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CHRISTOPHER MA

MD, MPH, FRCPC



Christopher Ma is an academic gastroenterologist at the University of Calgary. He has advanced training in inflammatory bowel disease, clinical trial design, and analytic research methods. He has published over 170 peer-reviewed manuscripts and received over \$6.5 million in research grant funding. His clinical and research focus is on patients with advanced Crohn's disease, ulcerative colitis, and eosinophilic esophagitis who require advanced medical therapies.

Affiliations:

Division of Gastroenterology & Hepatology, University of Calgary
Department of Community Health Sciences, University of Calgary
Alimentiv Inc., London, Ontario

JAK Inhibitors for the Treatment of Inflammatory Bowel Disease

Introduction

Over the past decade, Janus kinase (JAK) inhibitors have been developed for the treatment of several immune-mediated inflammatory diseases, including ulcerative colitis (UC) and Crohn's disease (CD). The JAK-signal transducer and activator of transcription (STAT) pathway plays an essential role in coordinating the human immune response. Phosphorylation and activation of the JAK family of tyrosine kinases results in subsequent activation of intracytoplasmic STAT pathways with upregulation of inflammatory gene transcription.¹ Blocking this signalling results in broad-spectrum immunosuppression, which is effective in the treatment of rheumatoid arthritis (RA), psoriasis, atopic dermatitis, and inflammatory bowel disease (IBD).^{2,3} To date, three oral, small-molecule JAK inhibitors (tofacitinib, filgotinib, and upadacitinib) have received regulatory approval in various jurisdictions globally for the treatment of moderate-to-severely active UC. It is anticipated that upadacitinib will soon become the first novel, advanced oral small molecule therapy approved for

moderate-to-severely active CD. While these agents are highly effective, emerging data has highlighted potentially relevant safety signals associated with JAK inhibitors, and that the therapeutic index of these therapies may be distinct from that of monoclonal antibodies. Therefore, JAK inhibitors have a unique position in the therapeutic armamentarium for IBD. Here, we summarize the evidence supporting the use of JAK inhibitors and provide an overview of their practical applications in clinical care.

Evidence Supporting the Efficacy of JAK Inhibitors in IBD

Tofacitinib for UC

Tofacitinib is a pan-JAK inhibitor with preferential affinity for JAK1/JAK3.⁴ The efficacy of tofacitinib was demonstrated in the phase 3 OCTAVE program, which included two induction trials (OCTAVE-1 and 2) randomizing 1,139 patients with moderate-to-severely active UC to tofacitinib 10 mg twice daily or placebo for 8 weeks.⁵ A total of 593 responders

in induction were subsequently re-randomized to tofacitinib 5 mg or 10 mg twice daily or placebo in the 52-week OCTAVE-Sustain maintenance trial. At week 8, a significantly higher proportion of patients receiving tofacitinib achieved clinical remission (16.6%-18.5% vs 3.6%-8.2%); this difference was observed in both patients who were biologic-naïve and those previously failing tumor necrosis factor (TNF) antagonist(s).⁶ At 52 weeks, patients receiving either tofacitinib 5 mg (34.3%) or 10 mg (40.6%) were significantly more likely to be in clinical remission compared to placebo (11.1%, $p<0.001$ for both comparisons). In a post-hoc analysis, differences in mean stool frequency and rectal bleeding were detectable by day 3 of therapy.⁷ Several real-world cohorts evaluating the efficacy of tofacitinib have also been conducted: in a meta-analysis of 17 studies including 1,162 UC patients treated with tofacitinib, Taxonera et al showed that half of patients achieved clinical remission at Week 12-16, and 38.3% were in clinical remission by month 6.⁸ Recently, we reported the world's largest real-world experience with tofacitinib to date in the REMIT-UC multicenter Canadian IBD Research Consortium study, which included 334 UC patients who were predominantly biologic-refractory.⁹ Tofacitinib induced endoscopic remission, defined as a Mayo endoscopic subscore of 0 or 1, in 18.5%, 23.0% and 25.7% of patients at Weeks 12, 24 and 52, respectively.

Upadacitinib for UC

Upadacitinib is an oral, JAK1 selective small molecule that was evaluated for the treatment of moderate-to-severely active UC in the phase 3 U-ACHIEVE ($n=474$) and U-ACCOMPLISH ($n=522$) trials.¹⁰ These 8-week induction studies randomized patients 2:1 to upadacitinib 45 mg daily or placebo. Half of patients had previously failed a biologic therapy and nearly 70% had severe endoscopic disease activity at enrollment. At week 8, 26%-33% of patients treated with upadacitinib achieved clinical remission, compared to 4%-5% of patients receiving placebo (adjusted treatment difference 21.6%-29.0%, $p<0.0001$ in both trials). All secondary endpoints significantly favoured upadacitinib, including resolution of bowel urgency, endoscopic remission and mucosal healing (combined endoscopic and histologic remission). A post-hoc analysis demonstrated that statistically significant improvements in all UC symptoms were achieved between day 1 and 3 of therapy.¹¹ A total of 451 responders to upadacitinib induction were subsequently re-randomized to upadacitinib 15 mg, 30 mg or placebo in a 52-week maintenance trial. Both doses of upadacitinib were significantly

more effective than placebo for maintenance of clinical remission (adjusted treatment difference 30.7%-39.0%, $p<0.0001$), and for all secondary endpoints, including endoscopy and histopathology.

Upadacitinib for Crohn's Disease

Upadacitinib was evaluated in moderate-to-severely active CD in the 12-week, phase 3, placebo-controlled U-EXCEED ($N=495$) and U-EXCEL ($N=526$) trials.¹² These studies enrolled a highly refractory treatment population: approximately one-third of patients had failed at least 3 biologic therapies prior to enrollment. Furthermore, these trials were the first in CD to force a mandatory corticosteroid taper during induction, starting 4 weeks after the first dose of upadacitinib or placebo. Upadacitinib was significantly more effective than placebo for achieving the co-primary endpoints of clinical remission (adjusted treatment difference 25.9%-28.7%, $p<0.0001$) and endoscopic response (treatment difference 31.2%-33.0%, $p<0.0001$) at week 12. At Week 12, adjusted treatment differences of 30.2%-32.6% ($p<0.0001$) were observed favoring upadacitinib over placebo for achieving corticosteroid-free clinical remission. Both 15 mg and 30 mg upadacitinib were more effective than placebo for maintaining clinical remission and endoscopic response at week 52 in the maintenance U-ENDURE trial. At one year, 28.6% of patients treated with upadacitinib were in endoscopic remission (defined by a Simple Endoscopic Score for CD ≤ 4 , at least 2-point reduction compared to baseline, and with no subscore >1), compared to only 5.5% of patients treated with placebo ($p<0.0001$); one-quarter of upadacitinib-treated patients achieved complete ulcer-free remission.

What Evidence Supports the Safety of JAK Inhibitors?

Although JAK inhibitors have demonstrated a high degree of efficacy, their safety profile has come under scrutiny. This was underscored by results from the ORAL Surveillance trial.¹³ ORAL Surveillance was a U.S. Food and Drug Administration (FDA)-mandated post-authorization, open-label, non-inferiority study. Patients ≥ 50 years old with RA, with at least one established cardiovascular disease (CVD) risk factor, were randomized to tofacitinib or a TNF inhibitor, in combination with methotrexate. The incidence of the coprimary endpoints, major adverse cardiovascular events (MACE) and cancer (excluding non-melanoma skin cancer), was higher in patients receiving tofacitinib compared to that of TNF antagonists (3.4% vs 2.5% and 4.2% vs 2.9%, respectively), and there were increased incidences of herpes zoster

(HZ), infections and serious infections, and venous thromboembolism (VTE). This prompted the FDA to issue a black box warning, which applied not only to tofacitinib, but to other JAK inhibitors as a class, as well, and to limit their use to patients who had failed a TNF antagonist. In contrast, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee has recommended that JAK inhibitors be considered only if no suitable treatment alternatives are available in patients ≥ 65 years, current or past long-time smokers, and those with either CVD or malignancy risk factors. Health Canada has issued a public advisory that all JAK inhibitor labels will include warnings around the risks of serious cardiac complications, thrombosis, and malignancy, but both the EMA and Health Canada permit the use of JAK inhibitors as first-line therapy.

Whether the risks observed in ORAL Surveillance are generalizable to patients with IBD is unclear. There was effect modification by age and smoking status, and most IBD patients would not have met the high-risk eligibility criteria used in ORAL Surveillance. Safety data from tofacitinib- and upadacitinib-treated patients with UC is more reassuring. In an analysis of 7.8 years of tofacitinib exposure in UC patients, Sandborn et al did identify an increased risk of HZ (in patients who, generally, had not been vaccinated against zoster), but comparable rates of malignancy, MACE, and VTE compared to other biologics.¹⁴ In an integrated safety analysis of $>2,400$ patient-years of tofacitinib exposure in UC, only five cases of VTE were reported (all in patients with other VTE-related risk factors), and four UC patients developed a VTE while receiving placebo.¹⁵ Long-term safety results in IBD patients treated with upadacitinib are still needed. While rare cases of infections and serious infections have been reported with upadacitinib, the overall risk of serious adverse events was lower in trial patients receiving upadacitinib compared to placebo, likely reflecting better IBD control. An integrated safety analysis of RA trials did not demonstrate a significantly increased risk of serious or opportunistic infections (excluding HZ), malignancy, MACE, or VTE with upadacitinib compared to adalimumab.¹⁶

How Should JAK Inhibitors be Used in Clinical Practice?

JAK inhibitors are highly potent therapies for patients with moderate-to-severely active IBD. The primary advantage of this class is its efficacy: multiple network meta-analyses have found JAK inhibitors to be one of the most likely therapies to achieve remission in patients with UC and CD, particularly after previous biologic failure.¹⁷⁻¹⁹ Additional advantages include

convenient oral administration, lack of immunogenicity, short half-life with rapid onset, and coverage of certain extraintestinal manifestations (EIMs). However, safety concerns noted with this class of therapy should be balanced against its potential benefits.

