can be assessed by clinical examination or pelvic imaging (MRI, CT or ultrasound). An understanding of the perineal anatomy is essential to adequately diagnose perineal abscesses, as well as to identify the optimal and safest form of drainage that avoids any sphincteric harm or results in the fistula becoming even more complex. The Park's classification is typically used by the surgeon to understand and describe the fistula anatomy. This classification is interesting because it describes the relationship of the fistula to the anal sphincter, which plays a role in selecting the most favourable surgical treatment for fistula repair. The surgeon's objective should be to obtain adequate evacuation of the abscess by creating the shortest possible fistula tract and avoiding damage to the anal sphincter. Ischiorectal abscesses (the most frequently-occurring abscesses) require percutaneous drainage by an incision through the skin at the culminating point of the abscess. The skin incision should be large enough to allow for optimal wound care. Supra-levator abscesses that result from a fistula tract in the inter-sphincteric plane should be drained intra-anally to avoid the creation of a supra-sphincteric fistula.

The risk for an abscess recurrence following drainage is reduced by the placement of a seton drain, which is a thread that is positioned within the fistula tract, looping from the external to the internal opening. This drain keeps the external opening patent for better drainage of infected content of the fistula, thereby reducing the risk of abscess recurrence. This procedure is typically well-accepted by patients. While it can remain indefinitely, patients often ask surgeons to remove it at some point during the disease course.

Once the acute sepsis is controlled and the question of treating the fistula arises, surgeons can play a role in fistula treatment using several available surgical techniques. Each surgical technique aims at closing the internal opening of the fistula, which is at the high-pressure zone. Successful closure of this internal opening typically results in the healing of the entire fistula. This is, however, more challenging than it sounds! Therefore, it is important for patients to have reasonable expectations when it comes to success rates of fistula treatment. They need to understand that, frequently, symptom control is the highest achievable goal.

Despite the availability of high-quality imaging, the surgeon typically begins with an examination under anesthesia (EUA) to explore the fistula and obtain a

good mapping of the fistula, and to identify possible secondary tracts, horseshoe fistulas or extensions above the pelvic floor. In addition, the surgeon will assess the quality of the tissues and the degree of inflammation, rule out the presence of anal stricture. Anal stricture is a significant predictive factor for surgical failure. If a seton is not already in place, one will often be placed at this time to prepare for surgical repair. The seton remains in the fistula tract to better control for sepsis, minimizing the risk for recurrent abscess formation. There is no strict evidence guiding the timing of seton removal, however, in the PISA trial setons were removed at 6 weeks after initiating anti-TNF treatment to increase the odds for closure under medical therapy.⁵ In fact, the timing for seton removal remains at the surgeon's discretion, trying to find a balance between adequate sepsis control and keeping the opportunity for non-operative healing.

The surgical techniques used for closure of CD fistulas were initially described for the treatment of cryptoglandular fistulas. Only a minority of patients included in the literature are CD patients; therefore, the clinical evidence is quite limited. However, the success rate is lower in CD patients vs that of patients with cryptoglandular fistulas. It is also important to note that only select patients are eligible for surgical repair of their CD-related fistulas. In fact, patients with very complex fistulas (i.e., supra-sphincteric fistulas and those with multiple internal openings), rectal stricture and active proctitis are poor candidates for anal fistula repair. More recently, the PISA-II trial compared radiological healing in CD patients with a peri-anal fistula between short-term anti-TNF treatment and surgical closure with anti-TNF treatment alone.⁵ At a follow up of 18 months, radiological healing was significantly more common in the surgical group compared to the anti-TNF alone group (32% vs 9%, $p = 0.005$), further validating surgical repair of fistulas in Crohn's disease patients. It is however important to consider closure at the time of adequate sepsis control and disease control.

Fistulotomy

Simple, superficial fistulas can be successfully treated by fistulotomy. This procedure results in a high success rate, even in CD patients; however, it partially compromises the continence of the anus by dividing part of the sphincter. This technique should be used with great caution especially in CD patients as the risk for recurrence leading to potential subsequent surgeries is high; furthermore, the typical stool consistency of CD patients requires good sphincter function.⁶ Therefore, this technique should be reserved only for carefully selected patients at low risk for incontinence. Sphincter sparing techniques are therefore preferred in patients with CD. Several surgical techniques aim to close the internal opening without disrupting the sphincter integrity.

Rectal advancement flap (RAF)

The first sphincter-preserving technique is the rectal advancement flap (RAF). This technique aims at mobilizing a v-shaped mucosal flap to cover the internal opening. It has been reported multiple times in the literature, including a systematic review reporting an overall outcome of approximately 60%.⁷ Data specific to CD patients is scarce; however, poor long-term outcomes have frequently been reported. The difficulty in CD patients is the presence of rectal fibrosis restraining the ability of the flap to be mobilized sufficiently. Moreover, the presence of proctitis is a contraindication for this approach. A recent retrospective series has reported a lower success rate for RAF than for ligation of intersphincteric fistula tract (LIFT) in CD patients.⁸

Ligation of intersphincteric fistula tract (LIFT)

As an alternative to RAF, surgeons can use the LIFT technique. This technique aims at dissecting the intersphincteric plane through a semi-circular perianal incision at the level of the fistula.⁹ Once the intersphincteric plane is opened, the portion of the fistula in that plane is isolated, ligated and transected, which results in a closed internal opening, without damaging the sphincters. The external opening of the fistula is left open and should heal secondarily once the internal opening has healed. In this case, once more only limited data report on the healing rate in CD patients, with an early healing rate of 65% and a late healing rate of virtually 50%.^{10,11} The healing rate is lower than for cryptoglandular fistulas and reflects the challenge of treating CD-related perianal fistulas.

Anal fistula plug

The anal fistula plug is a bio-absorbable xenograft plug composed of porcine intestinal submucosa, which is introduced in the fistula, obturating the internal opening while providing a matrix for tissue regeneration in the fistula tract.¹² Its easy to use, not requiring challenging surgical dissection, has generated significant interest. Unfortunately, several clinical studies have demonstrated its lack of benefit, including one randomized trial that did not show any benefit vs placebo.^{13,14} The plug should therefore not be used in the treatment of fistulas related CD.

Video-assisted anal fistula treatment (VAAFT) and fistula laser closure (FiLaC)

Video-assisted anal fistula treatment (VAAFT) and the fistula laser closure techniques aim at introducing a scope or a probe in the fistula tract to cauterize the tract in order to de-epithelialize it, thereby initiating healing.^{15,16} However, closure of the internal opening is still a required step for healing. Therefore, these approaches should be considered as additions to the previously described techniques. VAAFT

has the theoretical benefit of providing improved visualization of the side tracts of the main fistula for a better understanding of the anatomy; however, the significance of this on the healing rate is unknown.

Mesenchymal stem cells (MSCs)

The newest development in the treatment of CD-associated perianal fistulas is the use of mesenchymal stem cells. This was first described in a case report in 2003 reporting on the healing of a recto-vaginal fistula which healed completely following injection with MSCs.¹⁷ Since then, multiple Phase 1 and Phase 2 studies have been conducted, leading to the publication of a Phase 3 randomized clinical trial (RCT) reporting on fistula healing in 212 patients.¹⁸ Perianal fistulas healed in 50% of patients treated with allogeneic MSCs derived from adipose tissue, while 34% of the patients in the placebo group demonstrated fistula healing, which was statistically significant. Following this study, MSCs were recognized as a viable form of treatment in Europe; however, the high cost of this procedure has been a significant barrier to its clinical use. A second randomized trial completed recruitment of more than 500 patients in February 2023 and the results are expected in Fall of 2023.

Fecal diversion

Patients with symptomatic peri-anal disease despite optimized sepsis control and medical therapy are likely going to benefit significantly from fecal diversion, usually using a loop ileostomy. This will result in better symptom control and reduced discharge and sepsis. However, the challenge is to decide when it is reasonable to close a patient's stoma. There is a high risk for disease recurrence. It is therefore important to inform patients about this significant risk while selecting patients strictly.

It is important to consider the use of a diverting stoma in patients with anal CD. Stomas allow for better control of fistula-related symptoms by minimizing active inflammation, sepsis, incontinence, and pain. Proceeding to a stoma is typically a major decision for patients; however, the majority of these patients experience a significant improvement in QOL with a well-functioning stoma.¹⁹ Selection of the optimal stoma site, and avoiding skin folds and other creases that might increase the risk of leakage are very important. Furthermore, when using an ileostomy, sufficient prolapse is essential for proper functioning. Often, a loop stoma will be considered, which is theoretically reversible and provides some peace of mind to patients who are not yet ready to accept a permanent stoma. It is important, however, to disclose to the patient that closure of their stoma is very likely to lead to recurring symptoms. Clinicians can, however, consider fistula repair under the protection of a stoma as a measure to enhance healing which, in the case of successful repair, will allow for closure of the stoma.

Conclusion

Although the surgical management of perianal CD is challenging, surgeons have multiple options at their disposal for the treatment of a select cohort of patients. Close collaboration between the gastroenterologist and the radiologist are essential for optimal treatment. In the majority of cases, patients undergo a combination of surgery and pharmacologic treatment.

Correspondence:

Dr. Anthony de Buck van Overstraeten

Email: anthony.debuck@utoronto.ca

Financial Disclosures:

Speaker's Fees: AbbVie, Janssen Pharmaceuticals, Takeda

References

- Eglinton TW, Barclay ML, Geary RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. *Dis Colon Rectum*. 2012;55(7):773-777. doi:10.1097/DCR.0b013e31825228b0
- Wewer MD, Zhao M, Nordholm-Carstensen A, Weimers P, Seidelin JB, Burisch J. The Incidence and Disease Course of Perianal Crohn's Disease: A Danish Nationwide Cohort Study, 1997-2015. *J Crohns Colitis*. 2021;15(1):5-13. doi:10.1093/ecco-jcc/jjaa118
- Vollebregt PF, van Bodegraven AA, Markus-de Kwaadsteniet TML, van der Horst D, Felt-Bersma RJF. Impacts of perianal disease and faecal incontinence on quality of life and employment in 1092 patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;47(9):1253-1260. doi:10.1111/apt.14599
- Lönnfors S, Vermeire S, Greco M, Hommes D, Bell C, Avedano L. IBD and health-related quality of life -- discovering the true impact. *J Crohns Colitis*. 2014;8(10):1281-1286. doi:10.1016/j.crohns.2014.03.005
- Meima-van Praag EM, van Rijn KL, Wasmann KATGM, et al. Short-term anti-TNF therapy with surgical closure versus anti-TNF therapy in the treatment of perianal fistulas in Crohn's disease (PIISA-II): a patient preference randomised trial. *Lancet Gastroenterol Hepatol*. 2022;7(7):617-626. doi:10.1016/S2468-1253(22)00088-7
- Park MY, Yoon YS, Kim HE, et al. Surgical options for perianal fistula in patients with Crohn's disease: A comparison of seton placement, fistulotomy, and stem cell therapy. *Asian J Surg*. 2021;44(11):1383-1388. doi:10.1016/j.asjsur.2021.03.013
- Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas - PubMed. Accessed February 17, 2023. <https://pubmed.ncbi.nlm.nih.gov/myaccess.library.utoronto.ca/31183438/>
- Ligation of the Intersphincteric Fistula Tract and Endorectal Advancement Flap for High Perianal Fistulas in Crohn's Disease: A Retrospective Cohort Study - PubMed. Accessed February 15, 2023. <https://pubmed.ncbi.nlm.nih.gov/myaccess.library.utoronto.ca/31696918/>
- Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. *J Med Assoc Thai Chotmaihet Thangphaet*. 2007;90(3):581-586.
- Kamiński JP, Zaghiyan K, Fleshner P. Increasing experience of ligation of the intersphincteric fistula tract for patients with Crohn's disease: what have we learned? *Colorectal Dis Off J Assoc Coloproctology G B Irel*. 2017;19(8):750-755. doi:10.1111/codi.13668
- Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn's disease. *Ann Surg*. 2014;260(6):1057-1061. doi:10.1097/SLA.0000000000000479
- Safar B, Jobanputra S, Sands D, Weiss EG, Noguera JJ, Wexner SD. Anal fistula plug: initial experience and outcomes. *Dis Colon Rectum*. 2009;52(2):248-252. doi:10.1007/DCR.0b013e31819c96ac
- Senéjoux A, Siproudhis L, Abramowitz L, et al. Fistula Plug in Fistulising Ano-Perineal Crohn's Disease: a Randomised Controlled Trial. *J Crohns Colitis*. 2016;10(2):141-148. doi:10.1093/ecco-jcc/jiv162
- Christoforidis D. Who benefits from the anal fistula plug? *Dis Colon Rectum*. 2010;53(8):1105-1106. doi:10.1007/DCR.0b013e3181e27efb
- Meinero P, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. *Tech Coloproctology*. 2011;15(4):417-422. doi:10.1007/s10151-011-0769-2
- Wilhelm A. A new technique for sphincter-preserving anal fistula repair using a novel radial emitting laser probe. *Tech Coloproctology*. 2011;15(4):445-449. doi:10.1007/s10151-011-0726-0
- García-Olmo D, García-Arriaza M, García LG, et al. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. *Int J Colorectal Dis*. 2003;18(5):451-454. doi:10.1007/s00384-003-0490-3
- Panés J, García-Olmo D, Van Assche G, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet Lond Engl*. 2016;388(10051):1281-1290. doi:10.1016/S0140-6736(16)31203-X
- Abdalla MI, Sandler RS, Kappelman MD, et al. The Impact of Ostomy on Quality of Life and Functional Status of Crohn's Disease Patients. *Inflamm Bowel Dis*. 2016;22(11):2658-2664. doi:10.1097/MIB.0000000000000930

VIRGINIA SOLITANO

MD

Dr. Solitano is an Advanced IBD fellow at Western University in London, Ontario and GI fellow at Humanitas University Milan. During her IBD fellowship at Western University she is focusing on IBD clinical trials design and analysis, and the development and validation of indices under the supervision of Professor Vipul Jairath.

