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Deprescribing Advanced Therapies in Inflammatory Bowel Disease

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Key Takeaways

- Deprescribing advanced therapies is a viable option for carefully-selected patients living with IBD.
- We propose a systematic approach for deprescribing advanced therapies in IBD, which comprises strategic patient selection, comprehensive risk assessment, shared decision-making, rigorous monitoring, and a pre-defined rescue strategy.
- Further research is needed to improve patient selection tools, optimize monitoring techniques, and clarify deprescribing strategies for newer agents.

Introduction

Deprescribing refers to the systematic process of discontinuing or reducing the dose of a medication under healthcare provider supervision to improve patient outcomes.[1] This concept is increasingly recognized across medical fields as a strategy to minimize medication burden, reduce long-term adverse effects, and improve health-related quality of life.[2] However, there is minimal guidance on *how* to deprescribe medications, leading to challenges with implementation.[3]

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic, relapsing-remitting inflammation of the gastrointestinal tract.[4] Recently, deprescribing has gained attention in IBD management, particularly given the serious adverse effects and high financial costs associated with prolonged use of advanced therapies.[5,6] In patients with IBD, the decision to deprescribe requires careful consideration of the serious risk of disease recurrence, and the challenge of recapturing response after relapse.[7] This review aims to synthesize existing literature on deprescribing advanced therapies in IBD, and to provide a practical framework for deprescribing in this context.

General Approach to Deprescribing

A methodical, risk-stratified approach is fundamental to identifying appropriate candidates for deprescribing in IBD, as not all patients in remission are suitable for medication withdrawal. The process may begin with clinician concerns regarding long-term medication safety (e.g., thiopurine deprescription in the elderly), or with a patient interest in deprescribing due to concerns around risk, medication burden, cost, or personal preference. Prior to deprescribing, patients must understand and accept the risks, desire medication reduction or cessation, and commit to the necessary rigorous monitoring. A comprehensive assessment of both clinical and medication-related factors can help predict the likelihood of relapse following medication withdrawal and identify high-risk candidates who should continue therapy when possible. For patients that opt to proceed with medication reduction or cessation, deprescribing should be performed with close proactive monitoring and a clear plan for reinitiating treatment in the event of a relapse. An algorithmic approach to identifying candidates for deprescribing is presented in **Figure 1**. Each aspect of this stepwise approach is discussed in detail in the subsequent sections.

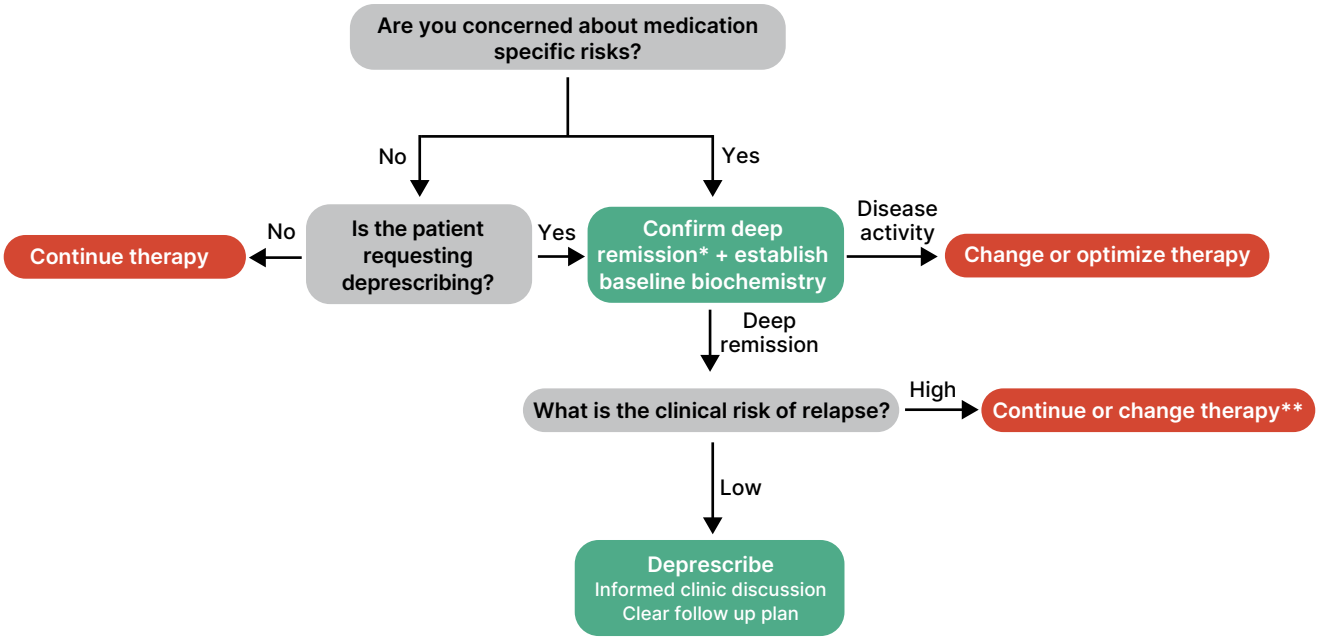

Figure 1. Algorithmic approach to identifying candidates for deprescribing; *courtesy of Elizabeth Squirell, MD, MSc, FRCPC, Jason Hearn, MD, MHSc and Mark McMillan, MD, FRCPC, CAGF.*

*Deep remission is characterized by endoscopic remission in accessible segments of the GI tract and/or radiographic remission in regions not amenable to endoscopic evaluation, such as the mid small bowel.
**If medication risks prompted consideration of deprescribing but there is a high risk of relapse, consideration should be given to a change in therapy (e.g., azathioprine in older adults).

Communication and Shared Decision-Making

Successful deprescribing in IBD hinges on shared decision-making and transparent communication. Clinicians must clearly articulate the potential advantages (e.g., reduced medication burden and drug-related toxicities) alongside the significant risk of relapse. This discussion should include a quantified estimate of relapse risk and address the possibility of severe relapse requiring hospitalization and/or surgery.[8] Exploration of patient values and preferences is critical, as some may accept an elevated relapse risk to avoid prolonged pharmacotherapy, whereas others may prioritize sustained disease control. A detailed monitoring plan, including a "rescue strategy" to be used in the event of disease relapse, should be mutually agreed upon prior to drug cessation.[9] Patients should be reassured that remission can typically be recaptured through prompt initiation of previously-effective therapies.[10]

Clinical Predictors of Relapse

Specific clinical factors have been associated with an increased risk of relapse following deprescribing in IBD.[9] These include younger age (i.e., under 30–40 years),[11] male sex,[12] active smoking,[13] ileocolonic disease location,[14] perianal and/or stricturing phenotypes,[15] and a history of previous IBD surgery.[16] Indicators of active disease at discontinuation are also correlated with an increased risk of relapse, including elevated inflammatory markers (e.g., fecal calprotectin level [FCP], C-reactive protein level [CRP]) and inflammation on endoscopy.[17] A shorter duration of remission prior to deprescribing (i.e., less than 2–4 years) appears to elevate the relapse risk, whereas longer remission is associated with a lower risk.[12,18] Both histologic remission and transmural healing show promise in relapse prediction.[19] However, there is limited prospective data using these stringent targets to guide treatment withdrawal, as most studies have relied on less strict clinical and endoscopic criteria.

	Thiopurines	Methotrexate	Anti-TNF agents	Other biologics	Small molecules
Adverse effects	Infection, hepatotoxicity, myelotoxicity, melanoma, lymphoma[20–23]	Hepatotoxicity, myelosuppression, pneumonitis, gastrointestinal toxicity[25]	Infection, melanoma, lymphoma[29,30]	Minimal risks[33,34]	Malignancy, major adverse cardiovascular events, thrombosis[38]
Risk of relapse with medication withdrawal	37% at 18 months[24] No significant effect when removed from combination regimen[27]	No specific studies for monotherapy withdrawal No significant effect when removed from combination regimen[27]	44% in CD and 38% in UC[32] Similar rates when removed from combination therapy[27]	Similar risk to anti-TNF agents[35–37]	81% in UC[39]
Reasons to consider deprescribing	Serious side effects, older patients, deep remission (i.e., >4 years)[24]	Serious side effects	Serious side effects, deep remission[32]	Serious side effects	Serious side effects

Table 1. Summary of deprescribing considerations by class of advanced therapy; *courtesy of Elizabeth Squirell, MD, MSc, FRCPC, Jason Hearn, MD, MHSc and Mark McMillan, MD, FRCPC, CAGF.*

Abbreviations: CD: Crohn's disease, **UC:** ulcerative colitis, **TNF:** tumour necrosis factor

Outcomes by Medication Class

The decision to deprescribe in IBD requires thoughtful consideration of factors specific to each medication class, including the potential adverse effects of continuing treatment and the risk of relapse with drug cessation. Key considerations for each medication class are summarized in **Table 1**.

