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BRINGING STRIDE2 TO LIFE IN CLINICAL PRACTICE

STRIDE2 – A Narrative Review

STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease [IBD]) is an initiative by the International Organisation for the Study of IBD that aims to delineate a core set of therapeutic targets for IBD based on literature review and expert consensus. The first iteration was published in 2015,¹ with an update in 2021 (STRIDE2),² which qualifies targets as short-, intermediate- or long-term and adds pediatric-specific targets.

The goal of treating any disease is to allow patients to feel well and to enjoy good quality of life (QOL), while avoiding disease- and treatment-related complications. The inflammatory bowel diseases, Crohn's disease (CD) and ulcerative colitis (UC), are no exception. Given this overarching objective, it is not surprising that the traditional target in treating IBD has been symptom resolution, while avoiding corticosteroids. The challenge is that symptom control neither guarantees the absence of intestinal inflammation in a cross-sectional fashion, nor prevents progression to "damage" (including, for example, fibrosis, strictures and fistulae). This does not imply that symptom alleviation is irrelevant; it is a necessary, but insufficient treatment target. STRIDE2 includes clinical response (immediate/short-term) and clinical remission (intermediate) as treatment targets, but the method of symptom assessment has shifted from the physician (physician-administered clinical activity indices) to the patient (patient-reported outcomes [PROs]),³ aligning with

the FDA's requirement for PROs as a co-primary endpoint in clinical drug trials (typically alongside an objective disease marker such as endoscopy). STRIDE2 also introduces restoration of QOL and disability avoidance as key treatment goals. This further highlights the importance of the patient experience, and acknowledges normal linear growth as a critical pediatric-specific clinical target.

IBD Treatment Targets

If not symptom control, what constitutes a sufficient IBD treatment target? The optimal target should satisfy several criteria; it should be 1) causally linked with improved long-term outcomes; 2) rooted in disease biology (i.e., biologically relevant); 3) measurable (feasibly, reliably and accurately); and 4) attainable with currently available therapies (although an argument can be made for "aspirational" targets that are not yet attainable). It is the advent of biological therapies, starting with the tumour necrosis factor- α (TNF) antagonist, infliximab, that raised the therapeutic efficacy ceiling and, in so doing, brought targets beyond symptom control into the realm of possibility.

Criteria #1 above (causal link between target and improved outcomes) warrants discussion. Numerous observational studies have demonstrated an *association* between deep remission and superior outcomes; invariably, the deeper the healing (histologic remission⁴ or even molecular remission⁵ > endoscopic remission⁶ > clinical remission), the better the outcome. Such studies should not be misconstrued as

evidence that treating to a given endpoint *causes* the better outcome. Causality can only be definitively established by randomized controlled trials in which a treat-to-target (T2T) intervention (treatment escalation based on failure to meet prespecified targets) is compared to a reference standard. The CALM trial, for example, showed that CD patients who were treatment escalated to weekly adalimumab ± azathioprine based on C-reactive protein (CRP) ≥5 and/or fecal calprotectin (FCP) ≥250 µg/g experienced higher rates of mucosal healing at one year.⁷

Consistent with the evidence generated by CALM, STRIDE2 introduces CRP normalization and FCP reduction to an “acceptable” level as formal intermediate treatment targets (previously adjunct targets in STRIDE1). A thorough discussion of these biomarkers is beyond the scope of this review, but it is important to recognize their imperfect accuracy for intestinal inflammation, with FCP being more sensitive, and CRP more specific.⁸ The concept of cut-offs is challenging, particularly for FCP as the relationship between inflammation severity/extent and FCP is not linear. Moreover, although progressively lower FCP values are generally associated with progressively deeper healing, there is significant overlap in cut-offs for each level of healing. Recognizing these limitations, STRIDE2 recommends FCP reduction to the 100-250 µg/g range.

At its core, IBD is a disease of dysregulated intestinal immune response and intestinal inflammation. Moreover, it is this unchecked intestinal inflammation that directly leads to the disease’s complications. By extension, resolution of the macroscopic manifestations of intestinal inflammation (i.e., endoscopic healing [EH]) would appear the most intuitive and biologically relevant treatment target. It is perhaps surprising, therefore, that the STARDUST trial, a T2T RCT in which CD patients not achieving a predefined endpoint including endoscopic improvement were escalated to ustekinumab every four weeks, did not meet its primary outcome.⁹ Whether this relates to the more refractory nature of the patient cohort (biologic/conventional treatment failures), or possibly the limited escalation options, is unclear. While we await additional high-quality data to confidently ascertain if treating to an endoscopic endpoint leads to superior outcomes, STRIDE2 has retained EH as a long-term treatment target. Acknowledging that there is no consensus definition for EH, STRIDE2 proposes an SES-CD¹⁰ score ≤2 or absence of ulcers for CD, and a Mayo endoscopic score of 0 or UCEIS¹¹ score ≤1 for UC.