Affiliations:

Western University, London, Ontario, Canada

Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy



VIPUL JAIRATH

MD

Dr. Jairath is a Professor of Medicine at the Schulich School of Medicine and Dentistry and holder of the John and Susan McDonald Endowed Chair in Inflammatory Bowel Disease (IBD) Clinical Research at Western University. He is the Program Director for the Advanced IBD Fellowship at Western and Research Chair for the Department of Medicine. His research interests focus on clinical therapeutics for IBD, clinical trials, development and validation of clinical indices and patient reported outcome measures. His clinical practice is based at University Hospital and he is principal investigator for several clinical trials.

Affiliations:

Western University, London, Ontario, Canada



ADVANCED COMBINATION THERAPY IN IBD: CAN IT BE ACHIEVED WITH SUCCESS?

Introduction

Conventional combination therapy in inflammatory bowel disease (IBD), which consists of an immunosuppressant agent and an anti-TNF agent, is a well-integrated strategy in clinical practice. The landmark SONIC and UC SUCCESS trials demonstrated that combining a thiopurine and infliximab was more effective than monotherapy and was associated with higher corticosteroid-free remission and mucosal healing rates.^{1,2}

The primary advantage of this traditional combination therapy derives from the immunomodulator's effect on the pharmacokinetics of anti-TNFs, with a lower rate of anti-drug antibodies detected in subjects administered combination therapy.³ Despite the growing therapeutic armamentarium and clinical study development pipeline for IBD, clinical remission rates at one year continue to range from 30% to 50%⁴⁻⁷ indicating that a therapeutic ceiling may have been reached with the use of single agents. In addition, agents that have proven effective for luminal disease may not be helpful for extraintestinal manifestations (EIMs) or for concurrent immune-mediated diseases (IMIDs).⁸ In light of this, the concept of advanced combination treatment (ACT), which entails the simultaneous administration of at least two biologic agents, or a biologic and a small-molecule drug, is emerging as a therapeutic approach for patients with refractory IBD, as well as for those with IBD and a concurrent IMID, or IBD with EIMs.⁹

Clinical Evidence for ACT

Previous clinical trials and reports

Several case series and small-cohort studies have provided interesting examples of successful use of ACT in patients with refractory IBD, or those with concomitant IMIDs (e.g., psoriatic disease, rheumatoid arthritis [RA], spondylarthritis [SpA]) or EIMs (e.g., erythema nodosum, pyoderma gangrenosum, uveitis).

Among cohort studies, Yang et al reported the results of 22 patients with long-standing Crohn's disease (CD) in a Canadian and U.S. centre, of whom the majority had undergone prior surgical resections and failed a median number of four biologics.¹⁰ The most common combination administered was vedolizumab plus ustekinumab, likely due to their favourable individual safety profiles.

An Italian retrospective cohort study reported improved outcomes in all 16 patients with either active IBD or active EIMs (e.g., active SpA and psoriatic disease), treated with ACT.¹¹ In this case series, only three adverse

events were reported (cutaneous reaction following certolizumab administration, a drug-induced liver injury, and a perianal abscess); however, none of these were serious.

A systematic review with meta-analysis including 30 studies involving 279 IBD patients found that the primary indication for ACT was refractory IBD, followed by concurrent EIMs or rheumatologic disease.¹² The most common combination was anti-TNF therapy plus anti-integrins (48%), followed by ustekinumab plus an anti-integrin. Over a median follow-up of 32 weeks, pooled rates of clinical and endoscopic remission were 59% (95% CI, 42%-74%), and 34% (95% CI, 23%-46%), respectively. Interestingly, rates of success were higher in those receiving ACT due to concomitant EIMs, corroborating the hypothesis that inhibiting more than a single mechanism of action might provide adequate disease control across multiple organ systems. The safety data revealed that rates of adverse events, infections, and malignancy were similar to those reported on anti-TNF monotherapy (pooled rate of adverse events 31.4%, 95% CI = 12.9%-53.7%)¹³.

The RCT conducted by Sands et al in 2007 represents the first attempt of ACT in IBD.¹⁴ In this study, 79 patients with active CD (Crohn's Disease Activity Index [CDAI] score $\geq$ 150) while on infliximab treatment were randomized 2:1 to receive three intravenous infusions of natalizumab (300 mg; n = 52) or placebo (n = 27) every four weeks. Patients received infliximab (5 mg/kg) every eight weeks for at least ten weeks prior to randomization and throughout the study. The percentage of patients experiencing adverse events was similar between the combination and the monotherapy groups (27% vs 30%, respectively). Although the trial was not powered to detect statistical differences in terms of efficacy, a higher proportion of patients in the combination group achieved clinical remission over the entire length of the study compared to the monotherapy arm. However, the use of natalizumab is associated with increased risk for developing progressive multifocal leukoencephalopathy and it is approved only for moderate-to-severe CD by the FDA.

The Phase 2, randomized, double-blind, controlled VEGA trial, whose results were published online in February 2023, demonstrated that the combination of the anti-TNF golimumab with the anti-interleukin-23 guselkumab was more effective for short-term induction treatment in UC than either agent alone.¹⁵

VEGA was a proof-of-concept trial conducted at 54 hospitals, academic medical centers, or private

practices in nine countries. Eligibility criteria included: Adults age ≥ 18 to 65 years with a confirmed diagnosis of UC at least three months before screening and moderately-to-severely active UC (Mayo score 6-12) with a centrally-read baseline endoscopy subscore of 2 or higher.

Three-hundred fifty-eight patients were randomly assigned (1:1:1) to combination therapy (subcutaneous golimumab 200 mg at Week 0, subcutaneous golimumab 100 mg at Weeks 2, 6, and 10, and intravenous guselkumab 200 mg at Week 0, 4, and 8, followed by subcutaneous guselkumab monotherapy 100 mg every 8 weeks for 32 weeks, $n=71$); golimumab monotherapy (subcutaneous golimumab 200 mg at Week 0 followed by subcutaneous golimumab 100 mg at Week 2 and every 4 weeks thereafter for 34 weeks, $n=72$); or guselkumab monotherapy (intravenous guselkumab 200 mg at Weeks 0, 4, and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks thereafter for 32 weeks, $n=71$).

The study's primary endpoint was clinical response at Week 12 (defined as a $\geq 30\%$ decrease from baseline in the full Mayo score and a ≥ 3 points absolute reduction with either a decrease in rectal bleeding score of ≥ 1 point or a rectal bleeding score of 0 or 1). A greater proportion of patients receiving combination therapy achieved clinical response (59/71, 83.1%) after 12 weeks vs monotherapy with either guselkumab (53/71, 74.6%, nominal $p=0.2155$) or golimumab (44/72, 61.1%, nominal $p=0.0032$). Interestingly, the composite outcome, including endoscopic improvement and histologic remission, was achieved in approximately twice as many patients with ACT vs monotherapy (40.8% vs 26.8% and 15.3% with guselkumab and golimumab, respectively). Consistent with safety data from real-world experiences, only one patient reported a serious infection of influenza and sepsis among 71 subjects on ACT. Infections were reported in 14% of patients receiving combination therapy or guselkumab monotherapy vs a rate of 22% in those receiving golimumab monotherapy.

Ongoing clinical trials

Several clinical trials on ACT in IBD are currently ongoing. EXPLORER is an open-label, uncontrolled study, investigating the role of triple combination therapy with vedolizumab, adalimumab and oral methotrexate in inducing endoscopic remission in selected patients with a recent CD diagnosis (within 24 months) and at high risk for complications (SES-CD score ≥ 7 , or ≥ 4 if isolated ileal disease).¹⁶ An interim analysis showed that the primary outcome of endoscopic remission (SES-CD 0-2) at 26 weeks was reached in 34.5% of patients, and that more than 50% of patients were in clinical remission at this time-

point. DUET-CD and DUET-UC are ongoing Phase 2b randomized, active-and placebo-controlled studies evaluating the efficacy and safety of induction and maintenance ACT with guselkumab and golimumab in participants with moderate-to-severe CD and UC, respectively.

ACT should be administered only in specific clinical situations following a comprehensive examination of the patient's needs and any potential safety issues. Specifically, ACT should be considered for treatment of luminal disease, which is medically refractory to all available monotherapy, in cases of concomitant EIMs or IMIDs, or in extremely high-risk phenotypes such as extensive small bowel disease, as well as structuring and penetrating disease at high risk of developing complications. When using ACT for an alternative concomitant, untreated inflammatory pathway, clinicians should take into account inflammatory pathways and downstream cascades that are targeted with potential ACT, avoiding agents with multiple crosstalk interactions (such as an anti-12/23 combined with an anti-IL-23). Finally, biologics that have previously resulted in immunogenicity should be avoided. Due to their favorable safety profiles, vedolizumab and ustekinumab appear to be the most suitable anchor biologics based on the clinical evidence currently available^{17,18}

An individualized approach to treatment is paramount in cases where there is a paucity of clinical data to support what appears to be the optimal combination. For instance, in individuals with concomitant EIMs/IMIDs who have shown response from one tissue target, such as the skin or joints with an anti-TNF or an (IL-12)/23 antagonists, the addition of a gut-selective compound such as vedolizumab seems reasonable in the setting of active luminal disease. The addition of vedolizumab or an oral small-molecule drug such as tofacitinib in UC should be considered in very high-risk phenotypes with partial response to IL-12/23-axis-blockade and a history of loss of response, intolerance to therapy with one or more TNF inhibitors, or both. Decisions should also be made based on the mode of delivery selected (e.g., subcutaneous vs oral), individual comorbidities, prior treatment failures, and disease subtype.

Despite the growing number of observational studies, the practice of ACT remains off-label and larger real-world clinical studies and RCTs are needed to better evaluate the effectiveness and safety of this treatment approach.

Conclusion

The concept of ACT has appeal as a method to raise the therapeutic ceiling for IBD. At present, its use is strictly off-label, and it should be used only in specific scenarios as discussed in this article (**Table 1**). Potential risks and benefits should be clearly documented, and ideally the decision to initiate should be made by a multidisciplinary team. In addition to traditional combination therapy, ACT including at least two advanced targeted therapies has proven to be useful for specific clinical scenarios following careful evaluation of the patient's needs, as well as potential safety issues. With the addition of ozanimod, upadacitinib, and other anti-IL-23 medications (such as risankizumab, guselkumab, and mirikizumab), it is anticipated that new drug combinations with varied effectiveness and safety profiles will be investigated in the near future, enhancing the current IBD treatment armamentarium. All of the available evidence should be considered hypothesis-generating for future well-controlled and adequately powered clinical trials, ideally in high-risk subjects.

Correspondence:

Dr. Vipul Jairath

Email: vjairath@uwo.ca

Financial Disclosures:

V.J.: Consulting/advisory board fees : AbbVie, Alimentiv, Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, AstraZeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Metacrine, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus, Reistone Biopharma, Roche, Sandoz, Second Genome, Sorriso Pharmaceuticals, Takeda, Teva, TopiVert, Ventyx, and Vividion; **Speaker's fees:** AbbVie, Ferring, Bristol Myers Squibb, Galapagos, Janssen, Pfizer, Shire, Takeda, and Fresenius Kabi

V.S.: None

References

- Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. <http://dx.doi.org/10.1056/NEJMoa0904492>. 2010;362(15):1383-1395. doi:10.1056/NEJMoa0904492
- Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2). doi:10.1053/J.GASTRO.2013.10.052
- Colombel JF, Adedokun OJ, Gasink C, et al. Combination Therapy With Infliximab and Azathioprine Improves Infliximab Pharmacokinetic Features and Efficacy: A Post Hoc Analysis. *Clin Gastroenterol Hepatol*. 2019;17(8):1525-1532.e1. doi:10.1016/J.CGH.2018.09.033
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT 1 randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/S0140-6736(02)08512-4
- Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65. doi:10.1053/J.GASTRO.2006.11.041
- Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015;42(2):188-202. doi:10.1111/APT.13243
- 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):1946-1960. doi:10.1056/NEJMoa1602773
- Schett G, McInnes IB, Neurath MF. Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs. *N Engl J Med*. 2021;385(7):628-639. doi:10.1056/NEJMRA1909094
- Danese S, Solitano V, Jairath V, Peyrin-Biroulet L. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). *Gut*. Published online 2022. doi:10.1136/GUTJNL-2022-327025
- Yang E, Panaccione N, Whitmire N, et al. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther*. 2020;51(11):1031-1038. doi:10.1111/APT.15719
- Privitera G, Onali S, Pugliese D, et al. Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease. *J Crohns Colitis*. 2020;15(2):335-339. doi:10.1093/ECCO-JCC/JJAA149
- Ahmed W, Galati J, Kumar A, et al. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. Published online 2021. doi:10.1016/J.CGH.2021.03.034
- Lichtenstein GR, Feagan BG, Cohen RD, et al. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience. *Inflamm Bowel Dis*. 2018;24(3):490-501. doi:10.1093/IBD/IZX072
- Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis*. 2007;13(1):2-11. doi:10.1002/IBD.20014
- Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol*. Published online February 2023. doi:10.1016/S2468-1253(22)00427-7
- Colombel JF, Ungaro RC, Sands BE, et al. 885: TRIPLE COMBINATION THERAPY WITH VEDOLIZUMAB, ADALIMUMAB, AND METHOTREXATE IN PATIENTS WITH HIGH-RISK CROHN'S DISEASE: INTERIM ANALYSIS FROM THE OPEN-LABEL, PHASE 4 EXPLORER TRIAL. *Gastroenterology*. 2022;162(7):S-215. doi:10.1016/S0016-5085(22)60514-6
- Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol*. 2018;53(9):1048-1064. doi:10.1007/S00535-018-1480-0
- Sandborn WJ, Rebutck R, Wang Y, et al. Five-year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: the IM-UNITI trial. *Clinical gastroenterology and hepatology*. Published online 2021. doi:10.1016/j.cgh.2021.02.025