Immunomodulators

Thiopurines (Azathioprine, 6-MP): Long-term thiopurine exposure is associated with several dose-dependent risks. Key concerns include serious infections (3–7% annually), a 4-to-6-fold increase in lymphoma risk, and an increased risk of hepatosplenic T-cell lymphoma.[20,21] Additionally, thiopurine treatment is a risk factor for non-melanoma skin cancer, with hazard ratios of 5.9 and 3.9 for ongoing treatment and past exposure, respectively.[22] Other potential adverse effects include hepatotoxicity and myelosuppression.[23] It is important to note that several of these risks—such as lymphoma and non-melanoma skin cancer—are significantly higher in elderly patients.[20,22] Encouragingly, the elevated lymphoma risk appears to return to age-related baseline levels after the medication is discontinued.[20]

Deprescription of thiopurine monotherapy has been associated with a significant relapse risk. A meta-analysis demonstrated a significantly increased risk of relapse in patients discontinuing a thiopurine at both 12 (33% versus 15%) and 18 months (37% versus 21%) compared to continued therapy; however, the difference was non-significant at 5 years (78% versus 67%). Longer remission (>4 years) prior to discontinuation was found to be protective.[24]

Methotrexate: Risks associated with methotrexate include hepatotoxicity with rare fibrosis, myelosuppression, pneumonitis, and gastrointestinal toxicity.[25] Serious infections and malignancies are not commonly associated with methotrexate. Though high rates of discontinuation due to poor tolerance are observed,[26] no formal withdrawal studies relating to methotrexate monotherapy could be identified. In women considering pregnancy, methotrexate should be routinely changed to a non-teratogenic therapy offering comparable effectiveness.

Combination therapy: Both thiopurines and methotrexate are used in combination with anti-TNF agents. The SPARE trial, which assessed medication withdrawal in stable CD patients on combination regimens, showed that

immunomodulator discontinuation (i.e., reduction to anti-TNF monotherapy) yielded statistically equivalent relapse rates at 2 years (10%) compared to continued combination therapy (12%).[27] As such, immunomodulator deprescription should be considered in patients with CD who are in deep remission while on combination therapy.

Biologics

Anti-Tumour Necrosis Factor (TNF): Long-term adverse effects of anti-TNF therapy include serious infections (3–5% annually), a modest 1.5-fold increased risk of melanoma, and rare paradoxical immune-mediated reactions.[28,29] While lymphoma risk is minimal with monotherapy, it increases when combined with an immunomodulator. Combination therapy is associated with a 100-to-1000-fold increase in hepatosplenic T-cell lymphoma, particularly in young males (affecting ~1/7400).[30] Additionally, anti-TNF agents are contraindicated in patients with severe heart failure.[31]

Deprescribing anti-TNF agents is associated with a consistently high risk of relapse following medication withdrawal. A 2015 systematic review including 27 studies of anti-TNF withdrawal identified an overall risk of relapse of 44% in CD and 38% in UC. Notably, remission was successfully reintroduced in 80% of cases using the same anti-TNF agent.[32] Similarly, the SPARE trial, which investigated the withdrawal of anti-TNF agents in stable patients with CD on a combination regimen of anti-TNF and an immunomodulator, found that anti-TNF cessation resulted in a substantially higher relapse rate at 2 years (36%) compared to continued combination therapy (12%).[27] It is important to note that medication withdrawal studies to date have enrolled patients in clinical remission without the requirement for endoscopic healing. Subgroup analyses suggest that mucosal healing before deprescription is associated with a lower relapse rate of 26%.[32] Based on this evidence, cessation of anti-TNF agents should only be considered for patients in deep remission, including endoscopic healing, or in those experiencing severe adverse effects and/or expressing a significant interest in deprescribing.

Other Biologics: Vedolizumab and ustekinumab have favourable safety profiles with no documented increase in serious infections or malignancies, though vedolizumab is linked to a higher rate of nasopharyngitis.[33,34] Although deprescribing data are less extensive for these agents, available evidence suggests a high relapse rate. One multicentre cohort study of vedolizumab withdrawal has shown a relapse rate of 64% within one year, with retreatment success in 63% of relapsed patients.[35] Ustekinumab withdrawal remains insufficiently studied, though recent studies suggest relapse rates are likely similar to those seen with anti-TNF cessation.[36,37] Given the safety profile and high likelihood of relapse with discontinuing vedolizumab or ustekinumab, very few patients stand to benefit from deprescribing these agents. Despite similar safety profiles, the withdrawal of newer biologics, such as IL-23 inhibitors, has not yet been studied.

Small molecules

Janus kinase (JAK) inhibitors have established safety concerns, most notably increased risks of infectious complications, malignancies, major adverse cardiovascular events, and thromboembolism.[38] Despite these potential risks, withdrawal evidence is minimal for these agents. A recent multicentre cohort study investigated outcomes for JAK inhibitor withdrawal amongst patients with stable UC, and found a dramatically increased risk of relapse (81% versus 8%) and shorter duration of mean relapse-free survival (882 days versus 1679 days) for patients who discontinued versus continued the medication. Notably, reinduction using JAK inhibitors was successful in 83% of relapsed patients.[39] Studies on the withdrawal of other small molecules, such as S1P receptor modulators, are currently lacking. Given the limited available evidence, it is difficult to make a recommendation on deprescribing small molecules in the absence of severe adverse effects. If deprescribing is considered, the same general principles described above should be adopted.

Monitoring Strategies After Deprescribing

Intensive proactive monitoring is *essential* for the early detection of relapse to allow prompt initiation of therapies, minimize flare severity and complications, and increase the likelihood of successful reinduction. Structured follow-up assessments should be undertaken quarterly during the first year, and patients should be counselled to seek medical attention if signs of disease relapse develop.[8]

Biomarker surveillance also allows early identification of relapse, even in asymptomatic individuals, as elevated FCP levels have been shown to precede clinically apparent relapse.[40] An optimal monitoring protocol includes measuring FCP and/or CRP at three-month intervals during the first year, with more frequent testing when clinically warranted.[41] FCP levels between 100 and 250 µg/g should prompt closer monitoring or holistic assessment, while levels above 250 µg/g suggest active inflammation warranting endoscopic assessment or consideration of therapy reinitiation.[42]

While mucosal healing should be confirmed prior to deprescription, the value of routine endoscopic surveillance after deprescribing remains debated. Some experts recommend routine colonoscopy within 6–12 months following medication withdrawal, particularly for patients at high risk of relapse.[41] Others prefer a reactive approach with endoscopic evaluation only when symptoms or biomarkers suggest relapse.[7] Given the variance in clinical practice, the approach to endoscopy should be individualized based on risk assessments and patient preferences.

Cross-sectional imaging techniques such as magnetic resonance enterography and intestinal ultrasound are non-invasive options to assess inflammation,[43] and are well suited for monitoring after deprescribing given their minimal risk profile.

Future Directions

Despite the expanding interest in deprescribing strategies, substantial knowledge gaps persist that necessitate dedicated research. Many foundational deprescription studies have primarily included patients in *clinical* remission; thus, the impact of initial endoscopic or histologic remission on relapse rates requires further study. Similarly, no definitive consensus has emerged regarding the requisite duration of remission prior to medication withdrawal. Comprehensive longitudinal data are also required to evaluate the impact of deprescribing on disease trajectory, disease complications, and health-related quality of life. Non-invasive imaging techniques, such as intestinal ultrasound, warrant further consideration as monitoring options of disease activity following drug cessation. Finally, the evidence regarding the deprescribing of newer therapeutic agents remains particularly scarce, underscoring the need for further study.

Conclusion

Deprescribing advanced therapies in IBD remains a complex decision. While not suitable for routine practice due to significant relapse risks, it is a viable option for carefully-selected individuals. We present a stepwise approach to deprescribing in this context.

- First, proactively **identify candidates** for deprescribing by focusing on those with confirmed endoscopic remission for a prolonged period (i.e., greater than 2–4 years), especially if the patient is motivated or facing risks associated with extended drug exposure.
- Second, perform a **systematic risk assessment** based on patient history, recent biomarkers of inflammation, and the depth of remission to inform counselling.
- Third, implement robust **shared decision-making** by quantifying relapse risks, discussing the high rates of successful response recapture in the event of relapse, and confirming the patient's understanding and explicit acceptance of risk.
- Fourth, use **medication-specific strategies**, such as considering thiopurine cessation in patients over 60 years or with prolonged drug exposure.
- Fifth, establish a **concrete monitoring plan** before cessation, including regular reviews and biomarker testing with clear thresholds for action.
- Finally, develop a pre-defined **"rescue plan"** for managing potential relapse, typically involving prompt reinitiation of therapy.