Arriving at a consensus definition for EH (and other targets as well) is particularly challenging due to the lack of data on the incremental gain associated with each deeper level of healing, and the counterbalancing costs/risks associated with the “extra” treatment needed to achieve it. This includes monetary terms (at a patient and societal level); adverse effects (e.g., increased immune suppression, risk of malignancy); and inconvenience (e.g., needing to take more medication). Is a UCEIS 0 a “better” target than a UCEIS 1? Without data characterizing the precise benefits

and risks of pursuing a UCEIS 0 over 1, with corresponding numbers needed to treat and numbers needed to harm, this question cannot be clearly answered.

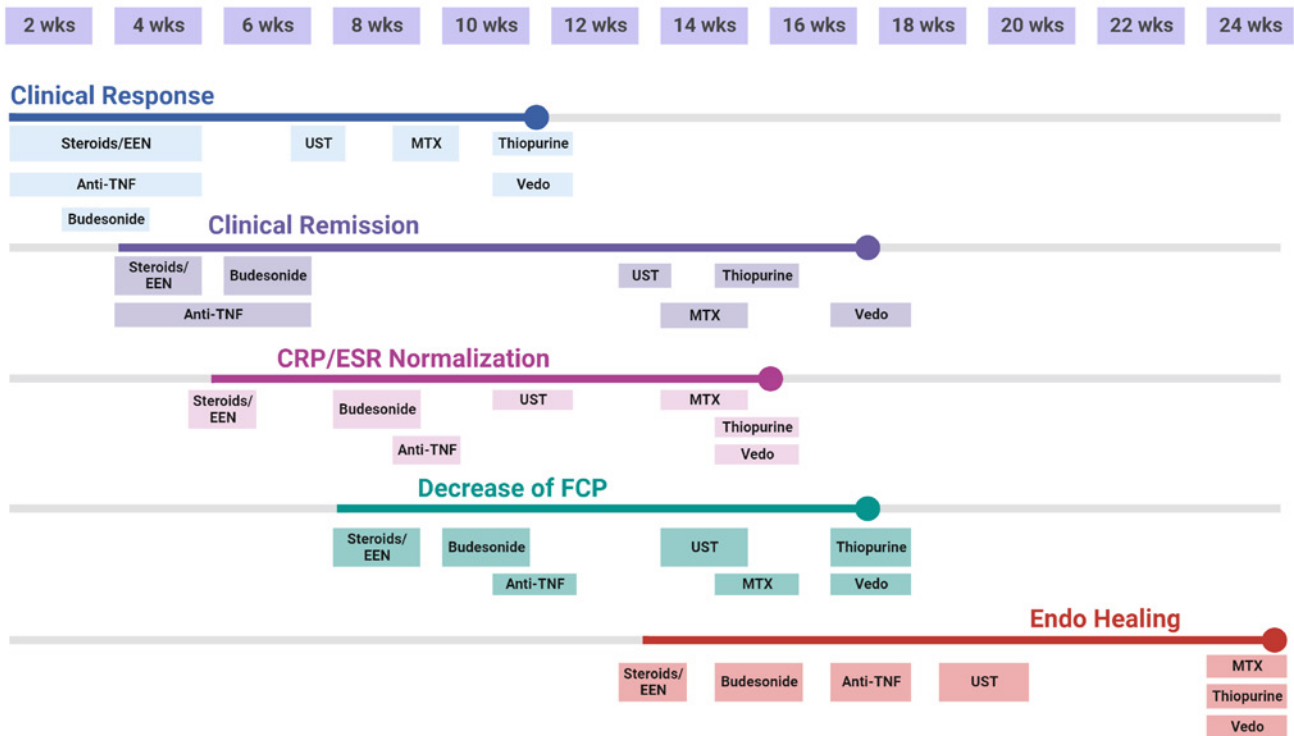
Bringing STRIDE2 to Life

To summarize, the STRIDE2 therapeutic targets include short-term clinical response; clinical remission; CRP normalization; FCP 100-250 µg/g (intermediate); EH; normal growth; and QOL without long-term disability. Even equipped with today’s armamentarium of biologics and small molecules, these are demanding targets, achievable in some, but certainly not all (and likely not most) patients. To modify treatment every time one of these targets is not achieved, blind to contextual factors, is ill-advised and would lead to rapid drug cycling and exhaustion of all available therapies in many patients.

In translating STRIDE2 to clinical practice, one must first consider the element of time. It would be nonsensical, for example, to assess for EH one month after initiating azathioprine given its prolonged time to effect. In other words, the reassessments that comprise the “tight monitoring” of STRIDE’s T2T paradigm must be adapted to both the endpoint and mechanism of action of the treatment in question. To assist with this, STRIDE2 presents the average time to its various targets for several commonly used medications (summarized in **Figure 1**). This provides an approximate framework/time for disease reassessment.