Population	Patients with IBD refractory to all medical therapy Patients with high-risk phenotypes (extensive small bowel disease, and stricturing or fistulizing disease behaviour) Patients with a concomitant IMID (e.g., psoriatic disease, RA, SpA) or EIMs (e.g., erythema nodosum, pyoderma gangrenosum, uveitis)
ACT	Preference for agents with the most favorable safety profile (e.g., vedolizumab and ustekinumab as anchor) Preference for anti-TNF agents in CD, especially in ileal CD or with bowel damage (eg, fistula, strictures, complex perianal disease) Preference for vedolizumab in UC patients Preference for anti-TNF agents or ustekinumab (or anti-IL-23 blocker); or a JAK inhibitor in patients with concomitant EIMs or IMIDs
Setting	Potential risks and benefits should be clearly documented; ideally the decision to initiate should be made by a multidisciplinary team

Table 1. Practical recommendations for the use of ACT in clinical practice; courtesy of Vipul Jairath, MD and Virginia Solitano, MD

JENNIFER LIPSON

MD



Dr. Lipson is a medical dermatologist in Ottawa practising at West Ottawa Specialty Care. She is a lecturer at the University of Ottawa and an associate physician at The Ottawa Hospital and the Children's Hospital of Eastern Ontario (CHEO). She serves as a committee member for the Ottawa Dermatology Clinical and Scientific Biannual Meeting, The Royal College of Physicians and Surgeons of Canada Subspecialty Committee for Dermatology and on the Ontario Medical Association Section on Dermatology Executive Committee. Her clinical interests include immune mediated inflammatory diseases, hormonal acne and skin cancer. Dr Lipson also serves on the medical advisory committee for the Acne and Rosacea Society of Canada.

Affiliations:

University of Ottawa, Ottawa, ON

The Ottawa Hospital, Ottawa, ON

Children's Hospital of Eastern Ontario, Ottawa, ON

CUTANEOUS MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: CLINICAL PEARLS FOR GASTROENTEROLOGISTS

Introduction

As clinicians' knowledge about the relationship between inflammatory bowel diseases (IBDs) and the integumentary system continues to expand, gastroenterologists and dermatologists need to know about the disease associations involved and understand the impact of treatments on these immune conditions in order to provide care to these medically complex patients.

Extra-intestinal Manifestations (EIMs)

IBD, Crohn's Disease (CD) and ulcerative colitis (UC) carry a broad range of associated extraintestinal manifestations (EIMS) which affect various body systems. The skin is one of the most commonly affected of these. At least 10% of patients with IBD have mucocutaneous EIMs, more commonly with CD where it has been reported in up to 44% of patients.^{1,2} In some cases muco-cutaneous manifestations are the presenting feature of IBD.³ Risk factors for mucocutaneous CD and UC include

female gender, younger age of diagnosis and eye or joint involvement. Additional risks in CD include family history of IBD and disease requiring immunomodulatory therapy.⁴

The possible mucocutaneous EIMs of IBD are abundant; therefore, they are best approached by classification according to pathophysiologic origin, including IBD specific; reactive conditions; associated conditions; nutritional deficiencies; and treatment-related conditions (**Table 1**). Due to their large number, it is not feasible to review every associated condition; only common and significant mucocutaneous EIMs will be addressed in this review. **Table 2** elaborates on the dermatologic conditions associated with nutritional deficiencies.

IBD-specific Mucocutaneous Conditions

IBD-specific mucocutaneous conditions affect the skin by the same mechanisms as in the gastrointestinal (GI) tract. This category is the most common group

IBD Specific Lesions	Reactive Conditions	Associated Conditions	Nutritional Deficiencies	Therapy Related Lesions
• Fissures & fistulas (peri-anal and peri-stomal) • Metastatic Crohns Disease • Oral Crohns Disease	• Aphthous Ulcers • Epidermolysis Bullosa Aquisita • Erythema Nodosum • Sweet Syndrome • Polyarteritis Nodosa • Pyoderma Gangrenosum	• Finger Clubbing • Hidradenitis Suppurativa • Lichen Planus • Linear IgA Dermatositis • Palmar Erythma • Psoriasis • Vitiligo	• Acrodermatitis Enteropathica • Glossitis • Pellagra • Phrynoderma • Scurvy	• Alopecia • Drug rash/Drug Hypersensitivity Syndrome • Neutrophilic Dermatoses • TNF-alpha induced skin changes • Toxic Epidermal Necrolysis/ Steven's Johnson Syndrome

Table 1. Common and important mucocutaneous EIMs; courtesy of Jennifer Lipson, MD

Deficient Nutrients	Name	Cutaneous Manifestations
Vitamin B		Stomatitis, glossitis, angular cheilitis
Niacin (B3)	Pellagra	Photosensitivity, sunburn like rash (chest, dorsal hands, dorsal feet) which may blister, then become thick, rough and hyperpigmented. Casals' necklace (pigmentation around neck). Perigential inflammation and glossitis.
Zinc	Acrodermatitis enteropathica	Acral (elbows, knees, fingers, toes) and periorificial (mouth, anus) dermatitis, alopecia, glossitis and nail dystrophy
Vitamin C	Scurvy	Ecchymosis, perifollicular hemorrhage, corkscrew hairs, follicular hyperkeratotic papules, splinter hemorrhages, red bleeding gums
Vitamin A	Phrynoderma	Hyperkeratotic papules on anterolateral thighs and posterolateral arms
Vitamin K		Purpura

Table 2. Nutritional deficiency associated conditions; courtesy of Jennifer Lipson, MD

and includes metastatic CD (MCD), oral CD and contiguous lesions (perianal ulcers, fissures/fistulas).² MCD is an extremely rare entity. Accurate prevalence and incidence data are lacking, and the condition is most likely underdiagnosed due to its varied morphology.² This entity typically occurs in well-established GI disease. Skin disease preceding GI disease is seen more commonly in children and manifests with skin and genital lesions. There does not appear to be an association between MCD activity and GI activity. MCD can have numerous morphologies, including erythematous plaques, nodules, and linear ulcerations occurring more often than pustules, papules or abscess-like lesions. The most commonly affected site is the genitals; this occurs in two-thirds of children and half of adults with MCD. As a result of this, MCD is typically classified as genital and non-

genital MCD.² Genital MCD may present with genital edema, knife-like fissures, condyloma-like papules, and skin tags which show granulomas on pathology.² Vulvar CD occurs as four primary types: ulceration, vulvar swelling, hypertrophic lesions and chronic suppuration.⁵ Non-genital MCD most commonly affects the legs, abdomen, trunk and intertriginous sites; it rarely occurs on the face. As MCD is rare, treatment reflects anecdotal evidence from case reports and case series, and none of the available treatments are reliably efficacious.² Treatments with reported efficacy include intralesional and systemic glucocorticosteroids; oral metronidazole; tumor necrosis factor α (TNF α) inhibitors; azathioprine; methotrexate; cyclosporine; thalidomide; and surgical excision.²

The granulomatous process of CD extends to the oral cavity (known as oral CD) in 8%-9% of patients. This can present as cobblestone appearance of the mucosa, deep linear ulcers, indurated mucosal skin tags, gingivitis, or swelling of the face, tongue or lips. The lips are the most common site of swelling and may develop painful vertical fissures. This entity is referred to as granulomatous cheilitis (**Figure 1**).⁶ Oral lesions typically respond to treatment of the underlying disease; however, local treatment with topical or intralesional steroids; topical calcineurin inhibitors; topical anesthetic; acetylsalicylic acid (ASA) mouth rinses; topical non-steroidal anti-inflammatory paste; and antiseptic washes to prevent infection can also be used.



Figure 1. Typical granulomatous cheilitis with lip swelling and fissuring.

Controversy exists regarding whether or not perianal fissures and fistulas should be considered EIMs. The European Crohn's and Colitis Organization (ECCO) 2016 guidelines do not consider them EIMs when they occur within the GI tract.^{3,7}

Reactive Conditions

The most common mucocutaneous EIMs in the reactive category are erythema nodosum (EN) (7.4%), pyoderma gangrenosum (PG) (2.3%) and aphthous stomatitis.⁷

EN is an acute inflammatory process of the subcutaneous fat (panniculitis) presenting with rapid onset tender, deep, non-ulcerating 1-5 cm red-to-purple-brown bruise-like nodules (**Figure 2**). The most characteristic location is the shins, but the nodules can occur anywhere in the body. Patients may have associated fever, malaise and arthralgias. EN is the most common cutaneous condition affecting patients with IBD, although it is certainly not exclusive to IBD. EN is seen in up to 10% of patients with UC and up to 15% of patients with CD.¹ It is typically present in the

setting of established IBD; however, it precedes IBD in 15% of cases.⁸ EN is more common in female patients, patients with arthritis, and HLA-B27 positive patients. In patients with CD, it is often associated with colonic involvement.¹ EN activity tends to parallel IBD disease activity, often occurring during IBD flares; however, the severity of skin flares does not necessarily mirror IBD flare severity.^{1,3,7} In the majority of cases, EN is a self-limiting process or resolves with treatment of the underlying condition. Supportive measures such as leg elevation, non-steroidal anti-inflammatories (NSAIDs) for pain control and compression are helpful. Some cases may require systemic corticosteroids, steroid sparing anti-inflammatories such as colchicine, dapsone and potassium iodide, and occasionally immunomodulators such as methotrexate, azathioprine or TNF α inhibitors. Interestingly infliximab can treat and on occasion trigger EN, in particular in patients with ankylosing spondylitis (AS).⁸



Figure 2. Red-brown indurated plaques on the lower extremity typical of EN.

Photo ©Massimo Defilippo (Symptomeundbehandlung.com)

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis seen both idiopathically and concomitant with a variety of systemic diseases. IBD is the most commonly associated systemic disease, with a reported incidence of up to 3%.³ It has greater prevalence in patients with UC; a family history of UC; women; colonic involvement; permanent stoma; ocular involvement; and EN.³ Patients with IBD and PG are more likely to have arthritis and uveitis.⁷ PG has variable

presentations with five recognized subtypes. The most common subtypes associated with IBD are ulcerative and pustular, followed by peristomal, bullous and vegetative.¹ PG presents as a papule, pustule or nodule which rapidly ulcerates, becoming a severely tender ulcer with a classic inflammatory gunmetal grey border, ragged undermined edges and a purulent covering (**Figure 3**).¹ Due to its appearance and the intense pain it causes, PG is frequently misdiagnosed and treated as an infection. Diagnostic considerations for PG include pathergy (occurring in an area of trauma) and initiating as a pustule, which occurs in 30% of cases, although this often remains unnoticed before it ulcerates. PG occurs most commonly on the extensor lower extremities and peristomal, but can occur anywhere on the body.¹ PG classically heals with “cribriform scarring” which has a honeycomb-like appearance.

Similar to EN, patients with PG may have associated fever, malaise and arthralgias. Unlike EN, which typically occurs in the setting of well-established IBD, PG can precede, coincide with, or occur following the onset of IBD.³ It does not typically parallel underlying IBD disease activity, with the exception of the pustular variant.

An erosive pustular eruption of the lips and oral mucosa, pyostomatitis vegetans, is considered by many as a mucosal variant of pustular PG. This is thought to be more common in men aged 20-59 and typically occurs in the course of well-established IBD.³

Treating PG initially involves treatment of the inflammation with anti-inflammatories and/or immunomodulators, followed by treatment of the ulcer with appropriate wound care. Initial treatment may include intralesional and potent topical steroids and/or calcineurin inhibitors if the condition is in the early or mild stages. For more severe disease, prednisone and/or cyclosporine, mycophenolate mofetil, or a TNF α inhibitor are frequently used. Debridement should not be performed due to the risk of pathergy. Unfortunately, PG has a recurrence rate of up to 25%.³

Sweet syndrome, otherwise known as acute febrile neutrophilic dermatosis, is another less common neutrophilic dermatosis seen in a variety of inflammatory, drug-induced or malignant settings. It can occur in the context of IBD, during an IBD flare and in quiescent disease.⁹ It is more common in CD, women in the third to fifth decade and CD with colonic involvement.¹ Sweet syndrome presents with tender edematous purple-red papules, plaques, pustules, and sometimes bullae or “pseudobullae,” with a predilection for the head and hands. Patients often



Figure 3. Pyoderma gangrenosum with classic ragged, gunmetal grey border and epithelial stranding between ulcerations. Photo credit: Healthmd.net

have systemic symptoms including fever, malaise and arthralgia and, less commonly, can have inner organ involvement. This is often a self-limiting disorder. Treatment is very similar to that of EN and PG, specifically, topical and systemic anti-inflammatories; this disease is highly systemic steroid responsive.⁹

Bowel-associated dermatosis-arthritis syndrome (BADAS) is an extremely rare neutrophilic dermatosis which has been reported in patients with IBD or post-gastric bypass surgery. It manifests with fever, arthralgias, myalgias, abdominal pain, and polymorphous skin lesions mimicking PG, EN or hidradenitis suppurativa (HS). It is thought to be secondary to immune complexes which develop due to overgrowth of bacteria in the gut.¹ Treatment includes surgery, antibiotics and systemic steroids.