While current evidence provides a framework, further research to refine patient selection tools, optimize monitoring techniques, and clarify strategies for newer agents is crucial for enhancing the safety and success of deprescribing in IBD clinical practice.

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Travelling with Inflammatory Bowel Disease: Clinical Considerations

Catherine Rowan, MB BCh BAO, MD, MRCPI

Key Takeaways:

- Pre-travel consultation is essential for safe and enjoyable travel. IBD patients and physicians should discuss necessary vaccinations and action plans as soon as possible.
- Preparing for travel by packing a medical kit, necessary medications and obtaining adequate travel insurance can reduce stress and mitigate problems.
- Pre-travel vaccination is an important part of the preparations for many IBD patients. Live vaccines are contraindicated in patients taking immunosuppressant medications. Expert advice from a travel medicine specialist can identify individual patient vaccinations needs.
- There are several resources available to physicians and patients alike, to empower our patients and remove many of the barriers they face when travelling.

Introduction

Travel patterns have shown a sustained increase in annual volumes. In 2023, global tourism data show that the number of people travelling has increased to 1.3 billion arrivals, approaching levels seen before the COVID-19 pandemic.[1] A significant proportion of travellers, approximately 18% of those visiting developing countries, have a chronic illness.[2] In a survey by Greveson et al, most individuals with inflammatory bowel disease (IBD) reported that their diagnosis impacted on both their travel behaviour and choice of destination, particularly among those on immunosuppressive therapy. Despite this, only 23% of patients sought medical advice prior to their journey.[3] IBD patients report a number of barriers to travel. Medications, and the implications for infection and vaccination, access to clean toilet facilities, food availability, and appropriate medical services are the most commonly cited concerns.[4,5]

While the majority of patients remain well during their travel, a significant minority report travel-related illnesses. A study by Ben-Horin et al reported that the vast majority of recorded illnesses amongst patients with IBD were enteric in

nature.[6,7] Identified risk factors were elevated fecal calprotectin levels, frequent flares of IBD, and hospitalization due to IBD.[6,7]

Travel is an important and often necessary part of our patients' lives, be it for leisure, visiting friends or relatives, education, or business. The European Crohn's and Colitis Organisation recommends that patients with IBD receive pre-travel counselling and consult national and WHO guidelines.[8] However, a survey revealed that only half of gastroenterologists provided travel-specific advice to IBD patients, with varying levels of accuracy.[9] This article outlines general travel advice and specific points relevant to patients with IBD, aiming to support safe and enjoyable travel.

Preparation for Travel

People with IBD should discuss upcoming travel plans with their IBD care team as early as possible to facilitate safe travel. The specific advice will vary based on the patient's individual needs, duration of travel, destination, and current medical therapy. Conducting preliminary research based on the travel destination and the purpose of their journey can alleviate some of the stress associated with travel and inform decisions around whether a specialist pre-travel health consultation is required.

Important considerations include: **a)** local health services and physicians, **b)** emergency plan and travel kit, **c)** travel insurance, **d)** vaccinations, and **e)** medications.

Local Health Services

Health services can vary widely across the globe. Therefore, it is important for patients to familiarize themselves with the medical system infrastructure at their destination. It is also advisable to research local hospitals and gastroenterologists/IBD physicians in advance of their departure. As the patient's primary gastroenterologist, you may be able to recommend colleagues who work in that area. Otherwise, several resources are available to help patients identify local expertise such as the International Association for Medical Assistance for Travelers (**https://www.iamat.org**) or IBD Passport (**https://www.ibdpassport.com**). IBD Passport is a UK-based non-profit organization that provides evidence-based travel advice for patients with IBD, including country specific advice and a directory of IBD centres worldwide.[10]

Emergency Plan

Planning for an emergency can reduce stress and uncertainty associated with unexpected IBD flares while travelling. In addition to identifying local health resources and gastroenterologists, it is helpful to have contact details for local emergency medical services and the name and address of an adequately resourced local hospital. Patients should also have the name and contact details of their primary gastroenterologist/IBD physician to facilitate communication between healthcare professionals. A summary of their medical condition and a list of their current prescriptions can also be helpful.

Patients can prepare a travel medical kit as part of their carry-on luggage, containing loperamide, oral steroids (prescribed by a physician where appropriate), oral rehydration solution (ORS), oral antibiotics (for traveller's diarrhea), "Can't Wait" card, among others.[10] A "Can't Wait" card explains that the holder has a medical condition requiring urgent access to toilet facilities. It can be presented in stores and public places and is available in several languages.[10]

As part of travel preparations, it is worthwhile to develop a written action plan in collaboration with your patient (**Table 1**). This document should provide guidance for patients on how to identify and manage symptoms and it should be easily accessible to them, ideally as an electronic copy. The action plan can include a triage system that triggers appropriate responses, such as immediate medical assessment in the event of severe abdominal pain and fevers.

Travel Insurance

Adequate travel insurance is critical, even for short journeys. Travel insurance should cover medical evacuation and repatriation in the event of death. However, previous UK-based surveys found low uptake of travel insurance amongst people with IBD,[3] with nearly half of patients travelling without coverage and 7% being denied insurance altogether.[4] Pre-existing medical conditions such as IBD may affect health insurance, affecting both premiums and coverage.[11] An international survey of IBD patients reported that >70% of patients paid insurance premiums.[5] Patients should carefully review their policy and contact their insurance

Symptoms	I feel well, and my symptoms are stable	• Diarrhea • Abdominal cramps • Nausea, vomiting	• Bloody diarrhea • Fevers/chills • Severe abdominal pain/tenderness • Unable to keep fluids down
Actions	Continue my regular medication	Continue my regular medication	Seek medical attention immediately
		Stay hydrated by drinking bottled water and electrolyte solutions	Continue my regular medications
		Add extra salt to my diet	Contact IBD team
		If symptoms persist for >2 days speak with a local doctor	
		Contact IBD team	

Table 1: example of travel action plan; *courtesy of Catherine Rowan, MB BCh BAO, MD, MRCPI.*

agency to clarify how their IBD affects their coverage before travelling, preferably obtaining a written agreement or explanation to avoid subsequent issues with claims. Patients should always have the contact information of their insurance company readily available.

Travel Vaccinations

Pre-travel vaccination discussions should include those that are part of the routine vaccine schedule for healthy adults (not planning to travel) and those specific to the patient's travel plans and destination. An additional consideration for IBD patients is the use of immunosuppressant therapy, which precludes the administration of live vaccines.

Routine Scheduled Vaccines

Influenza is commonly acquired during travel. In temperate climates the peak influenza season is typically autumn and winter. Travellers should bear in mind that these seasons occur at different times in the northern and southern hemispheres. In contrast, tropical climates can experience year-round influenza circulation.[12] Influenza vaccination programs are effective and annual influenza vaccination is encouraged for patients. In addition, practicing good hand hygiene and respiratory etiquette can help to reduce the risk of influenza infection.

Travellers who are due for COVID-19 vaccination should aim to complete the vaccination at least 2 weeks prior to travelling.[13] Pneumococcal vaccination (pneumococcal conjugate 20-valent vaccine) is recommended for those >65 years, as well as for patients of all ages who are receiving immunosuppressive therapy.

The Hepatitis B vaccine should be offered to those who are not already vaccinated, particularly when travelling to an endemic area. If needed, it can be administered in combination with the Hepatitis A vaccine.[13]

Measles mumps and rubella present an ongoing risk in many countries. Travellers who have not had two doses of the measles, mumps, rubella (MMR) vaccine, or who lack laboratory-confirmed measles infection or laboratory-confirmed immunity, should receive the MMR vaccine, unless contraindicated. Vaccine requirements will depend on the travellers date of birth (full details are available in the Immunization of travellers: Canadian Immunization Guide website).[13] Similarly, varicella vaccination is recommended for susceptible travellers. However, both the MMR and varicella vaccines are **live attenuated** and are therefore **contraindicated** in patients receiving immunosuppressant therapy, making careful assessment essential for the IBD population.

A booster dose of the tetanus, reduced diphtheria, reduced acellular pertussis (Tdap) vaccine is recommended for those who have not received it in adulthood to prevent pertussis. Depending on their prior immunization status, travellers should also receive primary immunization or a booster dose of tetanus and diphtheria vaccines.

For poliomyelitis, the inactivated polio vaccine is recommended for incompletely or non-immunized adults, particularly if they are travelling to an area where poliovirus is circulating or if they are at higher risk, such as military personnel.[13]

Travel-specific Vaccines

These vaccines are indicated based on the traveller's destination, itinerary, and the legal or visa requirements of the destination country. They may include booster doses of routine childhood vaccines, such as meningococcal and poliomyelitis vaccines. For travellers who have previously been immunized against polio and are travelling to an area where polio is circulating or are at higher risk, such as military personnel, a single booster dose of the inactivated poliomyelitis vaccine is recommended.