In deciding which patients should be considered for a JAK inhibitor in the clinic, in those patients who have failed their first biologic, JAK inhibitors should be considered. The second-line treatment choice is a critical point in a patient's disease journey because efficacy rates are lower at that point and, given the potential consequences of uncontrolled inflammation (i.e., risk of colectomy, surgery or progressive mechanical complications such as strictures/fistula), the risk-benefit ratio heavily favours using the most effective second-line agent next. Some patients may be considered for a JAK inhibitor first-line. This includes: those with advanced endoscopic findings (e.g., severe pancolitis or deep extensive ulcerations); who strongly favour an oral advanced therapy; cannot tolerate or previously experienced corticosteroid-related adverse events; who are highly symptomatic and require immediate relief; or who have EIMs such as enteropathic arthritis, are likely to benefit from a JAK inhibitor. In contrast, patients over the age of 65, patients who are heavily comorbid, have a strong smoking history, or have pre-existing or uncontrolled risk factors for CVD, should also explore therapeutic alternatives.

Recognizing that there have been safety signals associated with JAK inhibitor use, risk mitigation strategies should be considered for all patients (**Table 1**). This includes pre-treatment testing for latent tuberculosis and hepatitis B; detailed medication review for potential drug-drug interactions; patient counselling on smoking cessation; ensuring up-to-date vaccinations for HZ and pneumococcus; evaluating the baseline lipid profile and CVD risk; and discussing contraception in women of child-bearing potential. Estrogen-containing oral contraceptives have been associated with an increased risk of VTE; therefore, progestin-only or other options (e.g., intrauterine device) should be considered. Two-dose, non-live recombinant zoster vaccination (Shingrix® [Mississauga, ON]) should be administered, with the first dose given either before or near the time of induction therapy. Tools such as the Framingham Risk Score or the atherosclerotic cardiovascular disease (ASCVD) Risk Estimator can be considered. In addition, efforts to control metabolic syndrome risk factors such as dyslipidemia, hypertension, obesity, and diabetes may mitigate long-term CVD risk.

Risk/Benefit Scenario	Potential Strategies
Pre-therapy	- Medical history, physical examination, IBD investigations: define IBD phenotype, disease activity and medical profile - Latent tuberculosis screening (quantiferon or tuberculin skin test) - Hepatitis B screening (HBsAg, anti-HBs, anti-HBc [total]) - Medication review for potential drug-drug interactions
Infection Risk	- Herpes zoster vaccination (Shingrix, inactivated recombinant vaccination, first dose before or near first induction dose) - Pneumococcal vaccination - Minimize corticosteroid use, if possible
Cardiovascular Disease Risk	- Evaluate and optimize CVD risk factors (diabetes, hypertension, dyslipidemia) - Consider using formalized risk tool to assess risk (e.g., Framingham Risk Score, American College of Cardiology ASCVD Risk Tool) - Counsel on smoking cessation as appropriate; consider nicotine replacement, pharmacologic therapy for smoking cessation
Malignancy Risk	Up-to-date age-appropriate cancer screening (e.g., Pap smear, mammogram, colonoscopy, skin examination as appropriate)
Teratogenicity Risk	- Ask about family planning - Counsel on contraceptive options: progestin-only or non-estrogen- containing oral contraception alternatives
Thrombosis Risk	Ask about thromboembolic risk factors (including personal and family history of VTE)
Post-therapy Monitoring	- Complete blood count and liver enzymes every 3 months - C-reactive protein and fecal calprotectin every 3-6 months - Lipid profile and renal function every 6-12 months - Colonoscopy 6-12 months after induction to evaluate mucosal response to treatment

Table 1. Practical considerations for starting and monitoring JAK inhibitor therapy in clinical practice; courtesy of Dr Christopher Ma, MD

After initiating a JAK inhibitor, I generally follow a treat-to-target approach, as endorsed by the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) guidelines.²⁰ This includes achievement of early symptom improvement, normalization of stool and serum biomarkers and, ultimately, targeting endoscopic normalization. Bloodwork including complete blood count (for cytopenias), C-reactive protein (for subclinical inflammation), and liver enzymes (for potential hepatotoxicity) are monitored every 3 months. Serum lipids are initially assessed within the first 3 months and then, along with renal function, are checked every 6-12 months. I generally do not monitor the creatine phosphokinase (CK): asymptomatic elevations in CK are common but should be checked

in patients with myalgia or substantial muscle weakness. Finally, I discuss with the patient dose de-escalation after induction. The efficacy and safety of JAK inhibitors are partially dose-dependent. Although de-escalation (to 5 mg BID tofacitinib or 15 mg daily upadacitinib) has been demonstrated to be potentially effective, up to 20% of patients may lose response.²¹ Therefore, I counsel high-risk patients (those with prior biologic failure, no other medical treatment options or severe endoscopic disease activity) on the risks and benefits of continuing on higher-dose maintenance therapy, and confirm clinical, biomarker and endoscopic remission prior to considering stepping down therapy.

Conclusion

JAK inhibitors are highly effective therapies for moderate-to-severely active IBD. They play an important role in achieving both symptomatic and objectively-defined remission, particularly in patients with difficult-to-treat disease. Ongoing trials will define the role of JAK inhibitors for specific phenotypes of patients, including those with postoperative CD, perianal fistulizing CD, or acute severe UC in hospital. While some safety signals have been observed, the majority of patients can be safely treated with a JAK inhibitor, and this class of therapy should be considered an integral part of every gastroenterologist's armamentarium when treating IBD.

Correspondence:

Christopher Ma

Email: christopher.ma@ucalgary.ca

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NEERAJ NARULA

MD, MPH, FRCPC



Neeraj Narula is currently an Associate Professor of Medicine at McMaster University and Staff Gastroenterologist at Hamilton Health Sciences, with a clinical and research focus in Inflammatory Bowel Diseases (IBD). He also serves as Director of the IBD clinic at Hamilton Health Sciences and Director of the IBD fellowship for McMaster University. During the course of his career, he has published over 120 peer-reviewed articles and 4 book chapters and he has received over \$3 million in research funding and grants. His advanced training includes Present-Levison Advanced Inflammatory Bowel Diseases Fellowship at Mount Sinai Hospital (New York, NY) and Masters of Public Health at Harvard TH Chan School of Public Health (Boston, MA). He has been an invited speaker at several international congresses including Digestive Diseases Week (American Gastroenterology Association), European Crohn's and Colitis Organization Conference, United European Gastroenterology Week, and Ontario Association of Gastroenterology Annual Meetings.

Affiliations:

Department of Medicine, Division of Gastroenterology, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON

Management of Pouchitis: Clinical Pearls for the Gastroenterologist

Introduction

Ileal pouch anal anastomosis (IPAA) is a surgical procedure conducted in patients with ulcerative colitis (UC) with medically refractory disease; in patients with the autosomal dominant inherited disease familial adenomatous polyposis (FAP); or in patients who have experienced dysplasia/colon cancer. The procedure aids in the management of these diseases, improves patients' quality of life, prevents the need for a permanent stoma, and reduces the risk of colorectal cancer. A common complication from IPAA is pouchitis, which is characterized as an idiopathic non-specific inflammation within the created pouch resulting in symptoms including increased frequency of bowel movements and abdominal pain. Pouchitis is much more common in patients treated for UC (up to 60%) than in those receiving treatment for other indications (0-10%).¹ This might be due to immune activation or dysbiosis in these patients.

Normal anatomy and function of a J pouch

The IPAA consists of an ileal-anal anastomosis and the creation of an ileal reservoir, the pouch, which is situated near the original space of the rectum.² The reservoir pouch is created by connecting the ileum to the anus to bypass the removed colon. Three types of pouches (J, S or W) can be created; they vary in shape. The most commonly used ileal pouch is the J pouch. This structure has improved storage and emptying function compared to the S and W pouch structures. The J pouch is created by folding two 15-20 cm loops of the ileum and stapling or sewing these together, after which the internal walls are removed to create a shape resembling the letter J. Most patients will have an average of five-six bowel movements per day after the IPAA, and one-two nocturnal bowel movements, and for patients who previously had medical refractory UC, this often is an improvement from their prior symptoms resulting in

enhanced quality of life. Pouch function has generally been reported as stable over the long term; however, complications may arise.

Pouchitis

Pouchitis is the most common long-term complication of the IPAA procedure. There are various presentations of pouchitis, and risk factors and characteristics vary. Therefore, treatment may depend on the type of pouchitis present in the patient.

Acute pouchitis lasts less than or equal to four weeks, while chronic pouchitis is characterized as pouchitis with a duration of more than four weeks. Chronic pouchitis can be classified as antibiotic-dependent or antibiotic-refractory based on the response to antibiotics treatment. Patients with chronic antibiotic-dependent pouchitis generally have continued relapses despite using antibiotics multiple times per year (at least three courses). Patients who continue to experience symptoms and have inflammation characteristics of the pouch, despite multiple courses of antibiotics and other treatments, are categorized as having chronic antibiotic-refractory pouchitis (CARP), which is the most challenging form to manage.

Diagnosis

Patients with increased urgency and stool frequency, blood in the stool, abdominal pain, extra-intestinal manifestations involving joints, eyes, skin, and liver, and/or fever, may have pouchitis. As these symptoms may also indicate other diagnoses, diagnostic procedures should include a pouchoscopy evaluation with biopsy. An activity score can be determined based on subjective information on symptoms obtained from patients and the objective data obtained from the pouchoscopy and histopathology determined from biopsies. The most used and validated scoring system for pouchitis is the Pouchitis Disease Activity Score (PDAI).³ Pouchitis is defined as a PDAI score of seven or higher. Although used within clinical trials, it has not been routinely adapted in clinical practice due to subjectivity in pouchoscopy interpretation and nuances in histology reporting. More recently, the Atlantic pouchitis index (API) has been suggested as a new way to assess endoscopic and histologic disease activity, which includes the simple endoscopic score for Crohn's disease and the Robarts histopathology index. The API has been shown to be reliable but needs to be validated in other datasets.⁴

Differential diagnosis

The differential diagnosis for symptoms that may indicate pouchitis are:

Inflammatory

- Cuffitis, which is defined as residual inflammation of the rectal cuff
- Infectious diarrhea, e.g., as caused by cytomegalovirus (CMV) or *Clostridium difficile*
- Crohn's-like phenomenon of the pouch

Mechanical/Structural

- Afferent and efferent limb syndromes
- Irritable pouch syndrome
- Pouch ischemia
- Pouch stenosis
- Pelvic floor dysfunction
- Adhesions
- Neoplastic complications (often in the cuff)