Aphthous ulcers affect approximately 20% of the general population and up to 33% of patients with CD and UC.³ Aphthous stomatitis manifests with recurring, painful, round and oval ulcers with an erythematous border and cream-colour base. The presence of aphthous stomatitis should trigger suspicion about IBD, especially in children as it occurs more frequently in this cohort and may precede diagnosis of IBD.⁶ The oral aphthae correlate with active GI disease and HLA-B27 positivity.¹

Cutaneous polyarteritis nodosa (cPAN) is an uncommon, recurring vasculitis of the small and medium vessels of the skin. Approximately 10% of

all cPAN cases are associated with IBD and it can precede the diagnosis of IBD. cPAN presents with erythematous nodules, most commonly on the lower extremities. Clinically, it can mimic EN, PG or metastatic CD. Biopsy is required for diagnosis. Disease activity does not parallel activity of the underlying IBD.³

Epidermolysis bullosa acquisita (EBA)

is an extremely rare autoimmune bullous disorder caused by autoantibodies against collagen VII. It presents with non-inflammatory bullae in areas of trauma, most commonly the hands and feet. The bullae heal with scarring and milia formation. Thirty percent of patients with EBA have IBD, CD more often than UC, and the majority of patients having a long-standing history of IBD. The co-occurrence of EBA and IBD is thought to be due to the phenomenon of epitope spreading.¹ Treatment of the underlying IBD typically results in improvement of the associated skin lesions.¹

Associated Conditions

Numerous inflammatory skin conditions are associated with IBD. A recent clinical study demonstrated that rosacea, psoriasis and atopic dermatitis have a strong association with IBD, while vitiligo and alopecia areata had a lesser or non-existent association.³

Psoriasis

The association between psoriasis and IBD is complex. There is a higher incidence of psoriasis, in particular plaque psoriasis, in patients with CD (11.2%) and UC (5.7%).¹ In addition, patients with psoriasis are predisposed to IBD. The severity of the psoriasis does not correlate with IBD activity. Additionally, certain therapies used to treat IBD can trigger drug-induced psoriasis. The co-occurrence of these inflammatory conditions and their therapeutic overlap suggest shared genetics and inflammatory pathways; it has been established that these conditions share genetic characteristics.

Psoriasis can be triggered or exacerbated by a variety of medications, including TNF α inhibitors. Drug-induced psoriasis occurs in 2% of patients treated with TNF α inhibitors and appears to occur most commonly in patients with underlying CD and treated with infliximab.^{1,10} Considerations for TNF α -induced psoriasis include a greater proportion of patients with palmoplantar pustular involvement; generalized pustular involvement; severe post-auricular involvement; severe scalp disease resulting in alopecia; and more than one morphology (rather

than typical plaque psoriasis).¹⁰ Fortunately, most patients have been reported to resolve (47%) or improve (46%) following cessation of the TNF α inhibitor. Nearly 50% of patients did not improve after transitioning to a different TNF α inhibitor.¹⁰ Preliminary reports suggest that the phenomenon can occur with other biologics as well, such as ustekinumab and vedolizumab.¹¹

Oral lichen planus can be associated with IBD.

It presents with reticulated, white plaques in the mouth (buccal mucosa, tongue, gingiva) which can ulcerate. In addition, oral lichenoid eruptions have been reported with the TNF α inhibitors sulfasalazine and mesalazine. **Cutaneous lichen planus**, which presents with itchy, violaceous flat-topped papules and plaques, has also been reported secondary to TNF α inhibitors.^{6,12,13}

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease manifesting with open comedones, cysts, nodules, scarring, and fistulous tracts; it occurs predominantly in skin folds. This disease is seen with 9-fold greater prevalence in patients with IBD, particularly CD. In cases of HS, the CD is often localized to the large bowel. It precedes the HS, which is often located in the perineal or perianal sites.¹⁴

Interestingly, the rare syndromes **SAPHO** (synovitis, acne, pustulosis, hyperostosis, osteitis) and **PAPA** (pyogenic arthritis, PG, acne) can be associated with IBD. SAPHO most commonly affects young patients with UC.¹

Linear IgA bullous dermatosis (LABD) is a rare blistering of the skin and mucous membranes which occurs in both children and adults. It is characterized by severe pruritis, with the tense vesicles and bullae appearing in an annular "crown of jewels" arrangement. It has been reported with both CD and UC. In a clinical study, linear IgA in association with UC was reported to remit with colectomy.¹⁵ This disease typically responds well to systemic steroids and the sulfone dapsone.

Additional associated conditions such as vitiligo, finger clubbing and palmar erythema occur to a lesser degree and have less impact on patients' overall health. The characteristics of various reactive and associated EIMs of IBD are described in **Table 3**.

Treatment-related Conditions

TNF α inhibitors commonly used to treat IBD have been reported to cause a variety of skin eruptions including, but not limited to, drug-induced lupus;

	More common in CD vs. UC	More common in Female (F) vs. Male (M)	Typically Parallels course of IBD	Associations	Typically Responds to treatment of underlying disease
Erythema Nodosum	CD > UC	F > M	Yes	Arthritis and uveitis	Yes
Pyoderma Gangrenosum	UC > CD (similar)	M > F	Not necessarily	Increased risk of uveitis and arthritis	No
Sweet Syndrome	CD > UC	F > M	Not necessarily	Fever, arthralgias, Other EIMs	Yes
Aphthous Stomatitis	CD > UC	M > F Children > Adult	Yes	HLA B27+	Sometimes
EBA	CD > UC	-	-	-	Yes
PAN	CD > UC	-	No	-	No
PsO	CD > UC	-	No	-	No

Table 3. Characteristics of common, major reactive and associated mucocutaneous EIMs of IBD; courtesy of Jennifer Lipson, MD

sarcoidosis; eczema; alopecia areata; pityriasis lichenoides et varioliformis acuta (PLEVA); and vasculitis.¹³ Sulfasalazine and azathioprine have both been reported to cause morbilliform eruptions and Sweet syndrome, as well as potentially fatal drug hypersensitivity syndrome (DISH),¹⁶ Stevens-Johnson syndrome, and toxic epidermal necrolysis.¹⁷⁻¹⁹ Azathioprine has also been reported to cause azathioprine hypersensitivity syndrome which includes rash, alopecia, Kaposi sarcoma, and non-melanoma skin cancer. Mesalamine is reported to cause rarely-associated photosensitivity, alopecia and pruritis.²⁰

Fortunately, treatments for IBD and dermatologic EIMs frequently overlap, allowing for both diseases to be treated with the same medication. This includes systemic immunosuppressants (prednisone, methotrexate, cyclosporine, azathioprine, sulfasalazine) and immunomodulators (TNF α inhibitors, IL 12-23 inhibitors, IL-23 inhibitors, JAK inhibitors). Further research is needed to establish whether or not the early introduction of advanced therapies, such as biologics, to patients with IBD may prevent EIMs, and which treatments are optimal for co-managing IBD and EIMs.

The evolving landscape of IBD treatments, and the increased use of gut-specific therapies introduces the question of whether or not these treatments will have any impact on the incidence and management of EIMs. Vedolizumab, a gut-specific monoclonal antibody targeting $\alpha 4\beta 7$ -integrin, was approved by Health Canada in 2016. It has proven efficacy in CD and UC, as well as a favourable side effect profile. The possibility of vedolizumab resulting in increased EIMs is

challenging to study: It is confounded by a significant number of patients transitioning from TNF α inhibitors which are known to treat numerous EIMs—in order to initiate the gut-specific agent.²¹ The effectiveness of vedolizumab on the EIMS of IBD is slowly emerging; however, the clinical data have shown inconsistent results. In 2018, a retrospective comparison study reported a lower incidence of EIMs, including EN and aphthous stomatitis, in patients treated with TNF α inhibitors vs vedolizumab.²² A systematic review of the effect of vedolizumab treatment on EIMs concluded that there exists no strong evidence that vedolizumab effectively treats the cutaneous EIMs of IBD, although it may decrease the occurrence of new EIMs.²³ A small prospective study demonstrated the successful resolution of EN and arthritis EIMs in patients with IBD.²⁴ The efficacy of vedolizumab on EIMs may be due to its enhanced control of gut disease as the activity of certain EIMs (including arthritis and EN) parallels gut activity.⁸ In a published case report of vedolizumab-induced psoriasis, the condition was shown to resolve with the cessation of the drug.²⁵ It is hoped that future clinical studies will better clarify the relationship between gut-targeted IBD treatment such as vedolizumab and EIMs.

Conclusion

Mucocutaneous EIMS occur commonly and are important to recognize as they not only cause significant patient morbidity, but may also be the first presentation of IBD, or may indicate ongoing disease activity in the absence of symptoms. A collaborative relationship between dermatologists and gastroenterologists is proving vital in providing comprehensive care to patients with IBD.

Key Clinical Pearls

- ✓ Mucocutaneous EIMs are common
- ✓ Mucocutaneous EIMs may precede the diagnosis of GI disease
- ✓ Not all EIMs parallel underlying GI disease activity
- ✓ A growing number of therapies are available which treat IBD and numerous mucocutaneous EIMs
- ✓ Currently, the impact of vedolizumab on mucocutaneous EIMs is unclear

Correspondence:

Dr. Jennifer Lipson
Email: jen1lipson@gmail.com

Financial Disclosures:

None

References:

1. Elisabetta Antonelli, Gabrio Bassotti, Marta Tramontana, Katharina Hansel, Luca Stingeni, Sandro Ardizzone, Giovanni Genovese, Angelo Valerio Marzano and Giovanni Maconi. Dermatological manifestations in inflammatory bowel disease. *Journal of Clinical Medicine*. 2021 Jan 19;10(2):364.
2. Kurtzman DJ, Jones T, Lian F, Peng LS. Metastatic Crohn's disease: a review and approach to therapy. *J Am Acad Dermatol*. 2014 Oct;71(4): 804-813.
3. Loredana Ungureanu, Rodica Cosgerea, Mihail Alexandru Badea, Alina Florentina Vasilevici, Iona Cosgerea and Simona Corina Senila. Cutaneous manifestation sin inflammatory bowel disease. *Experimental and Therapeutic Medicine*. 2020 20:31-37.
4. Roth N, Biedermann L, Fournier N, Butter M, Vavricka SR, Navarini AA, Rogler G, Scharl M; Swiss IBD Cohort Study Group. *PLoS One*. 2019 Jan 25;14(1):e0210436
5. Barret M, De Parades V, Battistella M, Sokol H, Lemarchand N, Marteau P. Crohn's disease of the vulva. *J Crohns Colitis*. 2014 Jul;8(7):563-570.
6. Muhvic-Urek M, Tomac-Stojmenovic M, Mijandrusic-Sincic B. Oral pathology in inflammatory bowel disease. *World J Gastroenterol*. 2016 Jul 7;22(25):5655-67.
7. Yüksel I, Başar Ö, Ataseven H, Ertuğrul İ, Arhan M, İbiş M, Dağlı Ü, Demirel BT, Ülker A, Seçilmiş S, Şaşmaz N. Mucocutaneous manifestations in inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2009 Apr 1;15(4):546-50.
8. Greuter T, Vavricka SR. Extraintestinal manifestations in inflammatory bowel disease-epidemiology, genetics and pathogenesis. *Expert Rev Gastroenterol Hepatol*. 2019 Apr;13(4):307-317.
9. Joshi TP, Friske SK, Hsiou Da, Duvic M. New Practical aspects of Sweet Syndrome. *Am J Clin Dermatol*. 2022 May ;23(3):301-318,
10. Brown G, Wang E, Leon A, Huynh M, Wehner M, Matro R, Linos E, Liao W, Haemel A. Tumor necrosis factor-α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. *Journal of the American Academy of Dermatology*. 2017 Feb 1;76(2):334-41.
11. Cottone M, Sapienza C, Macaluso FS, Cannizzaro M. Psoriasis and Inflammatory Bowel Disease. *Dig Dis*. 2019;37(6):451-457.
12. Lauritano D, Boccalari E, Stasio D, Della Vella F, Carinci F, Lucchese A, Petrucci M. Prevalence of Oral lesions and correlation with intestinal symptoms of inflammatory bowel disease: A systematic review. *Diagnostics(Basel)*. 2019 Jul 15;9(3):77
13. Moustou AE, Matekovits A, Dessinioti C, Antoniou C, Sfrikakis PP, Stratigos AJ. Cutaneous side effects of anti-tumor necrosis factor biologic therapy: a clinical review. *Journal of the American Academy of Dermatology*. 2009 Sep 1;61(3):486-504.
14. Kohorst J, Kimball A, Davis MDP. Systemic associations of hidradenitis suppurativa. *J Am Acad Dermatol*. 2015 Nov;73 (5 Suppl):S27-35.
15. Egan CA, Meadows KP, Zone J. Ulcerative colitis and immunobullous disease cured by colectomy. *Archives of Dermatology*. 1999;135:214-215.
16. Chen DH, Zhou HR, Zhang YG, Shen GY, Xu C, Guan CL. Drug induced hypersensitivity syndrome induced by sulfasalazine: A case report. *Medicine (Baltimore)*. 2022 Aug 19;101(33):e30060
17. McNally A, Ibbetson J, Sidhu S. Azathioprine-induced Sweet's syndrome: A case series and review of the literature. *Australas J Dermatol*. 2017 Feb;58(1):53-57.
18. Romdhane HB, Mokni S, Fathallah N, Slim R, Gharriani N, Sriha B, Ben Salem, C. Sulfasalazine induced sweet's syndrome. *Therapie*. 2016 Jun;71(3):345-7
19. Azathioprine® Product Monograph, Apotex Inc., Toronto, Ontario. October 28, 2020.
20. Mesalamine® Product Monograph, Aptalis Pharma Inc., Mont-Saint-Hilaire, Quebec. December 30, 2014.
21. Hanzel J, Ma C, Castele NV, Kanna R, Jairath V, Feagan BG. Vedolizumab and Extraintestinal Manifestations in Inflammatory Bowel Disease. *Drugs*. 2021 Feb;81(3):333-347
22. Dubinsky M, Cross R, Sandborn W, Long M, Song X, Shi N, Ding Y, Eichner S, Pappalardo B, Arit Ganguli, Wang A. Extraintestinal manifestations in vedolizumab and anti-TNF-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2018 Aug 16;24(9):1876 - 1882
23. Chateau T, bonovas S, Le Berre C, Mathieu N, Danese S, Peyrin-Biroulet L. Vedolizumab treatment in extra-intestinal manifestations in inflammatory bowel disease: A systematic review. *J Crohns Colitis*. 2019 Dec 10;13(12):1569-1577
24. Fleisher M, Marsal J, Lee S, Frado L, Parian A, Korelitz B , Feagan B. Effects of vedolizumab therapy on extraintestinal manifestations of inflammatory bowel disease. *Dig Dis Sci*. 2018 Apr;63(4):825-833.
25. Guedes T, Pedroto I, Lago P. Vedolizumab-associated psoriasis: until where does gut selectivity go? *Rev Esp Enferm Dig*. 2020 Jul;112(7):580-581.