Meningococcal vaccination is important for travel to regions with increased risk. This includes: Sub-Saharan Africa, where outbreaks are common, and Saudi Arabia, where proof of immunization is an entry requirement for those travelling for pilgrimage and for seasonal workers, among others. Entry into Saudi Arabia requires one dose of the quadrivalent meningococcal quadrivalent conjugate (Men-C- ACYW) vaccine, along with valid proof of vaccination.14 Otherwise, the decision to administer the Men-C-ACYW or a multicomponent meningococcal vaccine will depend on the risk of meningococcal disease in the destination area.

The yellow fever vaccine is a **live** vaccine. It is recommended for personal protection against infection when travelling to endemic areas, based on individual risk assessment. Moreover, under the International Health Regulations, proof of yellow fever immunization is required for entry into several countries. The list of these countries is updated annually and is available on the WHO International Travel and Health website. Proof of yellow fever vaccination must be documented using the International Certificate of Vaccination or Prophylaxis. For individuals with a medical contraindication to yellow fever vaccination, such as IBD patients receiving immunosuppressive therapy, an International Certificate of Medical Contraindication to Vaccination can be issued by designated Yellow Fever Vaccination Centres.[13] Travellers should discuss the need for the vaccine with a travel medicine specialist and obtain a valid certificate of immunization or exemption prior to travelling. Without valid documentation, travellers may be refused entry to a country, quarantined, or face other restrictions.[13] Travel medicine specialists should be fully informed of the patient's history and relevant medications, as inappropriate administration of the yellow fever vaccine has been reported in up to 27% of cases.[15]

Additional vaccines may be recommended, depending on the traveller's itinerary, such as the Japanese encephalitis vaccine. As with yellow fever vaccination, consultation with a travel medicine specialist is essential to determine which vaccines are recommended and to assess any contraindications based on the individual's health status.

Medications and Stoma Supplies

Travellers with IBD are advised to discuss their travel plans with their IBD physician to ensure uninterrupted care during travel. They should carry a sufficient supply of their medications for the entire duration of travel, packed in their carry-on luggage to ensure it is available at all times and to prevent loss/damage. A typed and signed letter from an IBD physician is helpful in explaining the necessity and type of their medications to customs or security personnel.

Medication storage requirements vary depending on the specific treatments a traveller is using. Some medications require strict temperature control, and the use of cooler bags may be necessary to maintain a stable temperature during travel (**Table 2**). Discussion with the IBD pharmacist, physician, or patient support program is essential in this regard.

For travellers receiving intravenous infusions, adjusting the infusion schedule in advance can help avoid missed or delayed treatments during the travel period.

Similar preparations are advised for patients with stomas. Patients should carry an ample amount of stoma supplies, preferably in their carry-on luggage. Since items such as scissors are restricted in hand luggage, patients are advised to pre-cut stoma bags and flanges in advance of travel. Healthcare physicians can provide a written letter to explain the presence of a stoma and the need for additional supplies, which can be helpful when navigating security protocols.

Medication	Temperature	Stability	Precautions
Adalimumab (Humira®, Hyrimoz®, Abrilada®, Amgevita®, Hulio®, Idacio®, Hadlima®, Simlandi®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (25 °C) for up to: • **14 days:** Humira®, Amgevita®, Hadlima®, Hyrimoz®, Hulio®, Simlandi® • **28 days:** Idacio® • **30 days:** Abrilada®, Yuflyma®	DO NOT FREEZE
Golimumab (Simponi®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (25 °C) for up to 30 days	DO NOT FREEZE
Ustekinumab (Stelara®, Steqeyma®, Wezlana®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (30 °C) for up to 30 days	DO NOT FREEZE
Vedolizumab (Entvyio®, subcutaneous injection only)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (25 °C) for up to 7 days	DO NOT FREEZE
Infliximab (Remsima®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (25 °C) for up to 28 days	DO NOT FREEZE
Risankizumab (Skyrizi®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (25 °C) for up to 24 hours	DO NOT FREEZE
Mirikizumab (Omvoh®)	Keep refrigerated at 2–8 °C, protected from light	Can be stored at room temperature (30 °C) for up to 14 days	DO NOT FREEZE

Table 2. Storage requirements for commonly used saubcutaneous medications; *courtesy of Catherine Rowan, MB BCh BAO, MD, MRCPI.*

Precautions During and After Travel

Traveller's Diarrhea

Traveller's diarrhea (TD) is one of the most common travel-associated illnesses, affecting approximately 30–70% of travellers depending on factors such as destination and season, among others.[16] The majority of TD cases (75–90%) are caused by bacterial pathogens, while viral pathogens account for 10–25% of infections. The most common causative bacteria are *Escherichia coli*, *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species. TD is typically associated with the ingestion of contaminated food or water.[17] Risk factors for TD include:

a. Poor hygiene practices in restaurants
b. Lack of sanitation infrastructure
c. Lack of handwashing/facilities
d. Lack of safe, potable water
e. Unreliable/unsafe food storage facilities

To reduce the risk of TD, Traveller's should take the following precautions:

a. Eat food that is well cooked and served hot
b. Practice rigorous hand hygiene
c. Drink only safe water (boiled, disinfected, or from a commercially sealed container), including for brushing teeth
d. Avoid tap water, as well as ice, or beverages made with tap water
e. Avoid high-risk foods, such as raw/unpasteurized food, mayonnaise, salads, food that has been left out for extended periods

TD usually resolves within a few days, and mild cases can often be managed with standard self-treatment.

Recommended self-treatment includes:

a. **Oral rehydration solutions (ORS):** These should only be prepared using safe water (boiled, disinfected, or from commercially sealed containers) and pre-packaged oral rehydration salts. While ORS is typically available from pharmacies in most low-middle income countries, it is advisable to purchase them prior to travelling.
b. **Anti-motility agents:** Loperamide can be used for symptomatic control but should be avoided if there is bloody diarrhea or fever.

Short courses of antibiotics can be used judiciously to treat moderate to severe TD, and self-medication with antibiotics should be offered to IBD patients.[8] Commonly used antibiotics include azithromycin, fluoroquinolones, and metronidazole. However, travellers with IBD who have bloody diarrhea, fever, or severe abdominal pain should seek immediate medical attention.

Thrombosis

There is a modest but dose-dependent link between travel and venous thrombus embolism (VTE),[18] with the risk of VTE increasing by approximately 18% for each 2 hour increase in travel duration.[19] The risk of travel-related thrombosis is higher in travellers with pre-existing risk factors. Currently, there are no specific guidelines governing VTE prophylaxis in IBD patients who are travelling. However, existing guidelines suggest that maintaining mobility during travel is an effective prophylaxis for VTE. The use of graded compression stockings is recommended for those at higher risk of VTE. Pharmacological prophylaxis is not universally recommended and should be considered based on an individual's risk profile. The use of anticoagulation is favoured over anti-platelet agents in these circumstances.[20]

Tuberculosis

Tuberculosis (TB) is endemic in much of the world and remains a major global health issue.[21] It is routine practice to screen for and treat latent tuberculosis infection (LTBI) prior to initiating biologic therapy.[8] TB risk assessment should begin prior to travel, taking into account the destination and proposed activities. Individuals at high risk of exposure/infection should undergo LTBI, if it has not already been performed. When prolonged exposure to persons with TB is anticipated during travel, risk reduction strategies, such as the use of personal protective equipment, should be implemented.[22]

Unfortunately, cases of presumed primary TB have been reported in patients with IBD following travel to a TB endemic area.[23] Similar concerns have been observed in other patient cohorts treated with anti-tumour necrosis factor agents.[24] The returning traveller should be assessed for evidence of active TB, and referred for a specialist opinion if there is concern for active infection. In asymptomatic patients with potential TB exposure, testing for LTBI using an interferon-gamma release assay or tuberculin skin test should be performed 8–10 weeks post-exposure.[22] It is reasonable to consider annual TB testing in those patients treated with immunosuppressants who travel or work in TB endemic areas.[8]

Discussion

Travel is a necessary part of life for many patients with IBD. Pre-travel counselling has been shown to improve outcomes for patients with chronic illnesses. Unfortunately, many gaps remain in pre-travel guidance for IBD patients. This is evidenced by surveys revealing that 63% of patients were unaware that live vaccines are contraindicated while taking immunosuppressive therapies.[4] Indeed, most gastroenterologists are uncertain about which vaccines are appropriate in a given situation. For example, 50–70% of gastroenterologists were unaware that oral typhoid, yellow fever, and Bacillus Calmette-Guérin (BCG) vaccines were contraindicated in patients taking immunosuppressive therapies.[9] IBD nurses and physicians remain the primary source of travel advice for patients, followed by general practitioners.[5] These findings highlight that education for both physicians and patients is imperative to ensure safe and enjoyable travel for IBD patients.