Ascertaining failure to meet a therapeutic target is easy enough; the decisions that ensue, however, are often highly complex and must consider several factors according to a shared decision-making process between physician and patient. The factors at play are summarized in **Figure 2** and include: 1) current disease severity (i.e., how far off target the patient is, clinically, biochemically and endoscopically), 2) the likelihood and severity of complications if no steps are taken (for example, the potential consequences of stricturing ileal CD are quite different from those of stricturing rectal CD); 3) the patient’s disease history, including treatments tried and response (proof of refractoriness); 4) therapies that remain to be tried and the likelihood that one or more of these will be more effective than previous therapies; and 5) patient values and preferences. The patient scenarios in **Figure 3** illustrate the process of working through these factors. In scenario A, the decision to treatment-escalate is obvious, with all factors weighing heavily in that direction. In scenario B, at first glance, the markedly elevated FCP and ongoing endoscopic disease would appear to mandate a treatment change; however, when one considers the other factors listed, the decision becomes less clear. In this scenario, the patient currently feels better than at any point previously in her disease course. She has previously proven to be refractory to several therapies and there is no compelling reason to believe a different biologic or small molecule will be more effective than her current combination adalimumab plus immunomodulator. The practical reality is that the more refractory the patient, the higher the bar (the sicker he/she needs to be) in considering abandonment of the current treatment.

Time to Target After Treatment Start Crohn's Disease (A)



Time to Target After Treatment Start Ulcerative Colitis (B)

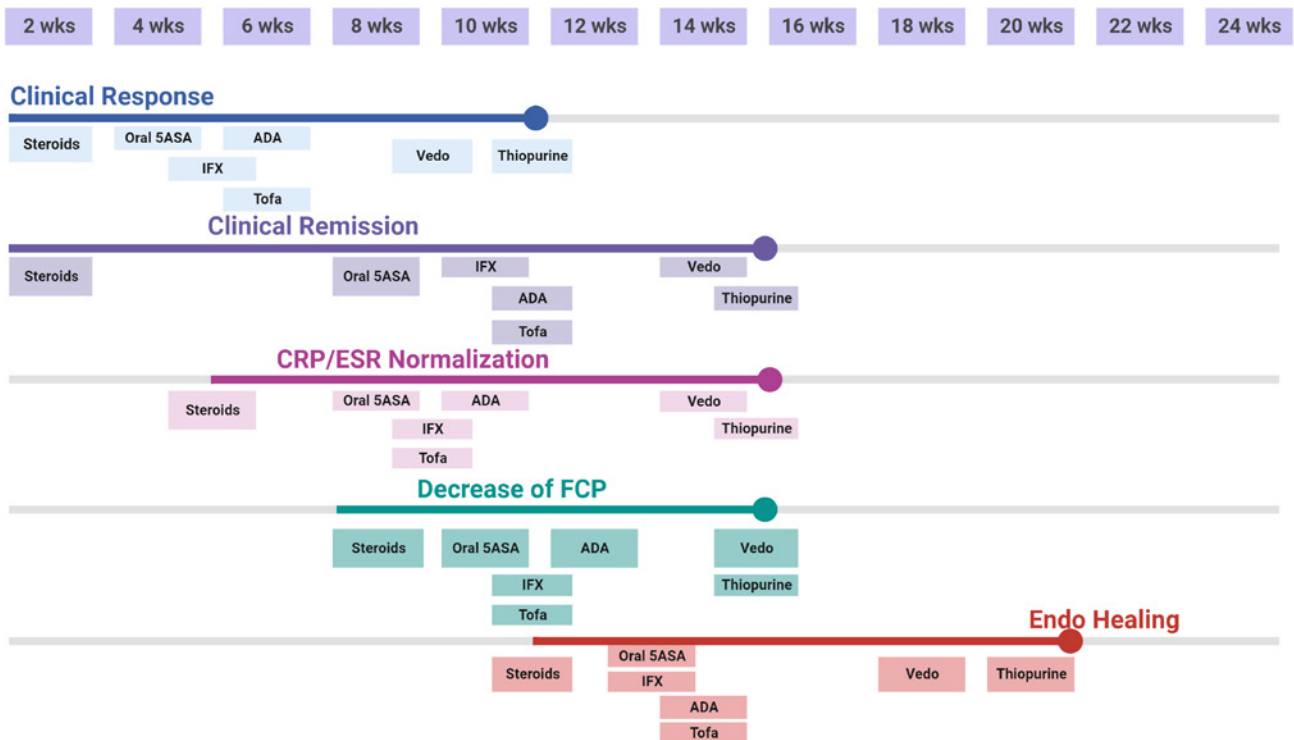


Figure 1. Mean number of weeks to achieve various treatment targets with commonly utilized therapies, based on Table 4 from STRIDE2² – CD (A), UC (B); Created with BioRender.com
5ASA – 5-aminosalicylic acid; EEN – exclusive enteral nutrition; MTX – methotrexate; TNF – tumour necrosis factor; UST – ustekinumab