MAXIME DELISLE

MD, FRCPC



Dr Delisle completed his medical degree and his specialization in gastroenterology at the University of Sherbrooke. He completed his fellowship in advanced inflammatory bowel diseases (IBD) at the University of Calgary. Dr Delisle is currently an assistant professor at the University of Sherbrooke and an attending gastroenterologist at the Centre Hospitalier Universitaire de Sherbrooke. He is certified in intestinal ultrasound by the International Bowel Ultrasound Group.

Affiliations:

Assistant Professor of Medicine
Faculty of Medicine and Health Sciences
University of Sherbrooke, Sherbrooke, Quebec

POST-OPERATIVE CROHN’S DISEASE: CURRENT AND EMERGING MANAGEMENT TECHNIQUES

Introduction

Numerous treatment options for Crohn’s disease (CD) have been developed since infliximab was approved in 1998. Treatment practices for CD have also evolved: therapeutic drug monitoring and a treat-to-target approach have replaced symptom control. Despite a decline in surgery rates in Canada and elsewhere in the world, bowel resection is still required for patients with refractory, fistulizing or fibrostenosing CD. Unfortunately, postoperative recurrence (POR) is common; endoscopic recurrence affected 70%-90% of patients at the five-year point.⁵ However, it is important to note that variations in recurrence were observed between randomized clinical trials (RCTs), referral centre studies and population-based studies. This article will provide an overview of the current monitoring strategies and therapies for CD patients who have undergone a bowel resection.

Post-operative Monitoring Strategies

Endoscopy is currently the cornerstone of post-operative follow-up care. Its usefulness has been demonstrated in the landmark prospective study by Rutgeerts et al.⁶ In their study, the authors monitored the natural clinical and endoscopic course of CD after an ileal resection. The study revealed the now established discordance between symptoms and endoscopic activity, as 20% of patients experienced symptoms and 73% had macroscopic inflammation. In addition, the authors reported the prognostic value of endoscopic activity. Since then, endoscopy and use of the Rutgeerts score (RS) (Table 1) have been recommended 6 to 12 months following bowel

resection to determine optimal management. A modified Rutgeerts score has also been developed to distinguish patients with a score of i2. (Table 2). A score of i2a indicates lesions confined to the anastomosis; i2b indicates more than five aphthous lesions in the neoterminal ileum, or which skip areas of larger lesions with normal mucosa between the lesions.

Determining which patients are high risk and deserve treatment post-surgery and prior to the recommended endoscopy continues to represent a challenge for physicians.

Several clinical studies have evaluated the association between a patient’s pre-operative clinical profile and their post-operative endoscopic findings. In the pivotal prospective REMIND trial, a bivariate analysis reported three predictors of an increased risk of post-operative endoscopic recurrence (RS ≥i2): male gender, active smoking at surgery and previous intestinal resection.⁷ A multivariate analysis was performed after adjustment for gender; age; pre-operative anti-TNF treatment; post-operative immunosuppressants; post-operative anti-TNF treatment; previous intestinal resection; penetrating behaviour; perianal disease; and active smoking at surgery. Male gender (OR = 2.48 [CI 95% 1.40-4.46]) active smoking at surgery (OR = 2.65 [CI 95% 1.44-4.97]) and previous intestinal resection (OR = 3.03 [CI 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence, while post-operative anti-TNF treatment was associated with a lower risk (OR = 0.50 [CI 95% 0.25-0.96]). There were no interactions between the gender and other variables.⁷

Rutgeerts score	
i0	No lesions
i1	Less than 5 aphthous lesions
i2	More than 5 aphthous lesions with normal mucosa between the lesions; skip areas of larger lesions; or lesions confined to the anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse ileitis with large ulcers, nodules and/or narrowing

Table 1. Rutgeerts score⁶

Modified Rutgeerts score	
i0	No lesions
i1	Less than 5 aphthous lesions
i2a	Lesions confined to the anastomosis
i2b	More than 5 aphthous lesions; skip areas of larger lesions with normal mucosa between the lesions
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse ileitis with large ulcers, nodules and/or narrowing

Table 2. Modified Rutgeerts score⁷

The current American Gastroenterological Association (AGA), European Crohn's and Colitis Organisation (ECCO) and British Society of Gastroenterology (BSG) guidelines list comparable but not identical high-risk clinical features, such as active smoking, prior intestinal surgery, and penetrating and perianal disease.⁸⁻¹⁰ The above-mentioned determination is not an ideal solution and the risk of overtreatment or undertreatment remains. This was demonstrated in a recent retrospective study in which high-risk profiles defined by these association did not correlate with increased endoscopic POR (ePOR).¹¹

Non-invasive diagnostic modalities are gaining momentum in POR monitoring. They allow accurate, safe and repeatable assessment of inflammatory activity. They provide critical information since pre-operative factors alone are not always accurate in predicting post-operative recurrence and since clinical symptoms are absent in up to 46%-67% of patients with ePOR.¹²

Fecal calprotectin (FC) is of particular interest. In a meta-analysis, FC showed a sensitivity of 82% and a specificity of 61% for the detection of ePOR, defined as RS ≥ 2 .¹³ FC thresholds used in this study were variable. Although the ideal thresholds are unknown, FC remains a reliable, repeatable and safe indicator. Its suitability for identifying recurrence prior to the 6–12-month colonoscopy has been demonstrated. In a prospective study, FC < 65 $\mu\text{g/g}$ at 3 months was associated with subsequent endoscopic remission at 6-12 months (OR 12.2, 95% CI [1.32–113.2]).¹⁴ In another multicentre study, serial FC were collected and colonoscopy was performed at six months.¹⁵ An increase of $\geq 10\%$ within the first three months predicted an ePOR, with a positive predictive value of 79%. Therefore, although additional studies are needed, the data support the use of FC, which ideally should be performed repeatedly.

In addition, imaging may have a place in monitoring for POR, particularly for 1) Patients who want to avoid invasive procedures, or 2) Patients who have a resection site out of reach of a standard colonoscopy.

Computed tomography (CT) and magnetic resonance (MR) enterography are alternatives to endoscopy. In a meta-analysis, MR enterography demonstrated a pooled sensitivity of 97% and a pooled specificity of 84% to detect RS ≥ 1 recurrences.¹⁶ Only three studies including 76 patients were analyzed. Since then, a prospective study has demonstrated that postoperative inflammatory changes were sometimes subtle, and that the use of single parameters, such as bowel wall thickness, appeared limited.¹⁷ To overcome

this problem, the MaRIA, Clermont and MR scoring systems have been developed for the detection of disease activity. Their clinical use remains limited.

Intestinal ultrasound (IUS) is a potential alternative to endoscopy. Previously limited to teaching centres, the use of IUS is growing steadily in Canada and around the world. Additionally, its potential for assessing Crohn's disease activity is supported by a growing body of literature.¹⁸ Its low cost, accuracy, safety, and repeatability make it an attractive imaging option. In the above-mentioned meta-analysis, IUS demonstrated a pooled sensitivity of 89% and a pooled specificity of 86%.

Video capsule endoscopy also allows the detection of POR, particularly prior to the recommended endoscopic evaluation. In a recent prospective study, 86% of patients showed inflammatory lesions within three months of surgery.¹⁹ Notably, half of the lesions were distant from the anastomosis. Despite its respectable performance, access remains limited. Capsule retention is another obvious limitation. In the above-mentioned study, 6 of the 48 patients were excluded due to patency capsule retention.

Post-operative Therapeutic Strategies

At a time when proactive care is becoming the norm, opting for a more aggressive approach appears to be promising for POR.

In the multicentre POCER study, patients were assigned to a proactive approach, with a six-month post-operative colonoscopy, or a more reactive approach.²⁰ In this study, all patients were administered metronidazole for three months. Then, patients were categorized as high or low risk. High risk features were: active smoking, penetrating disease, or previous bowel resection. Finally, high risk patients received prophylactic azathioprine. Thiopurine intolerant patients received prophylactic adalimumab. Low risk patients were immunosuppression free. Patients were randomly assigned to parallel groups: colonoscopy at six months (active care) or no colonoscopy (standard care). At 18 months, 49% of patients in the proactive group and 67% in the reactive group experienced ePOR, defined as RS ≥ 2 . Also, despite prophylactic medications, high risk patients experienced more POR. In a recent retrospective study, a top-down strategy was compared to the down-top strategy to prevent endoscopic POR. Strategies were selected according to physician judgment. Top-down patients received anti-TNF and anti-IL12/23 therapies within the first month post-surgery; down-top patients received thiopurines, 5-ASA, or no medication.²¹ At six months, 66% of patients in the top-down cohort and 47% in the step-up cohort experienced POR.

In this context, again, questions remain unanswered. Treating an RS i3 or RS i4 recurrence is consensual because of the poor clinical outcome. The practice of following rather than treating an RS i1 recurrence is also common. Opinions differ on the management of lesions confined to the anastomosis and lesions without ileitis (RS i2). In a recent systematic review, similar clinical and surgical outcome were observed in the two cohorts.²² A recent retrospective study reported opposite results, demonstrating that severe endoscopic progression was observed in a greater number of RS i2b patients.²³ The risk of progression was similar in RS i0, RS i1 and RS i2a patients, which suggests that RS i2 patients do not share the same outcome.

To date, only three clinical trials have been dedicated to POR. The first trial, conducted in 2009, compared infliximab and placebo for the prevention of ePOR, defined as RS $\geq$ i2.²⁴ At one year, 9% of patients on infliximab had endoscopic activity vs 85% of those on placebo. In 2016, the landmark PREVENT trial, a large multicentre study using the same medication, reached a similar conclusion regarding ePOR (22% vs 51%).²⁵ It should be noted that clinical recurrence, the primary endpoint, was not statistically different. Recently, the REPREVIO trial compared vedolizumab and placebo. Initiated four weeks post-surgery, vedolizumab 300 mg IV at Weeks 0, 8, 16 and 24 was superior to placebo for the prevention of ePOR at six months. Despite its positive results, the trial has not yet been published. In the absence of RCTs, real-world studies including bio-experienced patients, have confirmed the value of adalimumab and ustekinumab for the same indication.²⁶ Additional advanced therapies may prove effective, as well. Evidence-based data also supports azathioprine use.²⁷

In 1995, Rutgeerts et al demonstrated the potential role of antibiotics for the prevention of POR. Since then, several studies supported the use of low-dose metronidazole for three months. In a recent retrospective study, 20% of the antibiotic-exposed patients had POR at one year, vs 54% of those receiving placebo.²⁸ Of note, 23% of patients experienced adverse event with the antibiotics. Unfortunately, antibiotics are only effective while being taken; it is unclear if their effects continue following cessation of therapy; therefore, it is not known whether or not they will have long-term impact on outcomes. For this reason, the routine use of antibiotics for POR has not been widely adopted in clinical practice.

Despite the availability of effective medications, determining which patients to treat can be challenging, as individual risk is not always

crystal clear. Preventive treatments are therefore administered on a case-by-case basis.²⁹ Without preventive treatments, therapies are administered in the presence of a POR.

Summary

POR in CD is common. Evidence-based management includes endoscopy at 6-12 months to guide therapeutic management. Preventive treatments are available. However, their use must be individualized. The role of non-invasive modalities is likely to increase, particularly for the evaluation of patients with early or late disease recurrence. Additional clinical studies are necessary to determine the optimal management for the greatest number of patients.