IBD teams should encourage patients to discuss travel plans well in advance to allow ample time for appropriate preparation and administration of vaccinations. Several resources are available to support both patients and healthcare providers, including patient foundations and government

Travel Guidance Resource
International Association for Medical Assistance for Travelers (**https://www.iamat.org**)
Canadian Embassy/Consulate (**https://travel.gc.ca/assistance/embassies-consulates**)
Government of Canada Travel & Tourism (**https://travel.gc.ca/**)
IBD Passport (**https://www.ibdpassport.com**)
Crohn's and Colitis Canada (**https://crohnsandcolitis.ca/About-Crohn-s-Colitis/IBD-Journey/Travel-and-Lifestyle/What-to-Bring**)
Crohn's and Colitis Foundation (**https://www.crohnscolitisfoundation.org/what-is-ibd/traveling-with-ibd**)
WHO International Travel and Health (**https://www.who.int/health-topics/travel-and-health**)
Travel Health Pro (**https://travelhealthpro.org.uk/countries**)
Ileostomy & Internal Pouch Association (**https://iasupport.org/wp-content/uploads/2020/11/TravelTips.pdf**)

Box 1. Travel guidance resource; *courtesy of Catherine Rowan, MB BCh BAO, MD, MRCPI.*

travel advisories. However, many patients remain unaware of travel services such as the "Can't Wait" card or the IBD Passport, which can be easily provided during a pre-travel consultation.[4] **Box 1** includes helpful travel resources covering topics such as local healthcare services, vaccinations, and basic travel precautions.

Routine vaccinations are part of a patient's pre-travel consultation. However, vaccine uptake can be affected when responsibility for the vaccine is unclear or divided between general practitioners and gastroenterology teams, making clear delineation of roles paramount. Furthermore, effective communication between IBD teams and travel clinics is crucial to ensure that patients, particularly those taking immunosuppressive therapy, receive safe and complete travel vaccinations and advice.

Many travel-related barriers can be addressed with basic pre-travel counselling and preparation. IBD physicians and nurses can empower patients with information and an action plan to navigate common situations such as travelling with medications, accessing health care, and self-treating TD. A structured, collaborative approach to travel guidance can facilitate safe, enjoyable travel for our patients with IBD.

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Cytomegalovirus Colitis in Inflammatory Bowel Disease The Eternal Debate: Foe or Innocent Bystander?

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Key Takeaways:

- The prevalence of CMV infection among patients with IBD ranges from 2 to 29%, with a higher prevalence in those with UC compared to CD.
- Immunohistochemistry and tissue PCR, or both, are the recommended tests for diagnosing active CMV colitis.
- CMV may be an active pathogenic participant in cases with a high density of CMV and severe disease activity. Thus, we recommend testing for CMV colitis in patients with a severe inflammatory burden who are not responding to conventional IBD therapy.
- Patients with low CMV viral burden can likely be treated with immunosuppression alone, while patients with high viral density or medically refractory disease should be treated with antiviral therapy.

Cytomegalovirus : Overview

Cytomegalovirus (CMV), also known as *Herpesvirus*-5, is a double-stranded deoxyribonucleic acid (DNA) virus and a member of the *Herpesviridae* family. Its global seroprevalence is approximately 83%, while in the Canadian population it is approximately 46%.[1] CMV may be transmitted horizontally through close contact with biological fluids,[2] vertically from mother to fetus, leading to viral congenital infections, or via solid organ or hematopoietic stem cell transplantation.[3,4]

CMV enters and replicates within numerous cell types, including fibroblasts, endothelial cells, epithelial cells, and monocytes. Entry into host cells is mediated by CMV glycoproteins on the surface of the virion, which interact with receptors on cell surfaces, leading to entry by various mechanisms depending on the cell type.[5] Once acquired, the virus persists in cells, resulting in lifelong viral latency. In healthy individuals, a combination of innate and adaptive immune responses work to prevent CMV reactivation and replication.[5] Therefore, CMV infection in healthy individuals is usually asymptomatic or results only in mild, self-limiting symptoms. However, factors leading to a compromised immune system, such as use of immunosuppressive medications, pregnancy, organ or hematopoietic stem cell transplantation, acquired immunodeficiency syndrome, chemotherapy, or severe sepsis can induce CMV reactivation. In these immunocompromised states, CMV infection can lead to end-organ disease including colitis, esophagitis, hepatitis, retinitis, pneumonia, encephalopathy, and disseminated CMV infection.[6]

The pathogenesis of CMV in the gastrointestinal tract is not entirely understood. It is possible that CMV infection in the colon leads to vascular endothelial changes, resulting in ischemic damage to the colonic mucosa and localized ulceration.[7] Additionally, CMV replication may cause disruption of epithelial tight junctions, leading to translocation of gut bacteria and ultimately intestinal inflammation.[8]

CMV in Inflammatory Bowel Disease

The prevalence of CMV infection among patients with inflammatory bowel disease (IBD) ranges from 2 to 29%, with a higher prevalence observed in those with ulcerative colitis (UC) compared to Crohn's Disease (CD).[9] In these

individuals, CMV disease may result from reactivation of a latent virus, primary infection with a new virus, or reinfection with a different viral strain.

The involvement of CMV in IBD has been widely debated, with two competing hypotheses: **1)** CMV is an innocent bystander, reactivating in response to intestinal inflammation or **2)** CMV plays an active pathogenic role, where viral reactivation leads to disease exacerbation and worse clinical outcomes.

Data supporting the innocent bystander hypothesis predominantly stems from retrospective studies. Prior studies assessing colonic biopsies from patients experiencing IBD flares have reported that CMV DNA was detected in only 10% of all biopsies.[10] Furthermore, no correlation was found between the severity of IBD and the CMV viral load levels in the colonic mucosa.[10] In most CMV-positive patients, CMV cleared spontaneously upon IBD remission without the need for antiviral therapy.[10] Finally, CMV reactivation has been observed in steroid-naïve patients with UC, suggesting that severe inflammation of the colonic mucosa itself could act as a trigger for CMV reactivation.[11]

In contrast, other studies have associated CMV infection in IBD with worse clinical outcomes, such as increased hospitalizations, longer hospital stays, increased risk of surgical intervention, higher rates of rescue therapy, and increased mortality.[12,13] In a recent meta-analysis of over 2000 patients with UC, risk factors for CMV reactivation included severe phenotypes, pancolitis, older age, and prior exposure to corticosteroids or azathioprine.[14] Use of 5-aminosalicylic acid was the only protective factor against CMV reactivation.[14] Interestingly, infliximab therapy was not found to increase the occurrence of CMV reactivation in patients with UC.[14] A subsequent meta-analysis demonstrated that IBD patients with concurrent CMV infection had an overall poorer prognosis than patients without CMV.[13]

The true impact between CMV reactivation in IBD likely depends not only on its presence in colonic tissue, but on the viral density.[15] In a case-control study, among patients with CMV who were treated with antivirals, those with high density of CMV inclusions (defined as ≥5 inclusions per biopsy fragment) had lower colectomy rates compared to those with lower density of CMV.[15] Another study demonstrated that a dense CMV burden, specifically >10 inclusions per histologic section, was predictive of increased steroid resistance, higher rates of emergency surgery, and longer postoperative hospital stays.[16] Additionally, a retrospective multicentre analysis of patients with acute severe UC (ASUC) revealed that patients with elevated levels of mucosal CMV DNA (>2,000 copies/mg) faced a significantly higher risk of steroid failure and colectomy, independent of other prognostic indicators.[17] These results suggest that CMV may be an active pathogenic participant in cases with a high density of CMV and severe disease activity. Therefore, it is reasonable to consider and test for CMV colitis in patients with a severe inflammatory burden who are not responding to conventional IBD therapy.