Dysmotility

- Impaired pouch emptying
- Bile salt malabsorption
- Pouch stricture

Treatment

Acute pouchitis

Clinical studies assessing the optimal treatment strategies for acute pouchitis have been limited in number and generally consist of small cohorts, resulting in low quality of evidence. The majority of treatments focus on treating the potential underlying bacterial dysbiosis. The most common antibiotics prescribed are ciprofloxacin, rifaximin, and metronidazole. While all three medications can be effective, ciprofloxacin generally has better outcomes as it is better tolerated by the majority of patients.^{1,5} Biopsies have shown that antibiotics reduce the number of bacteria in the pouch that may be responsible for the inflammation. For example, ciprofloxacin has been shown to reduce *Clostridium perfringens* and *Escherichia coli*, while metronidazole reduced *C. perfringens* but not *E. coli*.² The majority of patients experience improvements in symptoms after one or two days of antibiotic treatment. Therefore, first-line therapy should consist of a two-week antibiotics treatment protocol for the first episode. In patients with multiple episodes or symptoms returning quickly after completion of an antibiotics course, a longer course (≥4 weeks) or an alternative antibiotic class could be

considered. Approaches may include to first assess the efficacy of ciprofloxacin 500 mg twice/day and if not tolerated, consider metronidazole 500 mg twice/day. Some case studies have also shown responses to tinidazole, doxycycline, erythromycin, tetracycline, rifaximin, and the combination of amoxicillin and clavulanic acid (clavulin), but the quality of evidence around these antibiotics is low.⁶

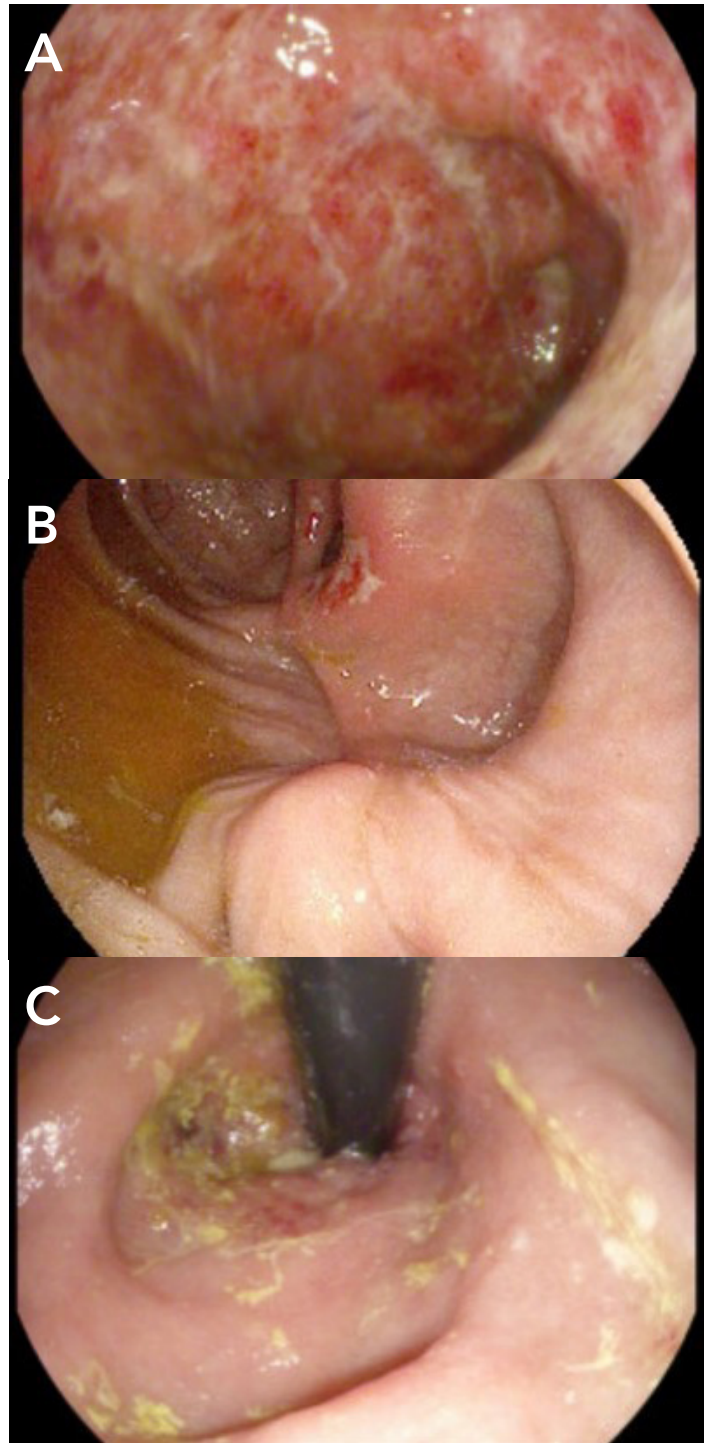


Figure 1. Pouchoscopy examples of A) Classic pouchitis; B) Ischemic pouchitis; and C) Cuffitis; courtesy of Neeraj Narula, MD

The use of probiotics has been shown to have potential as a prophylaxis to prevent pouchitis or to maintain remission following antibiotics. This is due to their alteration of the pouch flora. The most studied and most commonly-used probiotic treatment is VSL #3® (Alfasigma, Covington, LA), which has been shown to induce a remission rate of 85% over a median follow-up of one year.⁷ The mechanism of action of this treatment is a restoration of the bacterial and fungal balance in the pouch, as treatment results in an increase in bacterial and fungal diversity. Biopsy samples of patients treated with VSL #3 contain higher concentrations of *Lactobacilli spp*, *Bifidobacterium spp* and *E. coli*. Currently, the data does not support the use of probiotics as first-line therapy.

Treatment with 5-aminosalicylic acid (5-ASA) has been suggested for pouchitis;⁸ however, patients with cuffitis might benefit from this strategy to the greatest extent with the use of topical 5-ASA suppositories.⁹ The use of steroids can be considered in patients who are unable to tolerate antibiotics. Two clinical studies with small cohorts have demonstrated beneficial effects with budesonide (oral or enema), resulting in remissions, lower PDAI scores and endoscopic improvements.^{10,11}

Chronic pouchitis

Whether chronic pouchitis is antibiotic-dependent or refractory, escalation of therapy should be considered.

For patients who do not respond to initial antibiotics, a prolonged course (e.g. 4 weeks) or dual combined antibiotics can be provided. Dual antibiotics may consist of ciprofloxacin (500 mg twice/day) combined with metronidazole (500 mg twice/day) or rifaximin (550 mg twice/day).¹² Trials of antibiotics in other classes (some examples provided above) should be considered at least once or twice as well before exploration of other agents, such as biologics (discussed below).

Chronic antibiotic-dependent pouchitis

Patients who have continuing relapses despite antibiotics multiple times per year, are considered to have chronic antibiotic-dependent pouchitis and require long-term maintenance therapy. Those on maintenance treatment who lose response may benefit from rotating antibiotics in 1-3 week intervals (e.g. switching between metronidazole, ciprofloxacin, and rifaximin). These patients may also benefit from probiotics as a maintenance approach.

Chronic antibiotic-refractory pouchitis

Patients who do not respond to induction antibiotics

treatment and probiotics are considered as having CARP, which requires long-term maintenance therapy. This condition is difficult to manage. Secondary causes of pouchitis should be reconsidered (**see Differential Diagnosis**). Steroids could be considered for this group of patients and patients should be monitored for steroid-associated adverse events.¹² Budesonide has been assessed in small studies that showed 75% of patients had remission in response to this therapy, and could be considered in highly selected patients, such as those with primary sclerosing cholangitis-associated pouchitis and enteritis.^{12,13} Betamethasone has also been assessed in a small study, resulting in an 80% remission rate.¹⁴ Therefore, this strategy could be attempted for eight weeks in patients with antibiotic-refractory pouchitis.

Limited data is available regarding biologics for treatment in these patients, but those who respond to induction therapy with biological agents should receive those as maintenance treatment.¹² Vedolizumab is a monoclonal antibody directed at integrin $\alpha 4\beta 7$ which has undergone testing in patients with chronic antibiotic-refractory pouchitis. A meta-analysis assessing 15 clinical studies with a total of 311 patients demonstrated that vedolizumab treatment achieved endoscopic improvement in 61.2% of patients.¹⁵ A recent randomized, controlled, Phase 4 clinical trial assessed vedolizumab in 102 patients (51 of these received treatment). Sustained remission was achieved in 27.5% of patients, and endoscopic results revealed that treatment with vedolizumab resulted in reductions in the occurrence of ulcers. The treatment was well-tolerated.¹⁶ In the meta-analysis cited above, the anti-TNF α antibody infliximab reported endoscopic remission in 70.3% of patients.¹⁵ Adalimumab, also a TNF α inhibitor, was studied in a randomized, controlled trial in 13 patients (6 patients received treatment). Total PDAI improved in 100% of patients on treatment.¹⁷ Ustekinumab is an antibody directed at IL-12 and IL-23, which has been used in smaller clinical studies. A retrospective study of 24 patients revealed clinical responses in 50% of patients, and endoscopic data showed a reduction in ulcers in the majority of assessable patients.¹⁸ Larger randomized controlled trials are necessary to determine the optimal biologic for this patient cohort.

Other agents that have been used for maintenance therapy in CARP are immunomodulators, such as mercaptopurine and azathioprine. Limited published evidence for this treatment is available, but these strategies may benefit patients with immune-mediated pouchitis.¹² Furthermore, some case reports and case studies have suggested the use of topical ciclosporin or tacrolimus as treatment options for CARP.¹²

Future directions include FMT and diet

Given the implied importance of the microbiome in pouchitis, other strategies to alter the microbiome composition are being investigated. Fecal microbiota transplantation (FMT) is gaining attention for various conditions, having shown efficacy for *Clostridium difficile* infections. Few studies have assessed the use of FMT in chronic pouchitis. A meta-analysis revealed a lack of effectiveness, but the studies included were heterogeneous in their study design, had differences in the delivery of the fecal transplant, included few patients, and diagnostic criteria for pouchitis also varied, making the interpretation of studies challenging.¹⁹ A current Phase II randomized controlled trial investigates FMT once a week for six weeks in patients with active pouchitis (NCT03545386). Other options to improve the microbiome composition focus on diet. It has been shown that patients who consume more fruit in the first year after IPAA surgery have a reduced chance of pouchitis and have increased microbial diversity.²⁰ A small study assessing the elemental diet suggested that it may improve pouchitis symptoms in some patients but has limited effect at inducing remission.²¹ Therefore, further studies into the effect of diet on the microbiome in pouchitis are warranted.