Factors Informing Decision to Change IBD Treatment Approach when Therapeutic Target Not Met

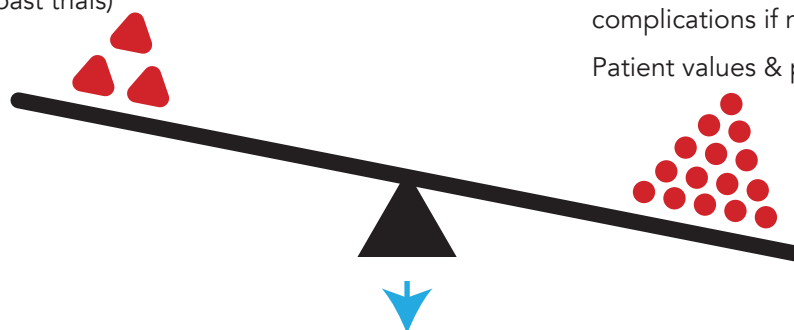
Therapies tried/failed
(refractoriness)

Available therapies
(and "confidence" they will be more
successful than past trials)

Disease severity, including objective
markers, symptoms, QOL
(How far "off target" is the patient?
How intolerable is the current state?)

Likelihood and seriousness of
complications if no changes made

Patient values & preferences



Option A - Carry on with Same Treatment

Option B - Change Treatment

Figure 2. Factors informing decision to modify treatment when therapeutic target not met; Created with BioRender.com
QOL – quality of life

Scenario A

40 yo M, pancolitis UC

- Current: severely clinically active, Mayo 3 on flex sig, 6 months on optimized oral + PR 5ASA
- Past Rx history: successful oral corticosteroid induction prior to %ASA; nil else tried
- Current state is unacceptable to patient and MD
- Risk of "doing nothing" is serious and high (perforation, emergent, colectomy)
- Patient has tried few therapies, there are several other options that are statistically more likely to be more effective (e.g., anti-TNF, vedo)



Favours change

Favours no change

Change

Scenario B

17 yo F, ileal CD x 20 cm

- Current: 2 y on ADA 40 mg weekly (drug level 30 + concomitant MTX, sustained clinical remission, great QOL, normal CRP, growing well)
- BUT FCP persistently up (1500 ug/u), SES-CD 6 (9 at Dx), early stenotic changes on MRE (unchanged over 2 y)
- Past Rx history: previous corticosteroid dependence, failed thiopurine and UST
- Patient is off target (FCP, endo)
- Risk of "doing nothing" is progression to frank structuring and/or penetrating disease requiring surgery
- There are other agents to try
- Several targets achieved (clinical, CRP)
- Risk of "doing nothing" is likely manageable with limited ileal resectional targets achieved (clinical, CRP)
- Patient has proven herself refractory, no compelling evidence next treatment will be better, it may be less effective
- Patient is moving out soon for college, does not want to "rock the boat" and risk what she feels is her current state of "good health" (she understands there is a risk of needing surgery over time and is okay with this)



Favours change

Favours no change

No Change*

*Optimize if room to optimize

Figure 3. Patient scenarios illustrating factors to consider in deciding whether or not to modify IBD treatment when therapeutic targets are not met, in a shared decision-making process between physician and patient; Created with BioRender.com
5ASA – 5-aminosalicylic acid; ADA – adalimumab; CD – Crohn's disease; CRP – C-reactive protein; Dx – diagnosis; FCP – fecal calprotectin; MTX – methotrexate; QOL – quality of life; Rx – treatment; SES-CD – simple endoscopic score for CD; TDM – therapeutic drug monitoring; TNF – tumour necrosis factor; UC – ulcerative colitis; UST – ustekinumab

In scenario B, the treatment regimen was purposefully presented as “optimized” (adequate anti-TNF level, combination immunomodulator) to make it more challenging. However, this underlines the concepts of optimization and “add-ons,” and that not all treatment changes need to involve completely abandoning the current therapy in place of a new therapy. This is particularly the case for the patient who has shown some response to a treatment but has not ticked all the STRIDE2 checkboxes. There are numerous options for optimization/add-ons, including but not limited to: ensuring compliance; ensuring adequate drug exposure (through proper dosing, therapeutic drug monitoring if available) with dose escalation if indicated; adding rectal 5ASA to the oral route in the UC patient; adding oral 5ASA to the UC patient who has not previously had a 5ASA trial (as in the corticosteroid refractory acute severe UC patient who receives infliximab upfront); adding an immunomodulator to a biologic (for its inherent efficacy and/or role in decreasing immunogenicity); and the addition of dietary interventions (e.g., CD exclusion diet), as well as combination biologics. The latter may become increasingly more commonplace as it is generally thought that combination therapy may be required to break through the therapeutic efficacy ceiling that has emerged in IBD. Finally, surgery should not be conceptualized as the end result of having failed all medical options, but rather as a treatment option in its own right for both CD and UC, at various timepoints, potentially even early in the disease course.