Correspondence:

Dr. Maxime Delisle

Email: maxime.delisle@usherbrooke.ca

Financial Disclosures:

Grants : Abbvie, Advanz, Amgen, McKesson, Organon, Pfizer, Sandoz, Takeda

Consulting fees: Abbvie, Bristol Myers Squibb, McKesson, Pendopharm, Takeda

Honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events:

Abbvie, Amgen, Fresenius Kabi, Janssen, Pendopharm, Pfizer, Takeda

References

- Garcia NM, Cohen NA, Rubin DT. Treat-to-target and sequencing therapies in Crohn's disease. *United European Gastroenterology Journal*. 2022 Dec;10(10):1121-8. doi: 10.1002/ueg2.12336.
- Turner D, Ricciuto A, Lewis A, D'amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J. 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. doi: 10.1053/j.gastro.2020.12.031.
- Ma C, Moran GW, Benchimol EI, Targownik LE, Heitman SJ, Hubbard JN, Seow CH, Novak KL, Ghosh S, Panaccione R, Kaplan GG. Surgical rates for Crohn's disease are decreasing: a population-based time trend analysis and validation study. *The American Journal of Gastroenterology*. 2017 Dec;112(12):1840. doi: 10.1038/ajg.2017.394.
- Lowe SC, Sauk JS, Limketkai BN, Kwaan MR. Declining rates of surgery for inflammatory bowel disease in the era of biologic therapy. *Journal of Gastrointestinal Surgery*. 2021 Jan;25:211-9. doi: 10.1007/s11605-020-04832-y.
- Buisson A, Chevaux JB, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. *Aliment Pharmacol Ther*. 2012 Mar;35(6):625-33. doi: 10.1111/j.1365-2036.2012.05002.x. Epub 2012 Feb 7. PMID: 22313322.
- Rutgeerts P, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990 Oct;99(4):956-63. doi: 10.1016/0016-5085(90)90613-6.
- Auzolle C, Nancey S, Tran-Minh ML, Buisson A, Pariente B, Stefanescu C, Fumery M, Marteau P, Treton X, Hammoudi N; REMIND Study Group Investigators; Jouven X, Seksik P, Allez M. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study. *Aliment Pharmacol Ther*. 2018 Nov;48(9):924-932. doi: 10.1111/apt.14944. Epub 2018 Aug 20. PMID: 30126030.
- Nguyen GC, Loftus EV Jr, Hirano I, et al.; AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the management of Crohn's disease after surgical resection. *Gastroenterology*. 2017;152:271-275.
- Gionchetti P, Dignass A, Danese S, et al. ECCO 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: surgical management and special situations. *J Crohns Colitis*. 2017;11:135-149.
- Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68:s1-s106.
- Joustra V, Duijvestein M, Mookhoek A, Bemelman W, Buskens C, Koželj M, Novak G, Hindryckx P, Mostafaei N, D'Haens G. Natural history and risk stratification of recurrent Crohn's disease after ileocolonic resection: a multicenter retrospective cohort study. *Inflammatory Bowel Diseases*. 2022 Jan;28(1):1-8. doi: 10.1093/ibd/izab044.
- Ble A, Renzulli C, Cenci F, Grimaldi M, Barone M, Sedano R, Chang J, Nguyen TM, Hogan M, Zou G, MacDonald JK. The relationship between endoscopic and clinical recurrence in postoperative Crohn's disease: a systematic review and meta-analysis. *Journal of Crohn's and Colitis*. 2022 Mar;16(3):490-9. doi: 10.1093/ecco-jcc/jjab163.
- Yun Qiu, et al. Fecal Calprotectin for Evaluating Postoperative Recurrence of Crohn's Disease: A Meta-analysis of Prospective Studies. *Inflamm Bowel Dis*. 2015 Feb;21(2):315-22. doi: 10.1097/MIB.0000000000000262.
- Florian V, Gilles B, Meunier C, Charlotte C, Gay C, Anne-Laure C, Remi DL, Pauline D, Eddy C, Vahan K, Mialon A. Low Levels of Fecal Calprotectin 3 Months After Surgery Predict Subsequent Endoscopic Postoperative Remission in Crohn's Disease. *Digestive Diseases and Sciences*. 2021 Dec 1;66(12):4429-35.
- Boube M, Laharie D, Nancey S, Hebuterne X, Fumery M, Pariente B, Robin X, Peyrin-Biroulet L, Minet-Quinard R, Pereira B, Bommelaer G. Variation of faecal calprotectin level within the first three months after bowel resection is predictive of endoscopic postoperative recurrence in Crohn's disease. *Digestive and Liver Disease*. 2020 Jul 1;52(7):740-4. doi: 10.1016/j.dld.2020.03.020.
- Yung DE, Har-Noy O, Tham YS, Ben-Horin S, Eliakim R, Koulaouzidis A, Kopylov U. Capsule endoscopy, magnetic resonance enterography, and small bowel ultrasound for evaluation of postoperative recurrence in Crohn's disease: systematic review and meta-analysis. *Inflammatory Bowel Diseases*. 2018 Jan 1;24(1):93-100. doi: 10.1093/ibd/izx027.
- Baillet P, Cadiot G, Goutte M, Goutorbe F, Brixi H, Hoeffel C, Allimant C, Reymond M, Obrin-Guilhen H, Magnin B, Bommelaer G. Faecal calprotectin and magnetic resonance imaging in detecting Crohn's disease endoscopic postoperative recurrence. *World Journal of Gastroenterology*. 2018 Feb 2;24(5):641. doi: 10.3748/wjg.v24.i5.641.
- Fraquelli M, Castiglione F, Calabrese E, Maconi G. Impact of intestinal ultrasound on the management of patients with inflammatory bowel disease: how to apply scientific evidence to clinical practice. *Digestive and Liver Disease*. 2020 Jan 1;52(1):9-18. doi: 10.1016/j.dld.2019.10.004.
- Shiga H, Abe I, Kusaka J, Shimoyama Y, Moroi R, Kuroha M, Kakuta Y, Kinouchi Y, Masamune A. Capsule endoscopy is useful for postoperative tight control management in patients with Crohn's disease. *Digestive Diseases and Sciences*. 2022 Jan 1:1-0. doi: 10.1007/s10620-021-06841-6.
- De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, Liew D, Pridaux L, Lawrence IC, Andrews JM, Bampton PA. Crohn's disease management after intestinal resection: a randomised trial. *The Lancet*. 2015 Apr 11;385(9976):1406-17. doi: 10.1016/S0140-6736(14)61908-5.
- Buisson A, Blanco L, Manlay L, Reymond M, Dapoiny M, Rouquette O, Dubois A, Pereira B. Top-down versus step-up strategies to prevent postoperative recurrence in Crohn's disease. *Inflammatory Bowel Diseases*. 2023 Feb;29(2):185-94. doi: 10.1093/ibd/izac065.
- Rivière P, Pekow J, Hammoudi N, Wils P, De Cruz P, Wang CP, Mañosa M, Ollech J, Allez M, Nachury M, Kamm MA. Comparison of the risk of Crohn's disease postoperative recurrence between modified Rutgeerts score i2a and i2b categories: An individual patient data meta-analysis. *Journal of Crohn's and Colitis*. 2023 Feb;17(2):269-76. doi: 10.1093/ecco-jcc/jjac137.
- Bachour SP, Shah RS, Lyu R, Rieder F, Qazi T, Lashner B, Achkar JP, Philpott J, Barnes EL, Axelrad J, Holubar SD. Mild neoterminal ileal postoperative recurrence of Crohn's disease conveys higher risk for severe endoscopic disease progression than isolated anastomotic lesions. *Alimentary Pharmacology & Therapeutics*. 2022 May;55(9):1139-50. doi: 10.1111/apt.16804.
- Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology*. 2009 Feb 1;136(2):441-50. doi: 10.1053/j.gastro.2008.10.051.
- Regueiro M, Feagan BG, Zou B, Johans J, Blank MA, Chevrier M, Plevy S, Popp J, Cornille FJ, Lukas M, Danese S. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. *Gastroenterology*. 2016 Jun 1;150(7):1568-78. doi: 10.1053/j.gastro.2016.02.072.
- Yanai H, Kagramanova A, Knyazev O, Sabino J, Haenen S, Mantzaris GJ, Mountaki K, Armuzzi A, Pugliese D, Furfaro F, Fiorino G. Endoscopic Postoperative Recurrence in Crohn's Disease After Curative Ileocecal Resection with Early Prophylaxis by Anti-TNF, Vedolizumab or Ustekinumab: A Real-World Multicentre European Study. *Journal of Crohn's and Colitis*. 2022 Dec;16(12):1882-92. doi: 10.1093/ecco-jcc/jjac100.
- Beelen EM, Nieboer D, Arkenbosch JH, Regueiro MD, Satsangi J, Ardizzone S, López-Sanromán A, Savarino E, Armuzzi A, van der Woude CJ, de Vries AC. Risk prediction and comparative efficacy of Anti-TNF vs thiopurines, for preventing postoperative recurrence in Crohn's disease: a pooled analysis of 6 trials. *Clinical Gastroenterology and Hepatology*. 2022 Dec 1;20(12):2741-52. doi: 10.1016/j.cgh.2021.10.021.
- Glick LR, Sossenheimer PH, Ollech JE, Cohen RD, Hyman NH, Hurst RD, Rubin DT. Low-dose metronidazole is associated with a decreased rate of endoscopic recurrence of Crohn's disease after ileal resection: a retrospective cohort study. *Journal of Crohn's and Colitis*. 2019 Sep 19;13(9):1158-62. doi: 10.1093/ecco-jcc/jjz047.
- Dragoni G, Ding N, Gecse KB, Mansfield JC, Kopylov U, Beaugier L, Bossuyt P, Sebastian S, Milla M, Bagnoli S, Yassin NA. The prevention and management of Crohn's disease postoperative recurrence: results from the Y-ECCO/ClinCom 2019 Survey. *European Journal of Gastroenterology & Hepatology*. 2020 Feb 8;32(8):1062-6. doi: 10.1097/MEG.0000000000001729.

FELIX ZHOU

MD



Felix Zhou is a fourth-year gastroenterology resident at Dalhousie University. He obtained his honors degree in biology at the University of New Brunswick in Fredericton, New Brunswick. He completed his medical school training at Memorial University in 2019 and his internal medicine residency at Dalhousie University in 2022. Following his gastroenterology training he hopes to obtain further subspecialty training in inflammatory bowel disease in 2024.

Affiliations:

Division of Gastroenterology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia

KYLE KILBY

MD



Dr. Kyle Kilby is a second-year internal medicine resident at the University of Calgary. He completed a combined honours degree in biology, immunology, and microbiology at Dalhousie University in Halifax, Nova Scotia. He continued his studies at Dalhousie, graduating with his medical degree in 2021. Through medical school and his internal medicine residency, he has partnered with community groups to advocate for equity in healthcare and harm reduction. His research and clinical interests lie in health promotion and prevention of disease, as well as the role of robust social programming in improving the health of our communities.

Affiliations:

Department of Medicine, University of Calgary, Calgary, Alberta

JENNIFER JONES

MD



Dr. Jennifer Jones obtained her MD and completed her internal medicine and gastroenterology fellowship training at Dalhousie University in Halifax, Nova Scotia. She then completed an advanced fellowship in Inflammatory Bowel Diseases at the Mayo Clinic in Rochester, Minnesota, USA. Following this she obtained her MSc in epidemiology while working at the IBD Clinic at the Foothills Medical Center in Calgary, Alberta. After this she worked as an assistant professor of medicine at the University of Saskatchewan in Saskatoon where she established the Multidisciplinary Inflammatory Bowel Diseases Program. Dr. Jones moved back to her home province of Nova Scotia where she serves as the medical lead of the Nova Scotia Collaborative Inflammatory Bowel Diseases program. She is currently as Associate Professor of medicine within the Division of Digestive Care and Endoscopy within the Department of Medicine (DoM) and is Chair of the DoM Clinical Systems and Innovation Committee. She recently completed Implementation Science Certification training through the University of California, San Francisco (UCSF) and her research interests include implementation and evaluation of innovative models of healthcare delivery, patient oriented IBD research, and IBD outcomes research.

Affiliations:

Division of Gastroenterology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia

VACCINE PREVENTABLE DISEASE IN IBD: RELEVANCE, GUIDELINES AND CONSIDERATIONS FOR IMPLEMENTATION

Introduction

The increasing prevalence of vaccine-preventable diseases (VPDs) in patients with inflammatory bowel disease (IBD) has given rise to increased awareness of the need to educate clinicians and patients about the critical role of immunization in this patient population. In 2023, it was estimated that in the Canadian population, 320,000 individuals (0.83%) were affected by IBD.¹ Patients with IBD are at risk of vaccine-preventable diseases as the result of several factors, including potentially reduced efficacy and safety of vaccinations in the context of systemic immunosuppressive therapies administered for the management of IBD² and a state of malnutrition caused by the disease.³

Barriers to the administration of vaccinations include: Clinicians' reluctance to immunize patients with IBD³; patient lack of awareness regarding the critical importance of a structured vaccination protocol²; gastroenterologists' assumption that immunization falls under the auspices of the primary care provider (PCP); and limited time and resources.²

The objective of this paper is to highlight the need for broader implementation of the 2021 Canadian Association of Gastroenterology (CAG) Guidelines concerning both live and inactivated vaccines in patients with IBD. This overview focuses on commonly encountered VPDs for which administration of live and non-live vaccines may be required and for which an IBD-specific deviation from the NACI recommendations have been made. The vaccines selected for this brief overview are also commonly administered in clinical practice. Clinicians may experience uncertainty in relation to management of these vaccinations in practice.