Clinical Pearls

- All pouch problems are not necessarily pouchitis, think of other inflammatory/infectious/ischemic causes, structural causes, and dysmotility
- Proper evaluation of pouch problems requires proper endoscopic evaluation (often with sedation) as well as imaging (pouch-gram, MRE) to rule out alternative problems.
- Ischemia of the pouch can mimic pouchitis in its appearance but it usually manifests in the distal pouch and has a clear margin of demarcation or ulceration
- Cuffitis is best managed with suppositories targeting the site of inflammation. Suppository treatments to be considered are 5-aminosalicylic acid, hydrocortisone, and the immunosuppressant tacrolimus (calcineurin inhibitor).
- Inflammation in the afferent limb is not always an indication of Crohn's disease. A section of 10 cm of mild disease/aphthous ulcers in the afferent limb manifests in some instances of pouchitis. In these cases, antibiotics should be attempted before escalating to therapies used to manage Crohn's disease.
- Inflammation and ulceration along the staple line may not resolve and typically are asymptomatic. Familiarity with the anatomy of a pouch can allow the identification of patients with staple line/ischemic ulcers who are frequently asymptomatic and do not require management with therapy.

Conclusions

Use of colectomy with ileal-anal pouch anastomosis and J-pouch formation remains necessary for the management of certain patients, including those with medically refractory UC. Pouchitis is a common complication for patients with a pouch, and antibiotic therapy remains a mainstay of treatment in acute pouchitis. Response to manipulation of the microbiome with antibiotics provides clues into the pathogenesis of pouchitis, and further studies are needed to understand the role of other strategies of microbial manipulation (e.g. FMT, diet). Patients with chronic antibiotic-dependent or refractory pouchitis are candidates for advanced therapy including biologics, although the overall quality of evidence remains low.

Correspondence:

Neeraj Narula

Email: neeraj.narula@medportal.ca

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WAQQAS AFIF

MD



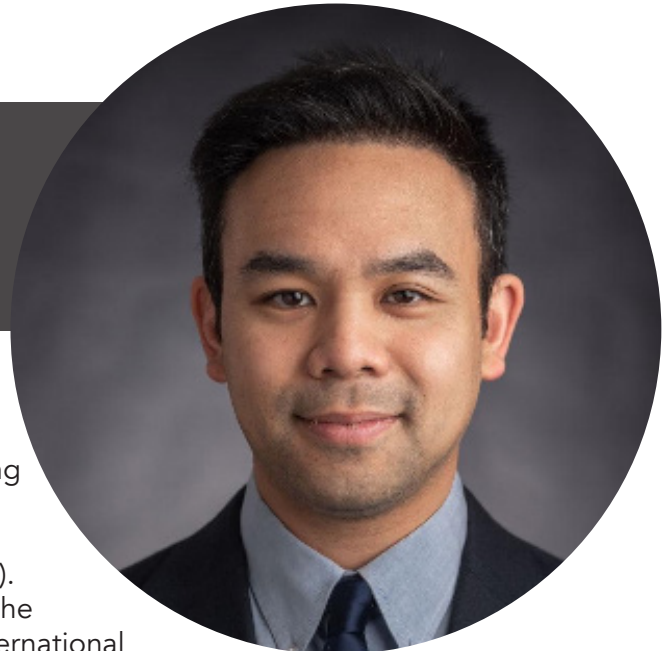
Dr. Waqqas Afif is currently an Associate Professor of Medicine in the Division of Gastroenterology and the Division of Clinical Epidemiology. He completed his medical school (2003), internal medicine and gastroenterology training at McGill University and completed an advanced fellowship in IBD at the Mayo Clinic in Rochester, MN. He returned to McGill to complete a M. Sc. (Epidemiology). He is the current Montreal General Hospital GI Site Director and McGill IBD Center Research Director

Affiliations:

Inflammatory Bowel Disease Centre, Division of Gastroenterology, McGill University Health Centre (MUHC), Montreal, Quebec

ARTI WONGCHA-UM

MD



Dr Arti Wongcha-um is currently a gastroenterology and hepatology resident at McGill University, Canada. After gaining his medical degree from the University of Southampton, he underwent internal medical training and gained his Membership of the Royal College of Physicians (London, UK). He has a wide-ranging clinical and research interests within the field of gastroenterology, and has presented at local and international conferences.

Affiliations:

Inflammatory Bowel Disease Centre, Division of Gastroenterology, McGill University Health Centre (MUHC), Montreal, Quebec

THERAPEUTIC DRUG MONITORING OF BIOLOGICS IN INFLAMMATORY BOWEL DISEASE: WHERE HAS THE PENDULUM SWUNG?

Introduction

Biologics have revolutionized the management of patients with inflammatory bowel disease (IBD), in both ulcerative colitis (UC) and Crohn's disease (CD). There are several classes of biologics used to treat IBD, including monoclonal antibodies directed against TNF, integrin, IL12/23, and IL-23 monoclonal antibodies. Despite the effectiveness of anti-TNF medications, approximately 30% of patients are primary non-responders (PNR), and another 50% lose response over time (secondary loss of response [SLR]).¹ Therapeutic drug monitoring (TDM) provides a tool for biologic dose optimization by measuring drug trough concentrations and anti-drug antibodies (ADA). Drug concentrations are positively correlated to therapeutic benefits, but questions remain on how, when and for whom to perform TDM. Successful implementation is challenged by several factors such as variations in optimal drug targets, different types of drug detection assays, individual pharmacokinetics, and disease severity. Over recent years, various expert groups have provided guidelines on reactive TDM of anti-TNF therapies; however, a knowledge gap still exists on the role of proactive TDM, as well as reactive TDM for non-anti-TNF biologics. The most recent and comprehensive expert consensus statement published in the *American Journal of Gastroenterology* (AJG), attempted to fill this gap by advocating for the use of reactive TDM for anti-TNF medications, as well as for proactive TDM in certain scenarios.¹

Biologic concentration targets and pharmacokinetics

Many exposure-response relationship studies have shown that higher biologic concentrations are associated with better therapeutic outcomes for IBD patients during both induction and remission.¹ The desirable thresholds vary depending on different therapeutic outcomes being investigated (i.e., clinical, biochemical, endoscopic, or histological remission) with higher concentrations typically being associated with more stringent endpoints.¹ The preponderance of data centers around anti-TNF medications, specifically infliximab and adalimumab. For example, the prospective PANTS study found that infliximab concentrations of $>7 \mu\text{g/mL}$ and adalimumab concentrations of $>12 \mu\text{g/mL}$ were associated with remission at weeks 14 and 54.² Features of high disease burden such as severe acute

UC and fistulizing (perianal) CD likely require even higher thresholds.³

There is significant inter- and intra-individual variability in the pharmacokinetics of biologic medications, particularly for anti-TNF medications. Patient-related covariates that are associated with increased clearance include male sex, increased body weight, immunogenicity, and increased inflammatory burden. Immunogenicity is increased in the absence of concomitant immunosuppressive medications, intravenous administration of drugs (versus subcutaneous), genetic factors (HLA-DQA1*05 carriage) and, most importantly, for anti-TNF medications (vs other biologics).^{4,5} The concept of increased inflammatory load can be defined by severe active disease clinically, biochemically (increased C-reactive protein or fecal calprotectin [FCP] and decreased albumin) or endoscopically and is particularly important in the proactive TDM setting.

Reactive TDM

Reactive TDM is completed in the context of biologic PNR, partial response or loss of response (LOR) to treatment to provide guidance for drug optimization. If the drug concentration is inadequate in the absence anti-drug antibodies (ADA), dose optimization is needed, whereas, if the drug concentration is high or with the presence of high ADA, biologic switching is needed (**Figure 1**).⁶ Yanai et al demonstrated that in patients with LOR infliximab concentrations of $>3.8 \mu\text{g}/\mu$, and adalimumab concentrations of $>4.5 \mu\text{g/mL}$ were suggestive of treatment failure and that switching biologic class may be beneficial.⁷ Kelly et al demonstrated that using reactive TDM to guide infliximab dose optimization was superior to empirical dose optimization in terms of achieving endoscopic remission and cost-effectiveness.⁸ When performing reactive TDM to guide clinical decisions, it is important to ensure that the drug concentration is optimized before discontinuing the first biologic. Several studies show subsequent inferior response to a second-line biologic, hence for LOR in both infliximab and adalimumab, discontinuation should not be considered until a drug of at least $10\text{--}20 \mu\text{g/mL}$ is achieved.^{1,9} In the absence of high-quality data, this range is set higher than the standard infliximab concentration target ($5\text{--}10 \mu\text{g/mL}$) or the adalimumab concentration target ($> 8\text{--}12 \mu\text{g/mL}$), primarily to