Conclusions and Future Directions

STRIDE is founded on the educated guess that actively treating toward its suggested targets will enhance a patient’s likelihood of experiencing a favourable disease course, and uses as its starting point the idealized notion that achieving these targets is feasible. These targets are based on the “best” currently available data and, as such, provide important guidance to the practicing IBD specialist. However, there are practical realities that need to be considered in translating STRIDE2 to real life and important knowledge gaps that remain to be addressed. One of the most critical of these is the lack of biomarkers to aid with predicting individual patient response to specific therapies in order to enable a personalized approach to positioning therapies. It remains likely that there is a finite window of time within which effective therapy has the potential to alter the natural history of IBD and it is therefore imperative to initiate treatment with the agent(s) most likely to be effective, while representing a sensible balance between benefits and risks for the disease severity in question. The advent of such biomarkers will power a shift from our current trial-and-error approach to a precision medicine approach, which will allow the T2T paradigm endorsed by STRIDE to achieve its full potential.

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PRACTICAL APPROACH TO ABNORMAL LIVER ENZYMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Introduction

Inflammatory Bowel Diseases (IBD) are chronic inflammatory conditions that can impact organ systems beyond the gastrointestinal tract. Extraintestinal manifestations (EIMs) of IBDs are common and can occur at any stage of the disease.¹ While EIMS most commonly involve the musculoskeletal system, up to 35% of individuals with IBD exhibit hepatobiliary involvement at some point during the course of their disease, often independently of disease activity.² Chronic hepatobiliary diseases are noted in 5% of patients with IBD.³ These diseases manifest with indicative symptoms, abnormal liver biochemistry tests, or radiological abnormalities. This review provides a comprehensive outline and approach to abnormal liver enzymes in individuals with IBD.

Approach to Liver Dysfunction in individuals with IBD

Liver biochemical tests are widely utilized to help diagnose and monitor liver damage or disease. These tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). ALT and AST are enzymes found throughout the body, including hepatocytes. Elevated levels of ALT and AST can be indicative of hepatocellular injury. ALP is an enzyme found in the intestine, bone, placenta, and liver. The hepatic origin of ALP is confirmed by elevated levels of GGT, which is indicative of cholestatic injury.⁴ Calculating the R-factor, defined as $(ALT \div \text{Upper Limit of Normal [ULN] ALT}) / (ALP \div \text{ULN ALP})$ with cutoff values defined in **Table 1**, can help determine the nature of the injury: hepatocellular, cholestatic, or mixed.⁵ Common causes of chronically abnormal liver enzymes are illustrated in **Figure 1**.⁴

R Factor		
<2	2-5	>5
Cholestatic	Mixed	Hepatocellular

Table 1. R Factor Thresholds; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD”

The liver performs vital functions including producing certain products such as glucose, proteins (including albumin and coagulation factors), and fat, detoxifying blood (medications, drugs, pathogens), storing glycogen, handling bilirubin, regulating circulation, and converting thyroid hormones. Abnormalities in the liver’s vital functions are referred to as liver synthetic dysfunction. When assessing liver abnormalities in patients with IBD, it is important to consider the type of enzyme elevation, duration (acute [< 6 months] or chronic), timing (flare, surgery, new medication, or routine follow-up), presence of synthetic dysfunction (jaundice, coagulopathy,

encephalopathy), and degree of hepatic fibrosis. Assessing fibrosis can be achieved with non-invasive tools such as the Fibrosis-4 (Fib 4) score calculated using $(\text{Age} \times \text{AST}) / (\text{Platelets} \times \sqrt{\text{ALT}})$ defined in **Table 2** and elastography in outpatients without acute hepatic injury.⁶ All patients with elevated liver enzymes (ELEs) should

Fibrosis 4 Score (Fib-4)				
Significant Fibrosis Excluded	1.3*	Indeterminate	3.25	Advanced Fibrosis

Table 2. Fibrosis 4 (Fib-4) Score Thresholds ; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD
* <2.0 in patients > 60 years old

undergo repeat testing.⁵ Initial assessment should review risk factors for viral diseases, metabolic syndrome, toxins, including drugs, medications, alcohol, and natural products, as well as associated systemic, auto immune, or genetic diseases. Subsequent evaluation will depend on the pattern of the ELE and evidence of synthetic dysfunction.⁵ Initial evaluation and management of patients with hepatocellular injury is outlined in **Figure 2** and cholestatic injury in **Figure 3**.⁵ In patients with IBD, most ELEs are transient and unrelated to IBD activity.^{7,8} Risk factors for ELEs include elevated body mass index, advanced age, and longer disease duration.^{7,8} ELEs hold prognostic significance in IBD, with an age-adjusted risk of death 4.8 times higher in patients with persistent ELEs.⁷