Role of Vaccination

Many pharmacologic therapeutic options for IBD, including corticosteroids, immunomodulators and biologics, leave patients in an immunosuppressed state.⁴ Additionally, patients with IBD have blunted innate immune responses and experience chronic damage to the gastrointestinal (GI) barrier, potentially increasing susceptibility to infection.^{5,6} Additionally, small-scale clinical studies identify hyposplenism as a complication of IBD infection.^{7,8} Hyposplenism in IBD is associated with decreased production of memory B cells and impaired antibody responses

to intravenous antigen.⁹ This theoretical basis for increased risk of infections in patients with IBD has been reflected in clinical studies examining clinical outcomes. The largest cohort trial to date, involving 190,694 IBD patients in France, reported an increased risk of infection vs untreated patients in those receiving thiopurine monotherapy (hazard ratio [HR] 1.32; 1.23-1.42), anti-TNF monotherapy (HR 2.26; 2.08-2.45), and combination therapy (HR 2.79; 2.40-3.25).¹⁰ A prospective, observational study of 6,273 IBD patients in the United States demonstrated an increase in infection risk associated with prednisone therapy vs untreated patients (HR 1.57; 1.17-2.10) and infliximab (HR 1.43; 1.11-1.84).¹¹

Vaccine Implementation in Clinical Practice

These studies highlight the importance of preventing infection in patients with IBD. Vaccines have been developed to reduce the risk of many infections, including hepatitis B and influenza. Unfortunately, vaccination rates in patients with IBD remain low. In one clinical study of 169 patients with IBD, only 45% were current with their tetanus vaccination; 28% regularly received their flu shots; and only 9% received their pneumococcal vaccine.¹² Several potential explanations exist as to why vaccination uptake among patients with IBD remains low. It may be due to lack of patient awareness of either the increased risks of infection associated with immunosuppressive therapies, or the benefits of vaccination.¹³ Similarly, a knowledge barrier exists amongst physicians who find themselves lacking accurate, up-to-date knowledge regarding the safety and schedule of specific vaccines in the context of immunosuppression.^{13,14} Additionally, controversy exists regarding whether or not vaccination management in clinical practice is the responsibility of the gastroenterologist, PCP or other healthcare practitioner.^{15,16}

Vaccine Selection in Pediatric and Adult Patients

In 2021, the Canadian Association of Gastroenterology (CAG) published guidelines to address potential knowledge gaps that may be acting as barriers to vaccine utilization in patients with IBD. The guidelines are divided into two parts, the first addressing live vaccines² and the second addressing inactivated vaccines.¹⁷ **Table 1** summarizes the Guidelines Consensus Recommendations for immunizations in patients with IBD.

Principles of immunization of patients with IBD • Recommendation 1: In all patients with IBD, a complete review of the patient's history of immunization and VPDs should be performed at diagnosis and updated at regular intervals by IBD care providers. Ungraded good practice statement. • Recommendation 2: In patients with IBD, all appropriate vaccinations should be given as soon as possible, and ideally prior to initiation of immunosuppressive therapy. Ungraded good practice statement. • Recommendation 3: In patients with IBD who require urgent immunosuppressive therapy, treatment should not be delayed in order to provide vaccinations. Ungraded good practice statement.
Live vaccines • MMR » Recommendation 4A: In MMR-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend MMR vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 4B: In MMR-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving MMR vaccine. GRADE: Conditional recommendation, very low CoE » Recommendation 5A: In MMR-susceptible adult patients with IBD not on immunosuppressive therapy, we recommend MMR vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 5B: In MMR-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving MMR vaccine. GRADE: Conditional recommendation, very low CoE • Varicella » Recommendation 6A: In varicella-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend varicella vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 6B: In varicella-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving varicella vaccine. GRADE: Conditional recommendation, very low CoE » Recommendation 7A: In varicella-susceptible adult patients with IBD not on immunosuppressive therapy, we suggest varicella vaccine be given. GRADE: Conditional recommendation, very low CoE Recommendation 7B: In varicella-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving varicella vaccine. GRADE: Conditional recommendation, very low CoE
Statements with no recommendations • No Recommendation A: In infants born of mothers using biologic therapies, the consensus group could not make a recommendation for or against giving live vaccines in the first 6 months of life. • CoE, certainty of evidence; MMR, measles-mumps-rubella; VPDs, vaccine preventable diseases.
Inactivated Vaccines • Hib » Recommendation 8A: In pediatric patients with IBD, 5 years of age and younger, we recommend HiB vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 8B: In unimmunized pediatric patients with IBD, older than 5 years of age, we suggest HiB vaccine be given. GRADE: Conditional recommendation, low CoE » Recommendation 9: In unimmunized adult patients with IBD, we suggest HiB vaccine be given. GRADE: Conditional recommendation, very low CoE • HZ » Recommendation 10A: In adult patients with IBD 50 years of age and older, we recommend recombinant zoster vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 10B: In adult patients with IBD younger than 50 years of age, we suggest recombinant zoster vaccine be given. GRADE: Conditional recommendation, low CoE • Hepatitis B » Recommendation 11: In pediatric patients with IBD, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 12A: In unimmunized adult patients with IBD with a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 12B: In unimmunized adult patients with IBD without a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, low CoE • Influenza » Recommendation 13: In pediatric patients with IBD, we recommend influenza vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 14: In adult patients with IBD, we recommend influenza vaccine be given. GRADE: Strong recommendation, moderate CoE • Pneumococcal vaccine » Recommendation 15: In pediatric patients with IBD, we recommend age-appropriate pneumococcal vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 16A: In adult patients with IBD not on immunosuppressive therapy, with a risk factor for pneumococcal disease, we recommend pneumococcal vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 16B: In adult patients with IBD on immunosuppressive therapy, we suggest pneumococcal vaccines be given. GRADE: Strong recommendation, low CoE • Meningococcal vaccine » Recommendation 17: In pediatric patients with IBD, we recommend age-appropriate meningococcal vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 18: In adult patients with IBD with a risk factor for invasive meningococcal disease, we recommend meningococcal vaccines be given. GRADE: Strong recommendation, moderate CoE • Diphtheria, tetanus, and pertussis » Recommendation 19: In pediatric patients with IBD, we recommend age-appropriate tetanus, diphtheria, and pertussis-containing vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 20: In adult patients with IBD, we recommend tetanus, reduced diphtheria, and acellular pertussis/tetanus and diphtheria vaccine be given. GRADE: Strong recommendation, moderate CoE • HPV » Recommendation 21: In female patients with IBD aged 9-26 years we recommend HPV vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 22: In male patients with IBD aged 9-26 years, we suggest HPV vaccine be given. GRADE: Conditional recommendation, very low CoE
Statements with no recommendations • No Recommendation B: In unimmunized adult patients with IBD on immunosuppressive therapy, the consensus group could not make a recommendation for or against giving double-dose hepatitis B vaccine. • No Recommendation C: In patients with IBD on maintenance biologic therapy, the consensus group could not make a recommendation for or against timing seasonal influenza immunization in relation to the biologic dose. • No Recommendation D: In adult patients with IBD not on immunosuppressive therapy and without a risk factor for pneumococcal disease, the consensus group could not make a recommendation for or against giving pneumococcal vaccines. • No Recommendation E: In adult patients with IBD without a risk factor for IMD, the consensus group could not make a recommendation for or against giving meningococcal vaccines. • No Recommendation F: In female and male patients with IBD aged 27-45 years, the consensus group could not make a recommendation for or against giving HPV vaccine.

Table 1. Clinical Practice Guidelines for Immunizations in Patients with IBD; adapted from Benchimol, E. et al, 2021

General population

The CAG guidelines recommend that in all patients with IBD, a complete review of immunizations be performed at diagnosis and at regular intervals. Observational studies have demonstrated significantly lower serological responses to routine vaccinations in IBD patients already being administered immunosuppressive therapies. Therefore, the ideal time to review a patient's immunization status is at diagnosis, prior to the administration of immunosuppressive therapies.¹⁷ The authors acknowledge that it may not be practical to take a detailed vaccination history at every patient visit but do provide important time points that may prompt immunization review, including changes to immunosuppressive regimens and changes in occupation/travel. When a healthcare provider determines that a patient requires certain immunizations, the guidelines recommend that they be administered as soon as possible, ideally prior to the initiation of immunosuppressive therapy. However, in patients who require urgent immunosuppressive therapy, treatment should not be delayed to administer vaccinations.²

Live vaccines

MMR vaccine

The guidelines recommend that patients with IBD not receiving immunosuppressive therapy receive the live measles, mumps and rubella (MMR) vaccine if they are susceptible. However, they recommend against giving live vaccines to those already being administered immunosuppressive therapy, due to efficacy and safety concerns.² In MMR-susceptible pediatric patients with IBD not on immunosuppressive therapy, the guidelines recommend that live vaccines be administered. In MMR-susceptible pediatric patients with IBD on immunosuppressive therapy, they recommend against administering the MMR vaccine.²

Varicella

Similarly, in varicella-susceptible pediatric patients with IBD not on immunosuppressive therapy, the recommendation is that the varicella vaccine be administered. In varicella-susceptible pediatric patients with IBD on immunosuppressive therapy, the guidelines suggest against its use.²

Timing of Live Vaccines

The American College of Gastroenterology (ACG) Guidelines stipulate that if an IBD patient's vaccination history is unknown or in cases where

there is no documentation of immunization in an IBD patient about to initiate immunosuppression, there is a conditional recommendation that the patients receive 2 doses of the MMR vaccine 28 days apart at least 6 weeks prior to the initiation of the immunosuppressive therapy. In the West, where the overall prevalence of measles is low, clinicians are advised to weigh the benefits of measles vaccination against the risks of delaying the initiation of immunosuppressive therapy for 10 weeks.¹⁸

Non-live vaccines

Influenza vaccine

The guidelines recommend that patients with IBD should receive the influenza vaccine yearly.

In clinical practice, clinicians often make recommendations about when to administer the influenza vaccine to patients on biologic therapies. The theory that giving the vaccine at a time during the biologic interval when the drug exposure is likely to be lowest will lead to improved effectiveness underpins this advice. One randomized controlled trial demonstrated no significant difference in immunogenicity when influenza vaccine was administered at the same time as biologic infusion compared to midway between infusions.¹⁹ However, the guidelines concluded there was insufficient data to make a recommendation regarding the timing of influenza vaccination in relation to the biologic. More importantly, risk factors for severe influenza (chronic medical comorbidities, women who are or will be pregnant, children on long term salicylate medications, residents of nursing homes or other facilities, indigenous people, and extreme obesity) should be considered and vaccination not delayed due to concerns about timing throughout biologic interval.

Herpes Zoster vaccine

The guidelines recommend that patients with IBD should receive the 2-dose series recombinant (non-live) zoster vaccine given the observed increased incidence of zoster in adults with IBD on immunosuppressive therapy.²⁰⁻²⁵ This is preferred over the live attenuated zoster vaccine because of superior efficacy and safety. This differs from recommendations for the general (non-IBD) population in which the zoster vaccine is recommended for patients aged 50 years and older.

Pneumococcal and meningococcal vaccine

The pneumococcal vaccine should be administered to patients with IBD on immunosuppressive therapy, as well as to non-immunosuppressed patients with a

risk factor for pneumococcal disease. This includes patients >65 years of age; who suffer from asplenia; are active smokers; have alcohol use disorder; and those with comorbidities such as diabetes, or chronic heart, liver or kidney disease.¹⁷ The meningococcal vaccine should be administered to patients with IBD with a risk factor for meningococcal disease, including asplenia or human immunodeficiency virus (HIV); who have had exposure to a confirmed case; or who engage in certain occupations such as the military. Finally, patients aged 9 to 26 years should receive the HPV vaccine.¹⁷

Hepatitis B vaccination

The Canadian guidelines support vaccinating both pediatric and adult patients with IBD, particularly if there is a risk factor for hepatitis B. In the United States, guidelines recommend the vaccination of patients with IBD against hepatitis B as hepatitis B infection and reactivation are a concern due to these patients' immunocompromised status. This is particularly true if tumour necrosis factor- α (TNF- α) therapy is needed, as fulminant and fatal cases have been reported in the literature. It is important for gastroenterologists and other clinicians to note that IBD patients, particularly those being administered TNF- α agents, do not achieve hepatitis B surface antibody (HBsAb) levels considered adequate for immunity at the same rate achieved in the general population.²⁶

In consideration of this, the guidelines recommend rechecking titers one month following the final dose of a 3-dose regimen (0, 1 and 6 months). If patients do not respond to this initial course of therapy, the recommendation is to revaccinate with the regular vaccine, revaccinate with a double dose vaccine, or revaccinate with a combined HAV/HBV vaccine. Currently, there is no consensus regarding the most appropriate method of revaccinating IBD patients unresponsive to the initial course of vaccination. The key consideration is to assess hepatitis B exposure and vaccination status prior to the initiation of any immunosuppressive agent in patients with IBD.¹⁸

SARS-CoV-2 vaccination

The international response to the COVID-19 pandemic ushered in a series of highly effective vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). However, patients with IBD were excluded from the clinical trials that led to the approval of these vaccines. While regulatory bodies were initially hesitant to endorse the use of COVID-19 vaccines in patients with IBD for this reason, real-world data has demonstrated that these vaccines are effective and safe in patients

with IBD. This has led to multiple expert panels, including the CAG, recommending vaccination against the SARS-CoV-2 virus.²⁷ Given that the SARS-CoV-2 vaccines are not live vaccines, there is no theoretical reason to believe that individuals with IBD on immunosuppressives would be at risk of virus reactivation, and multiple observational studies have not suggested any cause for concern. The rate of adverse events in a clinical study of 246 patients with IBD who received a SARS-CoV-2 vaccine was similar to that of the general population.²⁸

Another theoretical concern is whether or not SARS-CoV-2 vaccines would be effective in patients with IBD on immunosuppressive therapy. Observational studies have demonstrated reduced effectiveness of the SARS-CoV-2 vaccine in patients who receive the complete series. The CLARITY-IBD study reported less robust immune responses to the *first* dose of the Pfizer and AstraZeneca vaccine in patients with IBD on infliximab vs vedolizumab. However, in the same study, seroconversion was robust following the second dose of vaccine and in individuals who received a dose of vaccine following recovery from COVID-19 infection.²⁹ A separate clinical study of approximately 15,000 patients with IBD receiving a number of immunosuppressives reported 80.4% vaccine effectiveness rates for those who received their second dose of mRNA vaccine.³⁰ In fact, Canadian,²⁷ European³¹ and international³² gastroenterology organizations recommend that patients with IBD receive the primary series of the SARS-CoV-2 vaccine at the earliest opportunity. The IBD Task Force of Crohn's and Colitis Canada recommends the primary series of 3 doses of mRNA-based, bivalent or polyvalent COVID-19 vaccinations. After the primary series, they recommend boosters using bivalent or polyvalent vaccines every 4-6 months.