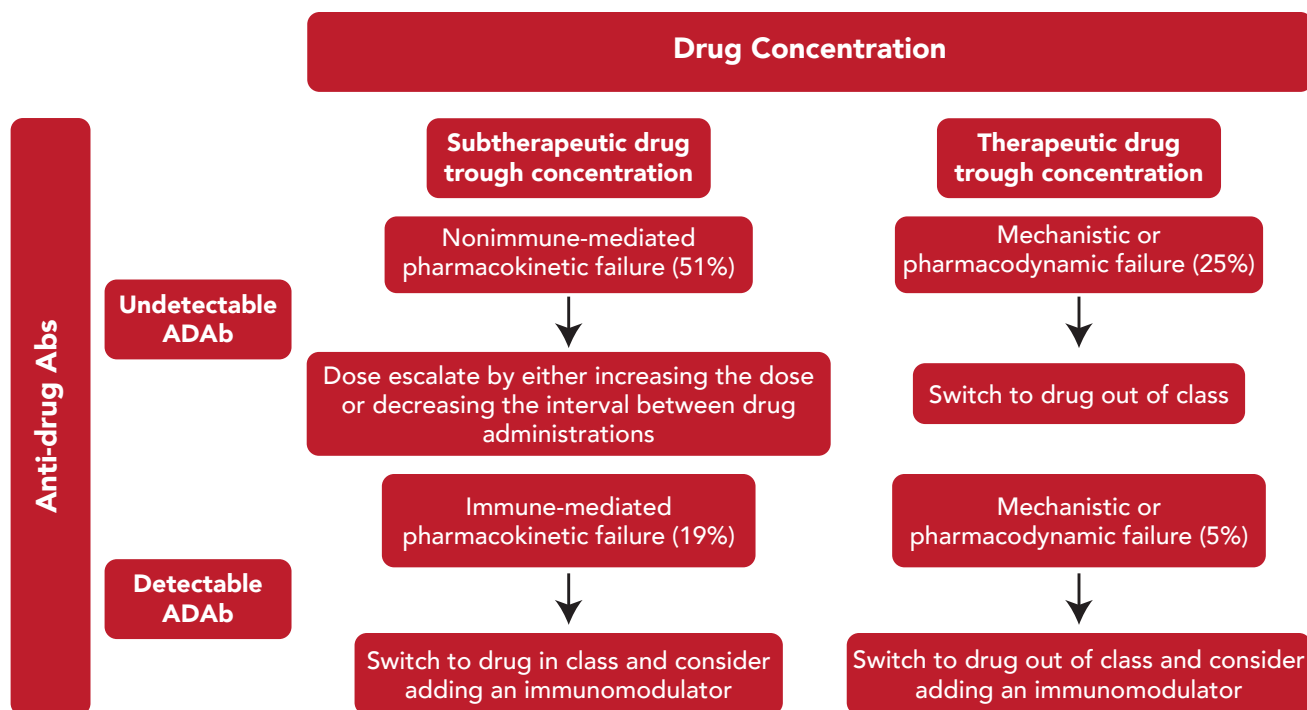


Figure 1. Therapeutic drug monitoring at secondary LOR (Vande Casteele N, et al. Gastroenterology 2017); adapted from Vande Casteele N, et al. Gastroenterology 2017

avoid unnecessary withdrawal of the biologic.¹ Most recommendations and guidelines are in favour of using reactive TDM in PNR and LOR to anti-TNF biologics.^{3,10}

Although most of the current evidence on reactive TDM is based on anti-TNF biologics, there is a definite exposure-outcome relationship that has been observed both clinically and endoscopically with non-anti-TNF medications. Higher serum concentrations of vedolizumab and ustekinumab are associated with better therapeutic response but the rates of immunogenicity are significantly lower, which may obviate the need for TDM for these non-anti-TNF medications.²³ In summary, there is little data to support routine clinical use of reactive TDM with these medications in the setting of LOR.^{11,12}

Proactive TDM

The role of proactive TDM is to enhance response rates and prevent treatment failure by determining whether the biologic dose is optimized during induction and maintenance therapy. Although this is theoretically logical, the data from multiple randomized control trials (RCTs) has been mixed. The PAILOT RCT study comparing the response to adalimumab induction between the reactive and proactive TDM groups, in children with luminal Crohn's disease, showed that the latter group had higher steroid-free clinical remission rates at week 72 (46% vs 82%, $p < 0.001$).¹³

Multiple other RCTs have failed to show a benefit of proactive TDM, although there were methodological concerns with these studies. The TAXIT (Trough Level Adapted Infliximab Treatment) study was a one-year RCT that did not show superiority of TDM based dosing over routine clinical management in achieving clinical remission, but it was associated with fewer flares over the course of treatment.¹⁵ Importantly, all patients were dose optimized to 3-7 µg/ml prior to initiation into the study, which could explain the lack of benefit for maintenance TDM based dosing. The TAILORIX (Tailored Treatment With Infliximab for Active Crohn's Disease) trial was another one year RCT found that proactive trough-level-based dose intensification was not superior to dose intensification based on symptoms alone.¹⁶ Long delays in treatment optimization and the inability to achieve adequate trough concentrations in 50% of the proactive group could again explain the lack of benefit with proactive TDM in this study. A recent meta-analysis of nine studies ($n = 1405$ patients) by Nguyen et al failed to show a benefit of proactive TDM to avoid treatment failure with anti-TNF therapy.¹⁴

Recommendations made for routine use of proactive TDM by various medical societies have been vague due to insufficient data (Table 1). There is no data on the use of proactive TDM with non-anti-TNF medications. Given the conflicting data, a more nuanced approach is recommended, rather than proactive TDM for all anti-TNF medications.

Consensus /Guidelines		Recommendations
	Reactive TDM	Proactive TDM
The American Gastroenterological Association (AGA) 2017 ⁷	Recommended for active IBD patients on anti-TNFs	Not recommended for patients on anti-TNFs with quiescent disease
AJG consensus 2021 ¹	Recommended for all biologics	Strong recommendations were made for performing proactive TDM for patients on anti-TNFs.
British guidelines 2019 ²⁵	Recommends incorporation of TDM conjunctively to aid decision to alter treatment (either dose or drug change)	Measurement of drug level and ADA in all IBD patients 2-4 weeks post induction, as good practice recommendation
European Crohn's and Colitis Organization (ECCO) 2020 ²⁶	Insufficient evidence to support the use of TDM for LOR in CD patients	Insufficient evidence to support the use of TDM for CD patients on anti-TNF in remission
Australian guidelines ²⁷	Recommended in patients in clinical remission following anti-TNF therapy induction	Inconsistent evidence. TDM should be performed for patients in stable remission only if results are likely to impact clinical management.

Table 1. Recommendations on TDM by various expert groups; courtesy of Waqqas Afif, MD and Arti Woncha-um, MD

Proactive TDM should be considered during or post-induction in patients with high inflammatory burden to avoid low drug concentrations and increased immunogenicity. In addition, proactive TDM for the pediatric population may be more important given patient/dosing heterogeneity. During maintenance therapy, a tiered approach of proactive monitoring of inflammatory activity (FCP) is recommended, followed by TDM in those patients with active inflammation (an early reactive approach during monitoring).¹⁹ Proactive TDM should also be considered in the setting of biologic dose de-escalation or withdrawal of immunosuppressive medications in patients on combination therapy. Lucidarme et al showed that the use of trough levels to guide infliximab dose de-escalation (with a concentration of $>7 \mu\text{g/mL}$) was associated with a reduced risk of relapse compared to clinical guidance alone.²⁰ Withdrawal of immunosuppressive medications has been shown to decrease infliximab trough concentrations by approximately $2 \mu\text{g/mL}$ over the course of two years, indicating that patients with borderline trough concentrations should be optimized prior to withdrawal.²¹ In addition, optimizing anti-TNF monotherapy through proactive TDM may obviate the need for concomitant immunosuppressive therapy.²²

Future of TDM

Reactive and proactive TDM measures drug trough and ADA concentrations and informs only two components of an individual's multi-factorial pharmacokinetic (PK) interactions and are prone to

lag between testing and dose adjustment. In recent years, a dashboard software-guided dosing system (**Figure 2**) has been developed to determine an individual's precise target trough level, incorporating TDM with population PK data, individual factors (such as sex and weight) and other clinical parameters (such as serum albumin and C-reactive protein).²⁴ The PRECISION trial demonstrated higher rates of sustained clinical remission after 1 year (88% vs 64%, $p=0.017$), as well as lower median fecal calprotectin levels in the precision group ($p=0.031$), when using the Bayesian dashboard software system compared to standard dosing.²⁰ A greater understanding of how the drug PK varies during the treatment cycle may also feed into the development of the dashboard system by considering TDM testing at different points of the dosing cycle, allowing more opportunities to perform TDM-based dose adjustment by finding the optimal point in time to measure the drug level other than at the trough (i.e., trough vs peak, induction vs post-induction).^{1,24} Other areas to consider as part of the future development of the dashboard system include: genetics, where carriers of HLA-DQA1*05 are more likely to develop ADA; mode of drug administration (subcutaneous vs intravenous); and new technology for TDM point-of-care home testing, which will allow more rapid decision-making.²⁴ TDM represents a small part of the dashboard, but moving towards a more personalized approach it will still play an important role in the foreseeable future with anti-TNF medications.

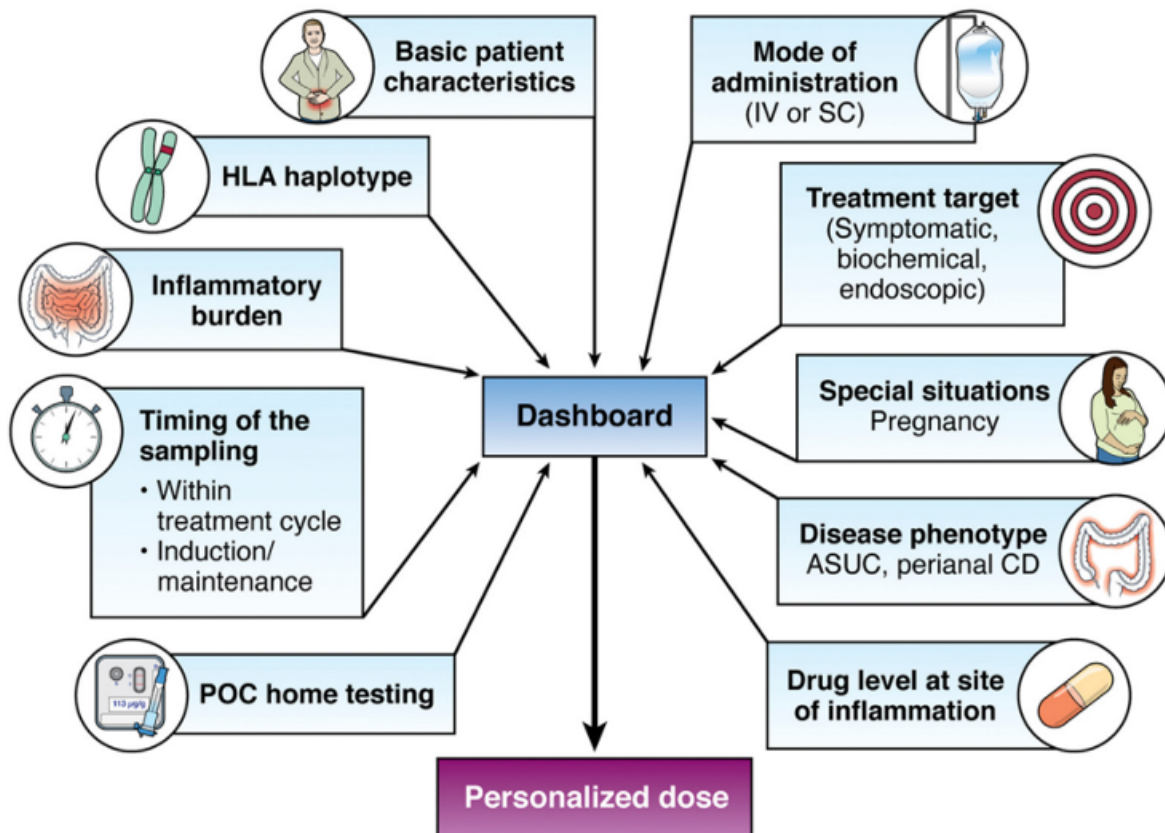


Figure 2. Personalized dosing in IBD (image from Irving et al, Gastroenterology 2022).