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease in the general population, is equally prominent among patients with IBD. A meta-analysis was conducted to examine the prevalence of NAFLD among 7,640 patients with IBD. The findings indicated a prevalence of NAFLD among patients with IBD of 32% compared with 25.2% in the general population.⁹ The study went on to report that advanced hepatic fibrosis was seen in 10.3% of patients with IBD.⁹ In addition, obesity, diabetes, older age, prior surgical interventions for IBD, and longer disease duration were found to be important risk factors for NAFLD in this population.⁹ Exposure to certain hepatotoxic drugs, such as methotrexate and biologics, can alter the body’s metabolic state and increase the risk of NAFLD.^{9,10}

NAFLD is largely asymptomatic and is commonly identified incidentally in patients with IBD, although abnormal liver enzymes or decompensated cirrhosis may be present. Similar to IBD, NAFLD is associated with changes in the gut microbiome.^{9,10} Underlying inflammatory and surgical changes observed in IBD can also disrupt bile acid metabolism in the ileum, leading to decreased levels of

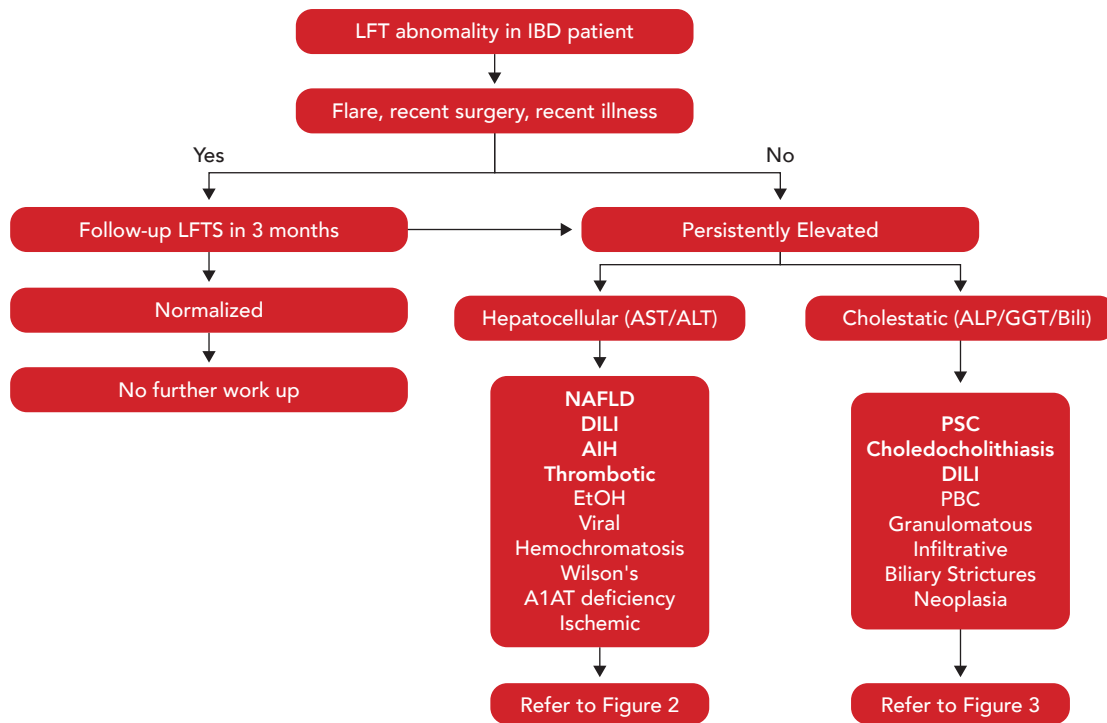


Figure 1. Simplified Approach to Liver Enzyme Abnormalities in IBD (Inflammatory Bowel Disease) Patients; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD

A1AT: Alpha-1-antitrypsin, AIH: Autoimmune hepatitis, ALP: Alkaline Phosphatase, ALT: Alanine Transaminase, AST: Aspartate aminotransferase, DILI: Drug Induced Liver Injury, EtOH: Alcohol, GGT: Gamma-Glutamyl Transferase, NAFLD: Non-alcoholic Fatty Liver Disease, PBC: Primary Biliary Cholangitis, PSC: Primary Sclerosing Cholangitis. Adapted from 2017 AGA guidelines.