CMV in IBD: Diagnosis

The most recent guidelines from both the European Crohn's and Colitis Organisation (ECCO) and the American College of Gastroenterology (ACG) recommend testing for CMV in IBD patients who present with steroid-refractory or severe colitis.[18,19]

Typical endoscopic features of CMV infection may include well-defined and longitudinal ulcers and a cobblestone-like mucosal appearance.[20] However, endoscopic examination alone is not sufficient to confirm CMV colitis, necessitating tissue sampling for a definitive diagnosis. The location and number of colonic biopsies during endoscopic assessment are important, with preference for tissue samples from the ulcer base and margins when present.[18] To avoid false negatives and achieve an 80% probability of CMV detection in appropriate clinical settings, it is recommended to obtain a minimum of 11 biopsies for UC and 16 biopsies for CD.[18]

Commercially available tests for detecting CMV include blood-based tests such as the pp65 antigenaemia assay and blood polymerase chain reaction (PCR), as well as colonic tissue-based tests such as haematoxylin and eosin staining (H&E), immunohistochemistry (IHC) and tissue PCR (tPCR). Blood-based PCR tests offer excellent specificity of approximately 99.9% but poor sensitivity at 50.8%, limiting their use in diagnosing CMV colitis in IBD.[21] Blood-based PCR testing is also not reliable for distinguishing latent versus pathologic reactivation states. Given that CMV reactivation initially occurs locally within the colonic mucosa of patients with IBD, current clinical guidelines recommend tissue-based CMV

diagnostic techniques for accurate detection.[18,19] In a study of patients with active UC, tissue CMV PCR was positive in 63% of these patients, while plasma PCR was positive in 59%. However, histologic confirmation using IHC was rare, with only 10% showing positive staining.[22] Thus, while high rates of CMV DNA are frequently detected in the active colonic mucosa of IBD patients, this does not always indicate true tissue-invasive infection. On H&E staining of the colonic mucosa, the presence of "owl-eye" inclusion bodies is considered pathognomonic for CMV infection. However, given the low sensitivity of H&E staining, IHC (which allows semi-quantification of viral infection), tPCR, or both are the recommended tests for diagnosing active CMV colitis.[18]

No specific viral cut off for CMV PCR in colonic tissue has been established. Currently, the assays used for PCR-based CMV testing have not been standardized, and as a result, cut-off values may not be directly comparable or generalizable across different institutions and testing platforms. A case-control study of steroid-refractory UC patients found that CMV positivity, defined as a tissue PCR viral load of >250 copies/mg of tissue, was associated with resistance to steroids and also to three additional lines of treatment. These findings suggest that initiating antiviral therapy early in the disease course in these patients may delay treatment resistance and thus improve the overall prognosis.[23]

Treatment of CMV Infection in IBD

Treatment of CMV infection with antiviral therapy may not be required for all IBD patients. A prospective study of 31 patients with UC and CMV infection found that those with symptom improvement while on steroids did not require antiviral therapy.[24] However, the remaining patients who did not respond to steroid therapy required ganciclovir treatment.[24] Another prospective series of IBD patients found positive CMV-DNA via colonic biopsy in 3 patients before receiving Infliximab; however after Infliximab, conventional histology and immunohistochemistry for CMV was negative in all.[25] Thus, patients with low viral burden demonstrated by only a few inclusions who are responsive to medical therapy can likely be treated with immunosuppression alone. In contrast, patients with high viral density or those with medically refractory disease should be treated with anti-viral therapy. For tissue-invasive CMV colitis, the recommended treatment includes induction therapy with intravenous ganciclovir at 5 mg/kg twice daily for 5–10 days, followed by oral valganciclovir at 900 mg daily to complete a 2–3 week course.[18] Protocols to determine CMV clearance and thus cessation of therapy are not well-defined and may require input from infectious disease colleagues. For patients who are intolerant to ganciclovir, or in rare cases of ganciclovir-resistant CMV, foscarnet may be used as an alternative treatment. Throughout antiviral treatment, patients should be carefully monitored for side effects, notably neutropenia, anemia, thrombocytopenia, renal injury, and electrolyte imbalances.[18]

The ECCO guidelines recommend that immunosuppressive therapy should generally be continued in IBD patients experiencing intestinal CMV reactivation, given its crucial role in controlling disease activity.[18] However, in cases of symptomatic, severe disseminated CMV infection, all immunosuppressive agents should be discontinued.[18] Given the substantial increased risk of CMV reactivation associated with glucocorticoid use, a steroid taper is recommended.[18]

Conclusion

CMV colitis remains a significant challenge in IBD given its overlapping features with severe disease, often leading to delays in both diagnosis and initiation of appropriate antiviral therapy. The longstanding debate over whether CMV acts as an "innocent bystander versus foe" debate likely can be settled by focusing on the density of CMV in intestinal tissue, with increasing viral loads suggesting pathogenicity. In the setting of severe, steroid-refractory IBD, CMV colitis may be a significant risk factor for poor clinical outcomes, including mortality. As such, maintaining a high index of suspicion in the appropriate clinical context will lead to achieving an accurate tissue diagnosis of CMV colitis and initiating appropriate treatment.

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Isolated Perianal Fistulas: When and How Should I Investigate for Inflammatory Bowel Disease?

Serre-Yu Wong, MD, PhD

Key Takeaways:

- Approximately, 5–10% of all perianal fistulizing Crohn's disease (PFCD) patients will have isolated PFCD. High or complex tracts, multiple internal openings, chronicity, and refractoriness to treatment—along with patient factors—should raise suspicion for PFCD (isolated or not).
- A negative initial luminal evaluation does not exclude CD — surveillance is key. Up to 25% of patients presenting initially with isolated complex fistulas develop luminal CD over time (median 2.5 years). Periodic reassessment with imaging, endoscopy, and symptom monitoring is critical to avoid missed or delayed diagnosis.
- Diagnosis and management of isolated PFCD requires a multidisciplinary, patient-centered approach. TOpClass criteria offer practical diagnostic guidance using clinical, radiologic, and histologic features. For patients with significant symptoms and complex isolated PFCD, anti-TNF therapy may be considered, though evidence is limited and optimal duration remains unclear.

Isolated Perianal Fistulas in Context

Perianal fistulas are a challenging manifestation of Crohn's disease (CD), affecting approximately one in five patients.[1,2] Perianal fistulizing Crohn's disease (PFCD) is associated with a complex disease course, distinct symptom burden, frequent need for surgical intervention, reduced quality of life, and increased healthcare utilization and costs.[3-5] Timely recognition and diagnosis are critical. Management strategies, both medical (e.g., anti-tumour necrosis factor (TNF) agents as first-line therapy) and surgical, differ significantly from those used for luminal CD alone and may prevent disease progression.[5-8]

Most PFCD cases present concurrently with or after a diagnosis of luminal CD.[9,10] However, in approximately 10% of patients, perianal fistulas appear in the absence of luminal inflammation.[11] Of these patients, we estimate that one-quarter will eventually manifest luminal CD, while 5–10% will remain as isolated PFCD.[10,11] Given that over 90% of perianal fistulas without luminal disease are cryptoglandular in origin, distinguishing PFCD in this context is diagnostically challenging.[12]

Cryptoglandular fistulas typically exhibit a simple anatomy—superficial, low-lying tracts with minimal sphincter involvement—and are more likely to heal.[2,12] In contrast, CD-related fistulas are often more complex, originating higher in the anal canal or rectum, with branching or multiple tracts, and are commonly refractory to standard treatment[2,12] Nonetheless, overlap exists: cryptoglandular perianal fistulas can be complex, and CD perianal fistulas can be simple. Importantly, no objective test currently exists to definitively distinguish CD-related from cryptoglandular fistulas.[13] This raises and important question: when—and how—should we evaluate for underlying inflammatory bowel disease (IBD)?

Evaluate the Nature of the Fistula

The first step in assessing a patient with an isolated perianal fistula is to carefully evaluate the nature of the perianal disease itself (**Table 1**). Features that should raise concern for PFCD include fistulas that originate high in the anal canal or rectum, have multiple internal openings, exhibit branching morphology, or present as multiple discrete fistulas. In addition to anatomy, fistula behaviour can also signal risk: fistulas that are chronic, recurrent, or refractory to treatment may be more likely associated with CD. The presence of other forms of perianal disease—such as strictures, ulcers, or fissures—further supports this suspicion, provided there are no alternative explanations such as infection, prior obstetric injury, or iatrogenic causes (e.g., from cancer-related procedures). Taken together, the anatomic complexity, clinical course, and associated perianal findings should all be considered in evaluating for potential PFCD.[13,14]

Assess Patient-level Risk Factors for CD

Beyond local findings, patient-level factors are essential in determining the likelihood of underlying IBD (**Table 2**). Younger age at fistula diagnosis, particularly under age 40, has been associated with an increased risk of CD in some studies.[11,13] A thorough clinical history should explore both current and past gastrointestinal symptoms, prior perianal disease, and any autoimmune or immune-mediated conditions, including extraintestinal manifestations of IBD and comorbidities such as hidradenitis suppurativa.[11,13,14] A detailed surgical history, including intestinal and perianal operations, as well as a family history of IBD, can provide further diagnostic clues.

During the physical examination, clinicians should assess for signs commonly associated with IBD, including ophthalmic and oral findings, and perform a comprehensive perianal exam to identify non-fistulizing manifestations such as skin tags, ulcers, or fissures. In selected patients, fecal calprotectin may serve as a useful adjunct.[13] While a normal result does not exclude CD in patients with high clinical suspicion, an elevated calprotectin level may prompt further evaluation in those with a lower pre-test probability of CD.