Correspondence:

Dr. Waqqas Afif
Email: Waqqas.afif@mcgill.ca

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MAY Y. CHOI

MD, MPH, FRCPC



Dr. May Choi is a rheumatologist and clinician scientist who started on faculty as an Assistant Professor at the Cumming School of Medicine, University of Calgary in 2020, and is a Member of the McCaig Institute for Bone and Joint Health. As an early career investigator, her research is focused on biomarker discovery and validation for prediction of clinical outcomes in autoimmune rheumatic diseases, and the prevention of autoimmune disease development and disease-related complications. She leads a research laboratory and biobank for local, national, and international collaborators. Her background and training include a Masters of Public Health in Epidemiology at Harvard University and a lupus fellowship at the Brigham and Women's Hospital (Boston, MA) under the supervision of Dr. Karen Costenbader (epidemiologist, lupus expert and Professor of Medicine at Harvard Medical School). Dr. Choi is also the Associate Director of MitogenDx Laboratory for novel autoantibody and biomarker testing for autoimmune diseases and the Associate Director of Research for the University of Calgary Lupus Centre of Excellence, which complement her research.

Affiliations:

Cumming School of Medicine, University of Calgary

DIANNE MOSHER

MD



Dr. Mosher is the Associate Dean of Indigenous, Local and Global Health and Professor of Medicine at the Cumming School of Medicine, University of Calgary. She is the past president of the Canadian Rheumatology Association and the Arthritis Alliance of Canada. She has over 30 years of clinical experience in Rheumatology with expertise in spondyloarthritis and Indigenous Health. Her research area of interest is in clinical outcomes, models of care and system level change.

Affiliations:

Cumming School of Medicine, University of Calgary

APPROACH TO MANAGEMENT OF INFLAMMATORY BOWEL DISEASE-RELATED ARTHRITIS

Introduction

The most common extraintestinal manifestation of inflammatory bowel disease (IBD) is arthropathy. These conditions have been reported in up to 50% of patients with IBD and are more common in Crohn's disease (CD), particularly colonic disease, and in females.¹⁻⁶

IBD-associated arthritis is classified as a type of spondyloarthritis (SpA). The treatment is dependent on the type of SpA involvement, which can be subdivided into peripheral and/or axial disease.^{7,8} The treatment approach consists of a combination of non-pharmacological and pharmacological therapies managed by a multidisciplinary team and is based on collaborative decisions between gastroenterology and rheumatology. In light of rapidly expanding therapeutic armamentaria for both immune-mediated arthritis and IBD, this paper will provide an overview of an approach to the treatment of arthritis associated with IBD, considering recommendations by recent guidelines^{1,9-11} and novel therapies.

Investigations

Peripheral arthropathies

Peripheral involvement in IBD includes type 1 and 2 peripheral arthritis, arthralgias, dactylitis, and enthesitis. Classification criteria for peripheral SpA based on the Assessment of SpondyloArthritis International Society (ASAS) include arthritis and/or enthesitis and/or dactylitis, plus (A) one or more of the following parameters: psoriasis, IBD, preceding infection, human leucocyte antigen [HLA]-B27, uveitis, sacroiliitis on imaging, or (B) two or more other parameters: arthritis, enthesitis, dactylitis, inflammatory back pain in the past, family history of SpA.⁸ Concomitant IBD as a SpA feature with any peripheral arthropathy is sufficient for peripheral SpA classification.

Two types of peripheral arthritis in SpA have been identified based on articular involvement and natural history.¹² Type 1 arthritis (pauciarticular) is characterized by involvement of fewer than five joints, primarily in the large weight-bearing joints of the lower limb. These are usually acute and self-limiting (less than ten weeks) without permanent joint damage and tend to correlate with IBD activity. Type 2 (polyarticular) affects more than five joints, predominantly in joints of the upper limbs and is usually in a symmetrical distribution. These typically last for months or years and are independent of IBD flares. Diagnosis of peripheral arthritis is based on clinical examination and may be supplemented by imaging and blood tests (e.g., inflammatory markers) to exclude other forms of arthritis such as psoriatic arthritis (PsA), rheumatoid arthritis (RA), osteoarthritis, and other connective tissue diseases and causes of arthralgias. Unlike PsA and RA, for instance, peripheral arthritis in IBD patients is generally non-erosive; in this case, imaging may be helpful.

Enthesitis describes inflammation at the insertion of a tendon to bone, which can lead to erosions and bone proliferation (spur formation). Symptoms include pain, tenderness and swelling at the site. Enthesitis has a prevalence that ranges from 7%-50% in IBD.²⁻⁶ It is often underdiagnosed on physical examination. Ultrasound has greater sensitivity as a diagnostic tool for enthesitis.¹³

Dactylitis is inflammation of the entire digit including soft tissue thickening, soft tissue edema, flexor tendon tenosynovitis, and joint synovitis. In addition to the clinical examination, it can be detected on MRI and ultrasonography. It has a prevalence of 2%-4% in individuals with IBD.^{4,12}

Axial arthropathies

Sacroiliitis detected on plain radiographs has been reported in 2%-68% of patients with IBD.¹⁴ However, in isolation, it is not diagnostic of axial SpA. According to the 2009 ASAS classification criteria for axial SpA, in patients <45 years of age with at least three months of back pain, sacroiliitis on imaging must be combined with at least one other SpA feature: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, IBD; favourable response to NSAIDs, family history of SpA; HLA-B27; and elevated C-Reactive protein (CRP).⁷ Patients with non-radiographic sacroiliitis (no radiological evidence but can be detected on magnetic resonance imaging (MRI) can also be classified with axial SpA if they are HLA-B27 positive with at least two other SpA features. An MRI with T1-weighted spin-echo [T1SE], short tau inversion recovery [STIR], and fat-saturated T2-weighted sequences is recommended. According to the European Crohn's and Colitis Organisation (ECCO) First European Evidence-based Consensus on Extra-intestinal Manifestations in IBD guideline, imaging in patients with inflammatory back pain is recommended, with the exclusion of patients who are HLA-B27-positive.¹ Only 25%-75% of patients with IBD-related axial SpA are HLA-B27 positive^{2,4,15} vs 90% of patients with idiopathic ankylosing spondylitis (AS). In patients with AS, clinically evident IBD has been observed in 6%-14%^{16,17} of patients; asymptomatic small bowel inflammation is found in up to 60% of patients with AS.^{18,19}

Treatment of Peripheral Spondyloarthropathies

Non-steroidal anti-inflammatory drugs (NSAIDs) and conventional non-biologic disease modifying anti-rheumatic drugs (DMARDs)

Effective treatment of the underlying IBD is frequently sufficient to control peripheral arthritis without additional therapy. As the arthritis associated with IBD is generally non-erosive, the treatment objective is symptom control. The choice of therapy should be made collaboratively in consultation with the rheumatologist and gastroenterologist.

Following optimizing therapy of active IBD, in the presence of ongoing joint symptoms, a short course of NSAIDs is recommended. Although it has been generally thought that NSAIDs are contraindicated in IBD patients due to their potential adverse effects on disease activity,²⁰ recent clinical studies,²¹ including a systematic review and meta-analysis of 18 studies did not find a consistent association between NSAIDs use and risk of CD and ulcerative colitis (UC) exacerbation.²² In one large cohort study, patients

receiving low-dose NSAIDs (aspirin ≤ 325 mg/day; ibuprofen ≤ 200 mg/day; naproxen < 220 mg/day; or prescription NSAID used less than daily) did not have an increase in disease activity. Conversely, high-dose NSAID resulted in higher disease activity in CD patients with colonic involvement.²³ However, it is important to note that the clinical studies reviewed in the meta-analysis were observational. Therefore, the cautious use of short courses of NSAIDs with careful monitoring of IBD activity is reasonable.²³ In the presence of new or worsened symptoms of active bowel disease following the initiation of a NSAID, the NSAID should be discontinued.

In patients who cannot tolerate or are resistant to NSAIDs, a trial of a DMARD can be initiated. Methotrexate typically is used either in oral or subcutaneous form and is maximized to 25 mg weekly for the treatment of peripheral arthritis. Methotrexate frequently is used in low dose with an anti-TNF (tumor necrosis factor) agent to decrease drug resistance. A trial of sulfasalazine may also be initiated for peripheral arthritis.

Biologic agents or targeted synthetic disease modifying DMARDs

In patients resistant to NSAIDs and non-biologic DMARDs, a TNF-alpha inhibitor should be initiated (**Figure 1**). Infliximab, adalimumab, golimumab, or certolizumab pegol can be used. Etanercept is used less often as it is ineffective for the treatment of bowel disease. The decision to initiate or change biologic therapy should be collaborative between the rheumatologist and gastroenterologist.