circulating fibroblast growth factor 19 (FGF 19), an important factor in lipid metabolism.^{9,11} In those identified incidentally, the first step is to obtain liver biochemistry tests, exclude co-contributing diseases, and establish the degree of hepatic fibrosis non-invasively using the Fib-4 or the NAFLD fibrosis score.¹² In patients with suspected significant hepatic fibrosis, confirmation by elastography and referral to hepatology should be considered. First line treatment for NAFLD is centred around diet, exercise, weight loss, and gaining control of metabolic co-morbidities.¹³ Screening becomes increasingly important because these patients are more likely to have concurrent extrahepatic disease, such as cardiovascular disease, emphasizing the importance of early identification and intervention.¹⁴

Primary Sclerosing Cholangitis

A systematic review that included 776,700 patients with IBD found the prevalence of primary sclerosing cholangitis (PSC) to be 2.16%, with a higher prevalence among individuals with ulcerative colitis (UC) than in those with Crohn's disease (CD) (OR 1.69, 95% CI 1.24-2.29).¹⁵ The prevalence of PSC may be underestimated among patients with IBD, as demonstrated by a study that assessed 322 patients who were screened with magnetic resonance cholangiopancreatography (MRCP), and found a prevalence of 7.5%.¹⁶ Conversely, studies have reported that 23-77% of patients with PSC have concomitant IBD.^{17,18} PSC is closely linked to disease severity. Patients with extensive UC were six times and patients with ileocolonic CD were four times more likely to develop PSC than their ileal counterparts.¹⁵ Moreover, a recent meta-analysis demonstrated a four-fold

increase in colon cancer amongst patients with PSC and UC compared to those with UC alone.¹⁹ The diagnosis of PSC is based on the presence of characteristic features such as biliary strictures, "beads on a string" appearance on MRCP, and exclusion of secondary causes.¹⁸ Histological confirmation is only necessary when small-duct PSC, with normal MRCP, is suspected.¹⁸ Patients can be asymptomatic or can experience fatigue, jaundice, pruritus, and even decompensated cirrhosis. There is no clear explanation for the relationship between PSC and IBD, though 3 candidate genes, *REL*, *IL2* and *CARD9*, are associated with both UC and PSC. Emerging research highlights the influential role of gut microbiota in the pathogenesis of PSC.²⁰ Treatment options for PSC remain limited. In addition, the efficacy of ursodiol (ursodeoxycholic acid) therapy remains uncertain. Liver transplantation is considered for those with decompensated cirrhosis or recurrent cholangitis, with a reported 5-year relapse rate of 20%.²¹ Given the strong association between PSC and malignancies, patients with PSC and IBD should undergo annual colonoscopy and abdominal imaging every 6 to 12 months, ideally with MRI Liver/MRCP, for surveillance of hepatobiliary malignancies.¹⁸

Autoimmune hepatitis

Patients with autoimmune hepatitis (AIH) and concurrent IBD demonstrate distinct characteristics, including younger age at onset, refractoriness to AIH treatment, higher rates of liver transplantation, and increased mortality.²² The diagnosis of AIH is based on evidence of hepatocellular injury, elevated IgG, positive results of serological markers, exclusion of other causes of ELEs, compatible histological abnormalities,