Comprehensive Luminal Evaluation

Once the decision is made to evaluate for CD (**Table 1**), the diagnostic workup should aim to definitively confirm or exclude the presence of luminal disease. This distinction matters: if CD is diagnosed, anti-TNF therapy is recommended as the first-line biologic treatment.

Ileocolonoscopy with segmental biopsies is the cornerstone for evaluating luminal disease—even in areas that appear endoscopically normal, as histologic inflammation may precede visible disease. We have observed cases of isolated perianal fistulas wherein we found histologic

Fistula characteristics	Other patient characteristics
Origin high in anal canal or rectum	Age <40 at fistula onset
Multiple internal openings	Family history of IBD
Branching or multiple tracts	IBD-related extraintestinal manifestations
Chronic, recurrent, or refractory course	Coexisting autoimmune or immune-mediated inflammatory diseases
Presence of non-fistulizing perianal disease (e.g. strictures, fissures, ulcers)	Prior intestinal or perianal surgeries
	Recurrent oral or genital lesions

Table 1. Fistula and patient characteristics to evaluate for when considering whether to evaluate for CD in patients who present with isolated perianal fistula; *courtesy of Serre-Yu Wong, MD, PhD.*

TOpClass consensus criteria for isolated perianal Crohn's disease
The following findings are sufficient for considering diagnosis of isolated perianal CD: • Histologically-confirmed disease: epithelioid granuloma in fistula or surrounding perianal tissue (excluding cryptolytic or foreign-body granulomas) • Crohn's perineum: anorectal stricture or inflammatory fissures or ulcers in the absence of another cause
Alternatively, consider isolated perianal Crohn's disease if score ≥5 based upon: **Major criteria** (3 points each): • Advanced fistula complexity • Family history of IBD in 1st or 2nd degree relative • Confirmed diagnosis of IBD-related extraintestinal manifestation or orofacial granulomatosis **Minor criteria** (1 point each): • Unconfirmed diagnosis of IBD-related extraintestinal manifestation (potential, past, or prior) • Suspected oral or genital CD • Presence of hidradenitis suppurativa • Minor perianal disease (single >1 cm edematous skin tag, ≥3 small skin tags, non-fistulizing perianal skin inflammation, or natal cleft ulceration) • Recurrence following fistula repair or lay-open procedure with curative intent

Table 2. TOpClass consensus criteria for isolated perianal Crohn's disease in patients presenting with perianal fistula and no luminal inflammation; *courtesy of Serre-Yu Wong, MD, PhD.*

evidence of inflammation that later manifested clinically and endoscopically as luminal CD. Other modalities that can be used include video capsule endoscopy, intestinal ultrasound, and magnetic resonance enterography.[15] Using a combination of these complementary tests may increase diagnostic yield, depending on the resources available at a given institution.[14]

Importantly, luminal disease may not be evident at initial presentation. In a case series from our institution, 25% of patients with isolated complex perianal fistulas developed luminal CD over time, with a median time to diagnosis of 2.5 years, and a range extending up to 10 years.[11] Therefore, a single negative evaluation should not be considered definitive. The TOpClass consortium emphasized the need for ongoing surveillance—though no consensus was reached on the optimal surveillance interval, with recommendations ranging from symptom-guided re-evaluation to routine annual screening.[14]

What if No Luminal CD is Found?

Between 5–10% of patients with PFCD will remain without evidence of luminal disease.[10,11] Historically, establishing a definitive diagnosis of isolated PFCD in such patients has not been clear. To address this gap, the international perianal disease TOpClass Consortium—a multidisciplinary panel of IBD gastroenterologists, surgeons, and radiologists—recently conducted

a systematic review and published consensus recommendations.[14] While not yet fully validated, these proposed diagnostic criteria offer practical guidance for clinical use (**Table 2**). According to these guidelines, the presence of diagnostic histopathologic features in fistula tissue or the surrounding area, as well as severe associated perianal disease, can independently establish a diagnosis of isolated PFCD. A total score of ≥5—achievable through either two major criteria, one major plus two minor criteria, or five minor criteria—is considered sufficient to support the diagnosis.

Effective diagnosis and management of isolated PFCD requires multidisciplinary collaboration. While gastroenterologists typically lead the evaluation for luminal disease, colorectal surgeons often have a clinical gestalt about whether a fistula's characteristics are more suggestive of CD rather than a cryptoglandular origin.

Managing Isolated PFCD

Shared-decision making is essential for managing isolated PFCD, and patients should be informed about both the knowns and unknowns of the disease. For patients experiencing significant perianal symptoms or whose fistulas are unlikely to heal with surgery alone, a trial of biologic therapy—typically anti-TNF agents—can be considered, provided the patient is amenable. Anti-TNFs may help reduce inflammation, support fistula healing, and facilitate surgical interventions.[16-18] However, it should be noted that the data supporting their efficacy is limited. One study, for example, reported lower remission rates in patients with complex idiopathic perianal fistula compared to those with confirmed PFCD.[19]

If a patient shows a positive response to optimized anti-TNF therapy, this treatment may be continued with regular monitoring. Yet, there is no consensus on the optimal treatment duration after clinical and radiologic remission—recommendations range from 3 months to lifelong therapy, reflecting the lack of data in this area. If there is no therapeutic response, anti-TNF therapy should be discontinued.[14] At that point, the diagnosis of isolated PFCD should be re-evaluated, and consideration given to initiating a second-line biologic.

Conclusion

Perianal fistulas without overt evidence of luminal CD present a clinical dilemma. While most are cryptoglandular in origin, a minority herald PFCD. Identifying these cases is important, as their medical and surgical management differs substantially from that for idiopathic fistulas. Comprehensive screening and luminal evaluation—including histology, imaging, and ongoing surveillance—are essential components of care. Yet, questions remain: Is isolated PFCD a distinct clinical entity? What constitutes the best treatment strategy? Further research is needed to clarify its natural history, guide treatment, and improve outcomes for this enigmatic subset of IBD.

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Prevention of Venous Thromboembolism in Patients with Inflammatory Bowel Disease

Michal Gozdzik, MD

Key Takeaways:

- When reviewing inflammatory bowel disease (IBD) patients in the clinical setting, remember to review their medical history and screen for venous thromboembolism (VTE) risk factors. This will help to risk stratify them for future decision-making.
- IBD patients admitted to hospital are at the highest risk of VTE. All IBD patients, regardless of reason for admission and disease activity, should receive VTE prophylaxis.
- In the post-operative and post-discharge setting, all IBD patients should be classified as low, intermediate, or high risk of VTE. After carefully weighing the risks and benefits, high risk patients should be considered for extended VTE prophylaxis beyond hospital discharge.

Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality worldwide and remains a preventable cause of death among hospitalized patients.[1] Given its potential devastating health consequences, VTE is one of the most important intestinal manifestations to monitor and prevent in patients with Inflammatory Bowel Disease (IBD). IBD patients are at an increased risk for VTE due to their underlying inflammatory state, which contributes to aberrant platelet and procoagulant alterations, dysregulated fibrinolysis, and endothelial dysfunction.[2] In addition to this hypercoagulable state, the risk of VTE in IBD patients is often compounded by other co-existing risk factors such as hospitalization or surgery.[3]

At baseline, IBD patients have an up to 3-fold increased risk of VTE compared to those without IBD. This risk climbs even higher during hospitalization, reaching a 6-fold increase.[4,5] The elevated risk of VTE persists after hospitalization, with population-based studies showing VTE rates

as high as 3% within 6 months after discharge.[6,7] Although the incidence is highest during hospitalization, the relative risk of VTE during an ambulatory flare is almost 16-fold greater than that of the general population.[4]

Identifying high-risk patients and providing prophylaxis in the appropriate clinical settings is critical for preventing thrombosis in this susceptible patient group. In this article, I will review the current evidence and recommendations, as well as highlight existing knowledge gaps related to VTE prophylaxis in IBD patients.

What Do the Guidelines and Current Evidence Recommend?