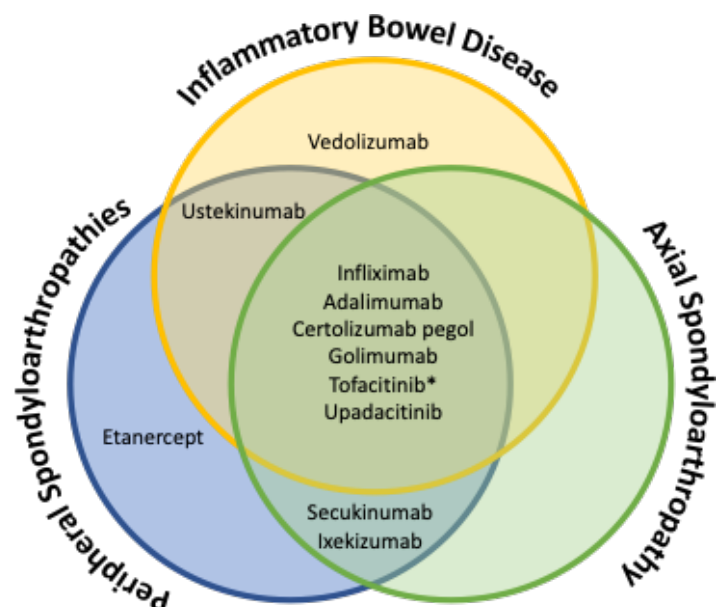


Figure 1. Biologic agents and targeted synthetic DMARDs used in IBD and SpAs. *Tofacitinib is not effective for Crohn's disease.

If a patient has tried more than one anti-TNF, alternatives include an interleukin (IL) 12/23 inhibitor (ustekinumab) and the Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib). While none of the clinical trials for these IBD therapies directly evaluated their effect on IBD-related peripheral arthritis, they are viable treatment options as they have been proven effective for other SpAs. Ustekinumab currently is indicated for both CD and PsA. Tofacitinib and upadacitinib are effective therapies for both IBD and SpA including AS, PsA and RA. Conversely, in a post hoc analysis of vedolizumab trials in patients with IBD, some patients demonstrate improvement in arthralgia/arthritis, possibly related to better control of gut inflammation.²⁴

Short courses of systemic corticosteroids can be used to bridge therapy for patients who require rapid relief until the DMARD takes effect. Local steroid joint injections can also be utilized if a small number of joints are affected.

Enthesitis and dactylitis

Treatment of enthesitis and dactylitis is similar to that of axial arthritis in SpA. A trial of NSAIDs is the recommended initial therapeutic agent. Conventional non-biologic DMARDs are ineffective. Local peritendinous glucocorticoid injections may be beneficial, although they are associated with an increased risk of tendon rupture at the Achilles, patellar and quadriceps tendons; therefore, these locations should be avoided. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 recommendations state that local glucocorticoid injections may be considered for dactylitis.¹¹ Since the publication of these guidelines, additional therapies have become available, and injections should be considered only if other therapies have failed or are contraindicated.

For patients who are unresponsive to the NSAIDs or corticosteroid injections, biologic DMARDs are effective. Based on limited evidence,²⁵ an anti-TNF such as infliximab, golimumab or certolizumab may be initiated. Evidence from PsA clinical studies has demonstrated that enthesitis can be treated with other therapies that are effective in IBD as well. These include, tofacitinib and upadacitinib. Infliximab, certolizumab, ustekinumab, tofacitinib, and upadacitinib have been proven beneficial for dactylitis in patients with PsA.²⁶

Treatment of Axial Spondyloarthropathies

The treatment of axial SpA in IBD is similar to that for idiopathic forms of axial SpA. Recent guidelines

on the treatment of AS and non-radiographic axial SpA have been published. These include the 2019 edition by the American College of Rheumatology (ACR)/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network (SPARTAN)⁹ and the 2016 update of the Assessment of SpondyloArthritis international Society (ASAS)-European League Against Rheumatism (EULAR) management recommendations for axial SpA.¹⁰ Canadian guidelines are expected to be released in the near future.

Non-pharmacological therapies

Back exercises are a cornerstone of AS treatment to improve or maintain spinal and thoracic flexibility and posture. A recent Cochrane review of 14 randomized controlled trials with 1,579 participants with AS demonstrated some evidence to suggest that exercise programs slightly improve function, reduce pain and decrease global patient assessment of disease activity, when compared with no intervention.²⁷ Specifically, the 2019 ACR Guidelines recommend land-based over aquatic physical therapy interventions.⁹

Non-biologic DMARDs

For patients with IBD and axial SpA with controlled IBD and mild axial disease, a trial of NSAIDs may be considered. The 2019 ACR guidelines do not recommend any specific NSAID to decrease IBD symptoms.⁹ For patients with axial disease who are intolerant or resistant to NSAIDs, there is no evidence to support the use of sulfasalazine or any other non-biologic conventional DMARD such as methotrexate, as the next line of therapy. If patients do not have prominent peripheral arthritis, these medications are not effective in controlling axial inflammation. The use of systemic corticosteroids is also strongly not recommended.

Biologic agents or targeted DMARDs

Anti-TNFs (e.g., infliximab, adalimumab, certolizumab pegol, and golimumab) (**Figure 1**) are the standard first-line biologic agents as they control axial disease, IBD and other extraintestinal manifestations of IBD. The choice of treatment should be a collaboration between the rheumatologist and the gastroenterologist as there are multiple factors to take into consideration. The 2019 ACR Guidelines conditionally recommend treatment of radiographic or non-radiographic axial SpA with an anti-TNF over treatment with other biologics.⁹ Again, it should be noted that the exception in this context is etanercept as, although it can be used to treat axial disease, it

is not an effective treatment for IBD. Furthermore, while the monoclonal anti-IL-17A antibody therapies secukinumab and ixekizumab are recommended in idiopathic AS, they are not only ineffective in IBD, but have been associated with flares of new or pre-existing IBD following initiation. In patients resistant to or unable to take anti-TNF agents, tofacitinib and upadacitinib^{28, 29} may be tried as they are effective therapies for both UC and AS. Upadacitinib is effective for CD. Ustekinumab and IL-23 inhibitors are not recommended due to their lack of effectiveness in axial SpA, as demonstrated in three placebo-controlled clinical trials.³⁰

Combination biologic therapies

The use of combination therapy for IBD may be considered in difficult-to-control cases or in the presence of extra-articular features, predominately seen in arthritis. There are no efficacy or safety trials of combination therapy, only case series and case reports. The most frequently-used combination therapy for IBD and SpA is vedolizumab or ustekinumab with an anti-TNF agent. No serious safety signals have been reported in the case reports to date.³¹ There is little evidence to support the use of tofacitinib and upadacitinib in combination with other biologics. Although clinical studies have demonstrated the efficacy of tofacitinib in axial SpA, it is not approved for this indication in Canada.

Conclusion

The management of IBD-associated arthritis has improved in the past two decades with the introduction of biologic and targeted synthetic DMARDs. Future research to increase practitioners' understanding of the disease pathogenesis of IBD-associated arthritis will lead to a broader choice of therapies for both immune-mediated arthritis and IBD, and an eventual cure.

Correspondence:

Dr. May Choi

Email: may.choi@ucalgary.ca

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STEPHANIE L. GOLD

MD



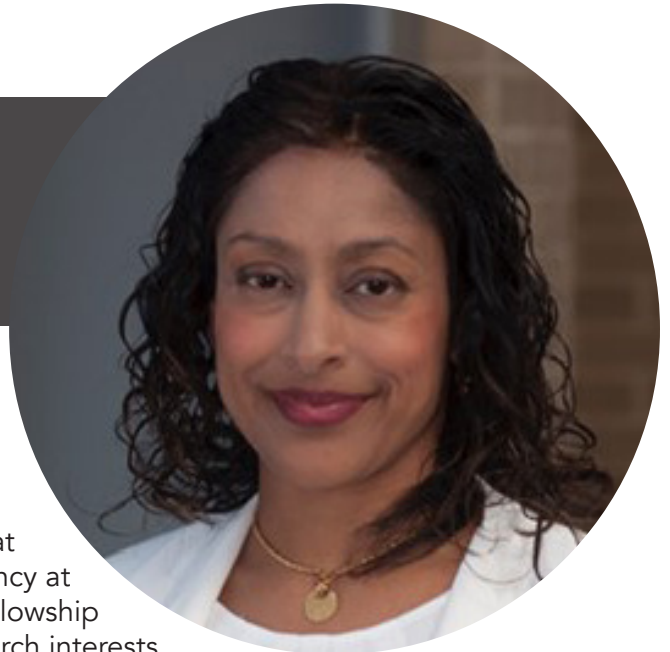
Stephanie L. Gold, MD is an Instructor of Medicine at the Icahn School of Medicine at Mount Sinai and a gastroenterologist at the Mount Sinai Hospital, with a focus on inflammatory bowel disease (IBD) and nutrition. Dr. Gold's clinical interests include nutrition optimization for patients with IBD and the use of diet as an adjunct therapy. She established a unique Nutrition-IBD clinic where patients have access to an in-depth nutrition and muscle health assessment as well as dietary guidance and support to complement their IBD care. Her research interests include improving the identification of malnutrition, micronutrient deficiencies and sarcopenia in patients with IBD.

Affiliations:

The Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

MAITREYI RAMAN

MD, MSc, FRCPC



Dr. Maitreyi Raman is a Gastroenterologist and Physician Nutrition Specialist, Clinical Associate Professor in the Department of Medicine and Division of Gastroenterology at the University of Calgary. She completed medical school at the University of Ottawa, and then Internal Medicine Residency at Dalhousie University, and subsequently a clinical nutrition fellowship at the University of Toronto. Dr. Raman has clinical and research interests in lifestyle as primary therapy for patients with digestive diseases. She investigates using dietary patterns and components in the management of digestive health disorders, and investigates the role of diet to modulate the gut microbiome and chronic inflammation in Inflammatory Bowel Diseases and Irritable Bowel Syndrome. In addition, Dr. Raman explores the role of the brain-gut axis through mind body interventions, and its impact on chronic disease outcomes.

Affiliations:

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

Malnutrition Assessment in Patients with Inflammatory Bowel Disease

Introduction

Inflammatory bowel disease (IBD) affects over 6.8 million people worldwide and is highly associated with the development of malnutrition.¹ Malnutrition in patients with Crohn's disease (CD) and ulcerative colitis (UC) is often due to the following: decreased oral intake; food avoidance; side effects of medications; malabsorption; chronic enteric losses; altered anatomy from luminal surgery; and increased nutritional needs in the setting of active inflammation and a high catabolic state.^{2,3} Approximately 20%-80% of patients with IBD are estimated to be malnourished at some point during their disease course; this wide range is likely secondary to significant heterogeneity in the definition of malnutrition in the literature, and due to the lack of robust, validated tools to identify individuals who are malnourished.⁴ While malnutrition is traditionally thought of as under-nutrition or protein calorie malnutrition, there are other nutrition phenotypes of significance in patients with IBD including micronutrient deficiencies, sarcopenia and obesity (over-nutrition).^{4,5} Malnutrition is

associated with poor outcomes in patients with IBD, including a high number of disease flares; impaired response to biologics; increased surgical complications; hospitalizations; and impaired quality of life, independent of disease activity.^{3,6,7} Given the significant prevalence of malnutrition, the impact it can have in patients with IBD, and its responsiveness to therapeutic interventions, it is crucial to accurately assess the nutritional status of patients at the time of diagnosis and regularly thereafter.