Effectiveness of Vaccinations

Clinical studies on the vaccination regimens in the IBD patient population have reported varied efficacy results. In a systematic review of observational studies, including 2,852 IBD patients receiving immunosuppressive therapies, in a comparison of immunosuppressive-exposed and non-exposed patients, some studies demonstrated a reduced serological response, while other showed no significant differences.²

Although results of observational studies are varied, one study of the serologic antibody status of adults administered the MMR vaccine suggested no difference in antibody concentrations between IBD patients who received MMR vaccines as children prior to their IBD diagnosis vs healthy controls. However,

the relevance of MMR serology is unknown as antibody titers may be low or undetectable despite previous remote vaccination. In this case patients may have an anamnestic response. In a pediatric study, reported serologic protection rates were: 67.6% for measles, 63.3% for mumps, and 81.4% for rubella.²

Vaccination for Infants When the Mother is on Biologic Therapy

The CAG guidelines could not make a recommendation for or against giving live vaccines in the first 6 months of life to infants born of mothers using biologic therapies. There is a theoretical risk of infection after administration of live vaccines in infants who have been exposed to biologic therapies from their mother via the placenta. Studies have demonstrated detectable levels of biologic therapies at birth, with some being detectable up to 12 months of age.³³ This is relevant because the live attenuated rotavirus vaccine is routinely given at 2 months of age. Some small cohort studies and case series have shown no serious adverse events among infants exposed to biologic therapies in utero who then received rotavirus vaccine.³⁴⁻³⁶ However from a health system perspective, routine rotavirus vaccination programs are not cost-effective in high-income settings, thus the guidelines could not recommend for or against their routine use in infants born to mothers on biologic therapies.^{37,38}

Future considerations for implementation of vaccines in patients with IBD

While the CAG guidelines provide clear recommendations on which vaccinations should be administered to patients with IBD, they do not provide guidance on how these recommendations can be implemented effectively in clinical practice. Many potential barriers to implementation of evidence based IBD vaccine preventable disease guidelines in clinical practice exist. These include patient education, knowledge gaps among healthcare providers, and uncertainty regarding whether gastroenterologists or PCPs are responsible for the management of vaccine preventable disease. Unfortunately, vaccination utilization among patients with IBD remains low.³⁹ A limited number of clinical studies have evaluated interventions designed to improve vaccination uptake in gastroenterology practices. One prospective interventional study at two outpatient clinics involving 50 patients with IBD demonstrated that an electronic medical record order set and a patient educational handout led to an increase in influenza and pneumococcal vaccination rates from 19% and 2%, respectively, pre-intervention, to 85% and 38%, respectively, post-intervention.³²

Likewise, few clinical studies have assessed patient, gastroenterologist and other important stakeholder perspectives concerning barriers to, and facilitators of, the implementation of evidence-based guidelines for VPD. A qualitative clinical study by Zhou et al (2022) assessing perceived barriers to implementation of IBD VPI guidelines among community and academic gastroenterologists and IBD nurses is underway.⁴⁰ The study participants agreed that assessment of immunization status and making appropriate recommendations for indicated vaccines is within the scope of practice of the gastroenterologist. However, preliminary themes indicate that additional support is needed to administer vaccines in clinical practice. Reported barriers to implementation of IBD VPI guidelines include incomplete understanding of coverage of, and access to vaccines; limited time in scheduled appointments to provide comprehensive patient care; and lack of access to primary care providers. Interventions that could potentially help overcome these barriers include clinical decision support tools, support from allied healthcare providers, and third-party support.

To date, no clinical studies have used rigorous implementation science approaches to design their intervention or to perform an analysis of the target behaviour or population. Implementation science is a growing field that attempts to close the gap between what healthcare providers know and the actions they take. Implementation frameworks allow for the characterization of behaviours that could facilitate or impede implementation.⁴¹ The application of these frameworks to understand the barriers, facilitators and potential intervention functions for the implementation of evidence-based guidelines is necessary to ensure that the design of the interventions and implementation strategy are appropriate and sensitive to the local context. At the same time, implementation strategies must be adaptable to facilitate their scale and dissemination. The study by Zhou et al seeks to understand the barriers from the academic and community-based gastroenterologist's perspective and is an important first step in developing an effective implementation strategy for the Canadian healthcare system.

Correspondence:

Dr. Jennifer Jones
Email: jljones@dal.ca

Financial Disclosures:

F.Z.: None
K.K.: None
J.J.: None

References:

1. Coward S, Benchimol EI, Bernstein C, Avina-Zubieta JA, Bitton A, Hracs L, Jones J, Kuenzig E, Lu L, Murthy SK, Nugent Z, Otley AR, Panaccione R, Pena-Sanchez JN, Singh H, Targownik LE, Windsor JW, Kaplan G. A35 FORECASTING THE INCIDENCE AND PREVALENCE OF INFLAMMATORY BOWEL DISEASE: A CANADIAN NATION-WIDE ANALYSIS. *J Can Assoc Gastroenterol*. 2023 Mar 7;6(Suppl 1):19–20. doi: 10.1093/cag/gwac036.035. PMID: PMC9991201.
2. Benchimol EI, Tse F, Carroll MW, deBruyn JC, McNeil SA, Pham-Huy A, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 1: Live Vaccines. *Gastroenterol*. 2021 Aug;161(2):669-680.
3. Waszczuk K, Waszczuk E, Szenborn L. Can we better protect patients with inflammatory bowel disease against infections – patient attitude and personal immunization knowledge. *Acta Gastro-Enterologica Belgica*. 2018 April-June;81:257-261.
4. Murdaca, G, Spanò, F, Contatore, M, Guastalla, A, Penza, E, Magnani, et al. Infection risk associated with anti-TNF- α agents: a review. *Expert Opinion on Drug Safety*. 2015;14(4):571-582.
5. Marks DJB, Harbord MW, Macallister R, Rahman FZ, Young J, Al-lazikani B, et al. Defective acute inflammation in Crohn's disease: a clinical investigation. *Lancet*. 2006; 367:668-678.
6. Casanova J-L, Abel L. Revisiting Crohn's disease as a primary immunodeficiency of macrophages: Figure 1. *JEM*. 2009;206(9):1839-1843.
7. Ryan FP, Smart RC, Holdsworth CD, Preston E. Hyposplenism in inflammatory bowel disease. *Gut*. 1978;19:50-55.
8. Rameh BS, Stevens F, McCarthy CF. Hyposplenism in inflammatory bowel disease. *Ir J Med Sci*.1988;157(1):8-9.
9. Ryan F, Jones JV, Wright J K, Holdsworth CD. Impaired immunity in patients with inflammatory bowel disease and hyposplenism: the response to intravenous cpx 1 74. *Gut*. 1981 Oct;22:187-189.
10. Kirchgessner J, Lemaître M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology*. 2018;155(2):337–346.e10.
11. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012 Sep;107(9):1409-1422.
12. Melmed GY, Ippoliti AF, Papadakis KA, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol*. 2006;101(8):1834-1840.
13. Yeung JH, Goodman K J, Fedorak RN. Inadequate knowledge of immunization guidelines: a missed opportunity for preventing infection in immunocompromised IBD patients. *Inflamm Bowel Dis*. 2012;18(1):34-40.
14. Wasan SK, Calderwood AH, Long MD, Kappelman MD, Sandler RS, Farraye FA. Immunization rates and vaccine beliefs among patients with inflammatory bowel disease: an opportunity for improvement. *Inflamm Bowel Dis*.2014;20(2):246-250.
15. Selby L, Hoellein A, Wilson JF. Are primary care providers uncomfortable providing routine preventive care for inflammatory bowel disease patients? *Dig Dis Sci*. 2011;56(3):819-824.
16. Wasan S K, Coukos J A, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists' knowledge. *Inflamm Bowel Dis*. 2011;17(12):2536-2540.
17. Jones JL, Tse F, Carroll MW, deBruyn JC, McNeil SA, Pham-Huy A, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 2: Inactivated Vaccines. *J Can Assoc Gastroenterol*. 2021 Jul 29;4(4):e72-e91.
18. Kochar B, Herfarth HH. Vaccinations in patients with inflammatory bowel disease in the west. *Inflamm Intest Dis* 2018;3:11–15.
19. DeBruyn J, Fonseca K, Ghosh S, et al. Immunogenicity of influenza vaccine for patients with inflammatory bowel disease on maintenance infliximab therapy: A randomized trial. *Inflamm Bowel Dis* 2016;22(3):638-47.
20. Khan N, Patel D, Trivedi C, Shah Y, Lichtenstein G, Lewis J, Yang YX. Overall and comparative risk of herpes zoster with pharmacotherapy for inflammatory bowel diseases: a nationwide cohort study. *Clinical Gastroenterology and Hepatology*. 2018 Dec 1;16(12):1919-27.
21. Chang K, Lee HS, Kim YJ, Kim SO, Kim SH, Lee SH, Song EM, Hwang SW, Park SH, Yang DH, Ye BD. Increased risk of herpes zoster infection in patients with inflammatory bowel diseases in Korea. *Clinical Gastroenterology and Hepatology*. 2018 Dec 1;16(12):1928-36.
22. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Alimentary pharmacology & therapeutics*. 2013 Feb;37(4):420-9.
23. Marebian J, Arrighi MH, Hass S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Official journal of the American College of Gastroenterology ACG*. 2009 Oct 1;104(10):2524-33.
24. Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*. 2006 Dec 1;4(12):1483-90.
25. Marra F, Lo E, Kalashnikov V, et al. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: A systematic review and meta-analysis. *Oct 1 (Vol. 3, No. 4)*. Oxford University Press.
26. Nguyen DL, Nguyen ET, Bechtold ML. Effect of immunosuppressive therapies for the treatment of inflammatory bowel disease on response to routine vaccinations: A meta-analysis. *Dig Dis Sci*. 2015;60(8):2446-2453.
27. Murthy SK, Kuenzig ME, Windsor JW, Ghia JE, Griffiths AM, Panaccione R, et al. Crohn's and Colitis Canada's 2021 Impact of COVID-19 and Inflammatory Bowel Disease in Canada: COVID-19 Vaccines-Biology, Current Evidence and Recommendations. *J Can Assoc Gastroenterol*. 2021 Nov 5;4(Suppl 2):S54-S60.
28. Botwin GJ, Li D, Figueiredo J, Cheng S, Braun J, McGovern DPB, Melmed GY, et al. Adverse events after SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *Am J Gastroenterol* 2021. Online ahead of print doi: 10.14309/ajg.0000000000001342. PMID: 34047304.
29. Kennedy NA, Goodhand JR, Bewshea C, Nice R, Chee D, Lin S, , et al. Contributors to the CLARITY IBD study. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut*. 2021 May;70(5):865-875.
30. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 vaccination in a veterans affairs cohort of patients with inflammatory bowel disease with diverse exposure to immunosuppressive medications. *Gastroenterology*. 2021 Sep 1;161(3):827-36.
31. Alexander JL, Moran GW, Gaya DR, et al. Inflammatory Bowel Disease section of the British Society of Gastroenterology and the Inflammatory Bowel Disease Clinical Research Group. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: A British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. *Lancet Gastroenterol Hepatol* 2021;6(3):218-224.
32. Siegel CA, Melmed GY, McGovern DP, et al. International Organization for the Study of Inflammatory Bowel Disease (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: Recommendations from an international consensus meeting. *Gut* 2021;70(4):635-40.
33. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151(1):110-9.
34. Duricova D, Dvorakova E, Hradsky O, et al. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: A controlled, multicenter observation. *Inflamm Bowel Dis*. 2019;25(4):789-96.
35. Beaulieu DB, Ananthakrishnan AN, Martin C, et al. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol*. 2018;16(1):99-105.
36. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis*. 2014;20(3):495-501.
37. Coyle D, Coyle K, Bettinger JA, et al. Cost effectiveness of infant vaccination for rotavirus in Canada. *Can J Infect Dis Med Microbiol*. 2012;23(2):71-7.
38. Kotirum S, Vutipongsatorn N, Kongpakwattana K, et al. Global economic evaluations of rotavirus vaccines: A systematic review. *Vaccine* 2017;35(26):3364-86.
39. Wasan SK, Calderwood AH, Long MD, Kappelman MD, Sandler RS, Farraye FA. Immunization rates and vaccine beliefs among patients with inflammatory bowel disease: an opportunity for improvement. *Inflamm Bowel Dis*. 2014 Feb;20(2):246-250.
40. Zhou F, Robar J, Stewart M, Jones J. Implementation of national guidelines on the management of vaccine preventable disease in patients with inflammatory bowel disease: barriers and facilitators in clinical practice. Abstract accepted for poster presentation at Canadian Digestive Disease Week 2023.
41. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011 Apr 23;6:42.

CANADIAN IBD TODAY

Clinical Insights, Perspectives
and Disease Management

Share our weblink on your social
media platform:



REGISTER FOR FUTURE DIGITAL AND
PRINT ISSUES BY VISITING US AT
[CANADIANIBDTODAY.COM](https://canadianibdtoday.com)

CALLING ALL AUTHORS!
DO YOU HAVE A TOPIC THAT YOU WOULD
LIKE TO SEE COVERED IN 2023?

DROP US A LINE AND TELL US ABOUT IT
OR SEND US A SHORT ABSTRACT

INTERESTED IN RECORDING A PODCAST?
WE WANT TO EXPLORE TOPICS WITH YOU!

EMAIL US: [INFO@CATALYTICHEALTH.COM](mailto:info@catalytichealth.com)

VOL 1
ISSUE 2
2023