The Toronto and International Consensus guidelines acknowledge the significantly elevated risk of VTE in IBD patients, particularly during periods of active disease and hospitalization.[8,9] Although the highest risk groups are those hospitalized with active disease flares, even patients in clinical remission who are hospitalized for unrelated reasons carry an up to 3-fold risk of VTE compared to non-IBD patients.[5] For this reason, both sets of guidelines have clear recommendations for thromboprophylaxis for hospitalized patients, irrespective of the reason for admission. These recommendations are in line with the most recent guidelines from the American College of Chest Physicians and the American Society of Hematology (ASH) on the prevention and prophylaxis of VTE in medical patients.[10,11]

Previous studies have demonstrated that chemical prophylaxis with anticoagulants is safe for IBD patients without a significant increased risk of bleeding, even among those presenting with rectal bleeding on admission.[12] Apart from clinical situations with severe IBD-related gastrointestinal bleeding, chemical prophylaxis remains the recommended primary treatment. In cases of severe bleeding, mechanical prophylaxis with intermittent pneumatic compression should be used instead until the bleeding is no longer severe.[8]

Although VTE risk is highest during hospital admission, it does not immediately return to baseline upon discharge from hospital. However, considering the diminished risk after hospitalization, there are no guideline recommendations supporting universal extended prophylaxis for all patients. Instead, the International Consensus Guidelines recommend considering extended prophylaxis for those with a "very high risk of VTE".[9] Similarly, the American Society of Colon and Rectal Surgeons recommends considering extended prophylaxis in the postoperative setting for IBD patients deemed to be at high risk.[13] A retrospective study by McCurdy et al. developed a risk prediction model to identify patients with IBD at increased risk for post discharge VTE.[6] This model enabled the authors to better identify patients at high risk of VTE who might benefit from anticoagulation. However, further external validation of this model is required before universal use. Based on available evidence, no guideline recommendations have clearly outlined which specific risk factors should be considered, or how many must be present before initiation of extended prophylaxis is warranted. Physicians caring for IBD patients must use clinical gestalt and shared decision making when considering the need for extended prophylaxis on a case-by-case basis.

Consensus guidelines do not routinely recommend prophylactic anticoagulation for patients with IBD flares undergoing treatment in the outpatient setting. Although the relative risk of VTE during an outpatient flare can be up to 16-fold higher compared to the general public, the absolute risk remains too low to recommend prophylaxis in the absence of other risk factors.[8,9] In addition, a previous Markov decision analysis found that this intervention is not cost effective.[14] However, certain cases may warrant prophylaxis in the ambulatory setting. Considering that the risk of recurrent VTE in IBD patients is 2.5-fold higher compared with non-IBD patients, the Toronto Consensus recommends thromboprophylaxis to prevent recurrent VTE during moderate-to-severe ambulatory disease flares.[8] Patients omitted from this recommendation include those whose initial episode of VTE was provoked by surgery, as these patients are considered to have a lower risk of recurrence.[15] In contrast, the International Consensus Guidelines recommend considering prophylaxis in ambulatory patients who have known major or multiple risk factors, not just those with a previous VTE history.[9] Given inflammation is a key driver of VTE risk in these cases, prophylaxis, if initiated, should be continued until remission is achieved. As with post discharge management, the decision to initiate VTE prophylaxis in the outpatient setting should be at the discretion of the treating physician on a case-by-case basis after an assessment of the patient's individualized risk.

Where Do Our Guidelines Fall Short?

Evidence and guideline recommendations are clear on the benefits of inpatient VTE prophylaxis and recommend its use for most patient populations. However, the role of extended and ambulatory VTE prophylaxis, is less clearly defined. Although current guidelines recommend consideration of prophylaxis for high-risk patients in these settings, there is a paucity of high-quality evidence to guide clinicians in identifying which patients are most likely to benefit. Key questions remain unanswered, such as which risk factors are most relevant, how many are needed to justify intervention, and what clinical decision tools should be used? Further evidence and guidance is needed to aid in identifying which patients are most likely to benefit from VTE prophylaxis.

How Do We Identify the High-risk Patients?

The challenge in implementing extended prophylaxis is identifying the patient group most likely to benefit. A review of this topic by Murthy et al. proposed an algorithm in which patients are classified into low (<1%), intermediate (1–5%) or high risk (>5%) categories, which recommended extended prophylaxis for the high-risk patient group.[7] This appears to be a reasonable approach, particularly considering a previous study had identified that extended prophylaxis with enoxaparin is cost effective when the risk of VTE exceeds 4.9%.[16] Although several clinical predictive models, such as Padua, IMPROVE, and Caprini are available to help identify high-risk patients, these tools were developed for the general population and are not specific to IBD patients.[17-19] A recent systematic review characterized IBD risk factors across multiple phases of care.[3] While many of the risk factors identified, such as a previous history of VTE and age, are well-established in the general population, the review also identified significant IBD-specific risk factors, such as corticosteroid exposure, *Clostridioides difficile* infection, malnutrition, and inflammatory disease extent. Of note, IBD-related medications were an important group of factors reviewed in the study. Corticosteroids were associated with increased VTE risk, although this is difficult to interpret considering these medications are typically used during active disease flares. Considering that active disease is a known independent risk factor for VTE, this association may simply be a surrogate marker for active disease. Importantly, other IBD therapies, including biologics, Janus kinase (JAK) inhibitors, 5-ASA, and immunomodulators, were not associated with an increased risk of VTE. In fact, anti-tumour necrosis factor (TNF) biologics were found to be protective against VTE with an odds ratio of 0.66 (95% confidence interval 0.46–0.97), which is consistent with previous studies and animal models suggesting that anti-TNF therapy may directly reduce VTE risk.[20,21] Notably, JAK inhibitor therapy was not associated with an increased risk of VTE in this systematic review, despite a potential risk identified in rheumatoid arthritis patients that resulted in an FDA warning.[22] The review examined multiple risk factor categories, including medical comorbidities, IBD characteristics, and surgical characteristics, among others. Many of these risk factors are specific to IBD, and can serve to guide future prospective studies and the development of IBD-specific clinical predictive models. Once developed and validated, these models can better inform clinicians when considering VTE prophylaxis.

How Can We Make VTE Prophylaxis Cost Effective?

To expand the use of VTE prophylaxis among IBD patient groups, it needs to demonstrate effectiveness in preventing VTE, maintain a favourable safety profile, and be cost effective. A 2019 Canadian study showed that a 28-day course of extended prophylaxis with enoxaparin, while associated with higher costs, improved quality-adjusted life-years along with incremental cost-effectiveness ratios in IBD patients undergoing colorectal surgery.[23] However, two additional cost-benefit decision analyses in IBD patients undergoing surgery found that extended prophylaxis was not a cost-effective intervention.[24,25] As discussed earlier, a previous decision analysis assessing the cost-effectiveness of VTE prophylaxis in ambulatory patients also concluded that it was not a cost-effective strategy.[14]

Several therapeutic options for anticoagulation prophylaxis exist, each with widely variable costs. Historically, studies on the cost-effectiveness of VTE prophylaxis in IBD

patients have largely investigated low molecular weight heparin (LMWH). However, alternative agents such as direct oral anticoagulants (DOACs) offer effective VTE prevention and treatment at significantly lower costs compared to LMWH. In the orthopedic literature, DOACs have been shown to be effective in preventing VTE after surgery,[26] and have been incorporated into Thrombosis Canada guidelines for extended prophylaxis.[27] Regarding non-orthopedic surgery, a 2022 study showed that oral rivaroxaban was more effective than placebo for extended VTE prophylaxis after laparoscopic surgery for colorectal cancer without an increase in major bleeding.[28] Finally, the ASH guidelines on VTE prevention in hospitalized surgical patients suggests using extended prophylaxis over short-term prophylaxis, citing a likely modest benefit in reducing VTE with comparable bleeding rates.[29] Importantly, the guidelines recognized that the evidence was limited to orthopedic and major oncologic surgeries.

In medical patients, there is currently no confirmed benefit to using DOACs for extended VTE prophylaxis after hospital discharge.[30,31] It is important to note that IBD patients are underrepresented in these studies, despite their inflammatory burden that places them at a greater risk for VTE compared to the general medical population. As such, more evidence is needed before these therapies can be recommended for routine use in IBD patients. However, if DOACS are shown to be effective for VTE prevention in carefully selected high-risk patient groups, they could offer a more cost-effective intervention compared to LMWH.

Conclusion

While the evidence and guidelines on inpatient VTE prophylaxis is clear, this does not always translate into clinical practice. Despite clear recommendations, adherence rates for VTE prophylaxis is suboptimal, with some studies reporting prophylaxis rates as low as 39.7% among hospitalized patients.[32] Physicians who care for patients with IBD should be aware of the benefits and safety of VTE prophylaxis for hospitalized patients.

To expand the use of extended VTE prophylaxis in IBD populations, it is essential to identify those who may benefit from targeted prophylaxis. This requires further research to stratify patients by risk and guide targeted prophylaxis. As our knowledge of IBD risk factors continues to grow, prospective studies will be needed for creating and validating clinical predictive models that can accurately and reliably identify these high-risk patients. To optimize the cost-benefit of extended and ambulatory prophylaxis interventions, future studies could investigate the use of low dose DOACs, particularly in the post surgical setting where evidence already exists for some patient populations. For now, clinicians will need to consider the known risk factors identified in the literature and assess patients on a case-by-case basis.

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