Malnutrition risk assessment and diagnostic tools

Malnutrition screening is a rapid, non-invasive technique to assess patients for nutritional risk that can be completed by any member of the clinical team in order to determine which patients are at increased risk of becoming malnourished and would therefore benefit from a referral to a dietitian. There are numerous questionnaire-based malnutrition risk assessment tools available, the majority of which were developed for the general population, and two that were designed specifically for patients with IBD. While there

is no “gold standard” or universally accepted malnutrition screening or diagnostic tool, the Malnutrition Universal Screening Tool (MUST) has been validated in an IBD cohort and is commonly used clinically and in nutrition studies. The MUST takes into account body mass index (BMI), recent unintentional weight loss and an acute illness evaluation.⁸ Of interest, the MUST can be completed by either the provider or the patient and can usually deliver similar results, increasing the ease of use in a busy clinical setting. Although the MUST was designed for use in the geriatric population, it has been used in several IBD nutrition studies in both the outpatient and hospital setting with non-geriatric patients.^{4,9-11} Additionally, two nutrition screening tools were designed specifically for patients with IBD: the Malnutrition Inflammatory Risk Tool (MIRT) and the Saskatchewan IBD Nutrition Risk Tool (SaskIBD-NR). These tools include disease specific features including gastrointestinal symptoms, as well as markers of systemic inflammation; however, to date, neither tool has been adopted for routine use.⁴

Traditionally, malnutrition is diagnosed utilizing criteria from the European (ESPEN) and American (ASPEN) nutritional societies, as well as the Subjective Global Assessment (SGA).¹²⁻¹⁴ Similar to the MUST, the SGA can be completed by the provider or patient, and studies have shown that the patient reported SGA has a high sensitivity for identifying malnutrition risk.⁸ The malnutrition diagnostic tools are generally more comprehensive than the screening tools mentioned above; however, the ESPEN, ASPEN and SGA were similarly designed for use in the general population and they are weighted towards low BMI and unintentional weight loss. However, patients with IBD can be malnourished despite a normal or elevated BMI and therefore these tools may lead to an underestimate of malnutrition in this unique patient population.^{15,16} Given this, the Global Leadership Initiative on Malnutrition (GLIM) published a novel set of criteria for identifying malnutrition that is more comprehensive than the ESPEN or ASPEN criteria.¹⁷ The GLIM includes etiologic criteria for malnutrition such as weight loss, BMI and reduced muscle mass as well as phenotypic criteria such as reduced

intake, inflammation and malabsorption.¹⁷ Although the GLIM has been studied in surgical IBD patients, there is no data on its use with IBD patients in an outpatient setting. Despite this, the nutrition research community is advocating for universal acceptance of the GLIM to provide a standardized and comprehensive tool that includes a broad definition of malnutrition and considers both inflammation and malabsorption.

Micronutrient assessment

Micronutrient deficiencies are commonly seen in patients with protein calorie malnutrition; however, these deficiencies can similarly occur in patients who are well nourished. In fact, in Western countries, the diets are often rich in energy and low in nutrients, resulting in “hidden hunger” or isolated micronutrient deficiencies.¹⁸ Traditionally, deficiencies in vitamin B12, vitamin D, folate and iron are commonly associated with CD; however, deficiencies in other vitamins and minerals can contribute to significant symptoms and complications.⁵ For example, in patients with large volume diarrhea or high output ileostomies, it is important to test for zinc and magnesium deficiencies, as these can lead to worsening of diarrhea, muscle weakness and poor appetite.^{5,19} Moreover, in patients with a history of ileal resection, vitamins B1 and B12, and folate levels should be assessed to prevent neurological complications, fatigue, and paresthesias.¹⁹ Finally, micronutrient deficiencies can occur secondary to specific medication use, such as vitamin B6 deficiency with isoniazid use, fat soluble vitamin loss in those on cholestyramine, and folate deficiency in patients on methotrexate as well as sulfasalazine.^{5,19} While there are many studies evaluating micronutrient deficiencies in those with IBD, there are two excellent review articles which highlight the identification and management of the common and less common deficiencies in IBD patients and these can be a great resource for IBD providers.^{5,19}

Micronutrients are typically assessed in the serum or plasma and these levels are thought to represent a measure of the total body nutrient stores. However, recent clinical studies have demonstrated that many of the nutrients are, in fact, acute phase reactants and therefore serum levels are significantly impacted by

systemic inflammation. In patients with IBD, this can result in inaccurate testing, making it difficult to provide supplementation. Therefore, researchers are looking for other modalities to accurately assess nutrient levels in patients with systemic inflammation, including testing of hair, sweat and even urine. While these micronutrient assessment techniques are only being used in research today, the authors are hopeful for their use in the future.

Sarcopenia assessment

Sarcopenia, a loss of muscle mass or function, is intimately linked to malnutrition and is independently associated with disease complications in patients with IBD. Sarcopenia is traditionally diagnosed utilizing the psoas muscle area or total skeletal muscle area on computerized tomography (CT) or magnetic resonance imaging (MRI) at the level of the third lumbar vertebrae (L3). While this is the gold standard, given the cost of an MRI or CT, the time it takes to obtain a scan and potential radiation exposure, cross-sectional imaging is not used routinely in clinical practice to assess for sarcopenia. Therefore, novel, bedside measures of muscle mass and function have been proposed, including handgrip strength (HGS) evaluation, mid-upper arm circumference (MUAC), and bioelectrical impedance analysis. Studies have demonstrated that HGS and MUAC are significantly lower in patients with active or inactive IBD vs healthy controls and that these metrics are more predictive of nutritional status than BMI in patients with CD.²⁰ While these tools provide a rapid assessment of muscle health, they have yet to be validated in the IBD population and thus are not routinely used.²¹ In the geriatric literature, ultrasound of the thigh and upper extremity muscles has been proposed as an accurate point-of-care modality to measure muscle mass.²² Learnings from geriatrics include the importance of measuring the cross-sectional area of the muscle and the pennation angle, echogenicity and fascicle length.²² Unfortunately, normative values for these muscle metrics are not clearly defined, which limits the use of these techniques to identify sarcopenia at the current time. While albumin has traditionally been associated with malnutrition and sarcopenia, many studies have demonstrated that low albumin is likely a

marker of IBD activity (given its role as an acute phase reactant) and less likely a reliable marker of low muscle mass or function.^{23,24} Future studies evaluating this relationship between albumin as well as total protein with sarcopenia and identifying novel serum markers associated with sarcopenia will be helpful in advancing this field. Looking forward, with the discovery of these easy-to-use, inexpensive and non-invasive muscle assessment modalities and defined normative values in a healthy population, it is hoped that sarcopenia evaluation will become more ubiquitous for those with IBD.

Conclusion and Practical Implementation of Nutrition Screening and Assessment in IBD

Although there is still a great deal to discover about malnutrition evaluation in patients with IBD, it is important to highlight a few practical guidelines for clinical care today. First, all patients with IBD should be screened for malnutrition at the time of diagnosis and regularly thereafter utilizing the MUST or SaskIBD-NR.^{4,8} Patients identified as being moderate or high risk for malnutrition should undergo further evaluation (micronutrient testing, as well as muscle health evaluation) and be referred to a registered dietitian with experience managing patients with IBD. Second, all patients should be weighed at every clinic visit, as this is a crucial “vital sign” to assess for malnutrition risk. With the shift toward telemedicine, it is important to ask patients about their weight when they are not seen in the clinic and to schedule routine in-person visits in order to obtain an accurate objective weight, and to establish a trend for these values longitudinally. To establish a diagnosis of malnutrition, the GLIM offers a comprehensive strategy that includes malabsorption and reduced oral intake, as well, as markers of muscle health, in addition to the more traditional measures of BMI and unintentional weight loss. However, the abridged SGA can be successfully completed by the patient (unlike the GLIM which requires a provider) and therefore may be a valuable tool to identify malnutrition in a busy clinic practice. Finally, regardless of disease activity and malnutrition risk, micronutrient levels should be measured at the time of diagnosis and at routine follow-up visits. While vitamin D, vitamin B12 and iron

deficiencies are commonly seen in IBD patients, it is important to consider zinc, vitamin B1, vitamin A, folate, and vitamin C deficiencies as well.⁵ In addition to the above, it is crucial to ask all patients with IBD about dietary avoidances, restrictions and patterns of eating, as these can help identify patients on highly restrictive diets.

Conclusion:

Malnutrition is a common complication in patients with IBD and is associated with poor outcomes independent of disease activity. Thorough malnutrition screening at the time of diagnosis and routinely thereafter of all patients with IBD, utilizing available screening and diagnostic tools as well as micronutrient assessments and dietary pattern evaluations are crucial to identify those at risk for developing IBD and nutrition related disease complications.

Correspondence:

Dr. Maitreyi Raman
Email Mkothand@ucalgary.ca

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None

Screening Item		Points
BMI	>20	0
	18.5-20	1
	<18.5	2
Weight Loss (3 months) %	<5	0
	10-May	2
	≥10	3
CRP (mg/)	<5	0
	5-50	2
	≥50	3

Table 1: Malnutrition Inflammation Risk Tool

Screening Item		Score
Have you experienced nausea, vomiting, diarrhea or poor appetite for greater than two weeks?	No symptoms	0
	1-2 symptoms	1
	≥3 symptoms	2
Have you lost weight in the last month without trying?	No	0
	Yes	2
	Unsure	1
If YES (you have lost weight in the last month without trying), how much weight have you lost?	<5 lbs	0
	5-10 lbs	1
	10-15 lbs	2
	>15 lbs	3
Have you been eating poorly because of a decreased appetite?	No	0
	Yes	2
Have you been restricting any foods or food groups?	No	0
	Yes	2

Table 2: Saskatchewan IBD Nutrition Risk Tool (SaskIBD-NR)

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