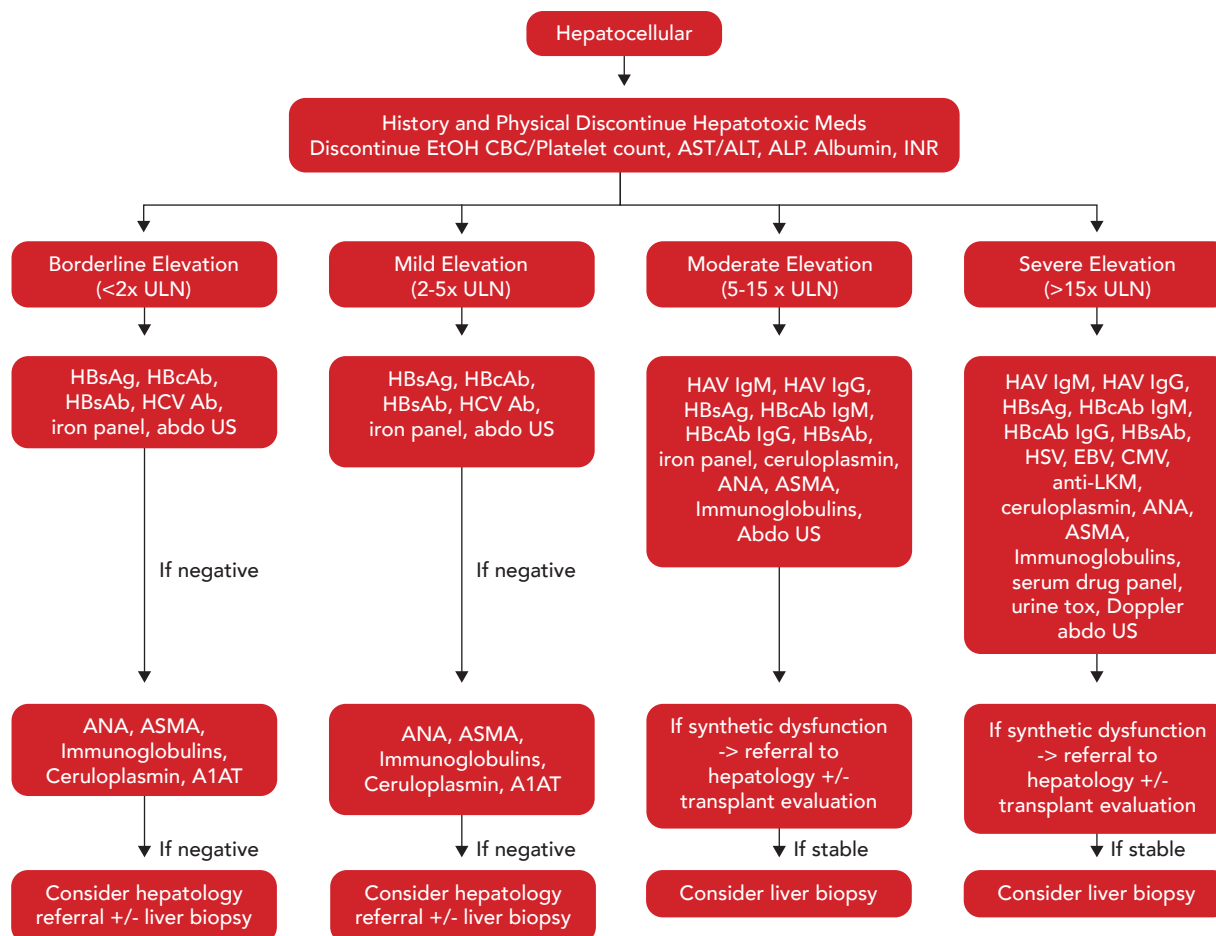


Figure 2. Approach to Patients with Hepatocellular Injury: Adapted from 2017 AGA guidelines⁵

A1AT: Alpha-1-antitrypsin, ALT: Alanine Transaminase, AMA: Antimitochondrial antibody, ANA: Antinuclear antibody, anti-LKM: anti-Liver-Kidney Microsomal, ASMA: Anti-smooth muscle antibody, AST: Aspartate aminotransferase, CMV: Cytomegalovirus, EBV: Epstein Barr Virus, EtOH: Alcohol, HAV: Hepatitis A Virus, HBcAb: Hepatitis B core antibody, HBsAb: Hepatitis B surface antibody, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C Virus, HSV: Herpes Simplex Virus, ULN: Upper Limit of Normal US: Ultrasound.

and response to therapy using validated scoring systems.^{23,24} Patients with AIH can experience a range of liver disease presentations, from asymptomatic hepatocellular injury to fulminant liver failure or decompensated cirrhosis. Overlap with AIH-PSC should be suspected in patients with AIH and pruritus, cholestatic injury, and typical bile duct abnormalities on imaging. Although no clear mechanism has been established, current evidence points to a key role for the composition of the gut microbiome in the inflammation that is seen in both AIH and IBD.^{22,23} Infliximab is also known to cause a specific drug induced liver injury (DILI) that can mimic AIH.²⁵ First line treatment for patients with AIH is glucocorticoids combined with a steroid sparing agent, such as azathioprine.²²

Portal Vein Thrombosis

Patients with IBD are in a hypercoagulable state and are 3.4 times more likely to develop venous thromboembolisms (VTE) than the general population, which further increases to 8.4 times during disease flares.²⁶ While portal vein thrombosis (PVT) is a rare complication of IBD, it is frequently observed in the post-operative period with a prevalence ranging from 39% to 45%.^{27,28} Patients with PVT can be identified incidentally during routine imaging,

or with abdominal pain and even mesenteric ischemia if mesenteric vessels are involved.²⁹ Diagnosis is established using doppler ultrasound or cross-sectional imaging with intravenous contrast. Management takes place in collaboration with thrombosis experts and includes anticoagulation therapy and, if no cause is identified, investigation for underlying thrombophilia and malignancy.³⁰

Cholelithiasis

The relationship of IBD with gallstones is well established. In a systematic review and meta-analysis of 53,543 patients with IBD, the prevalence of cholelithiasis was 2.16% compared with 0.78% in the general population.³¹ Further subgroup analysis revealed a prevalence of cholelithiasis of 1.84% in patients with UC, and 2.89% in patients with CD.³¹ This association is particularly pronounced in patients with CD following ileal resection or with ileal disease, because these conditions disrupt bile reabsorption and lead to the development of cholesterol-supersaturated bile. Another proposed mechanism to account for the presence of cholelithiasis involves the colonization of anaerobic bacteria in the ileum following ileal resection, which impairs mucosal absorption. Additionally, patients with IBD often experience reduced gallbladder motility

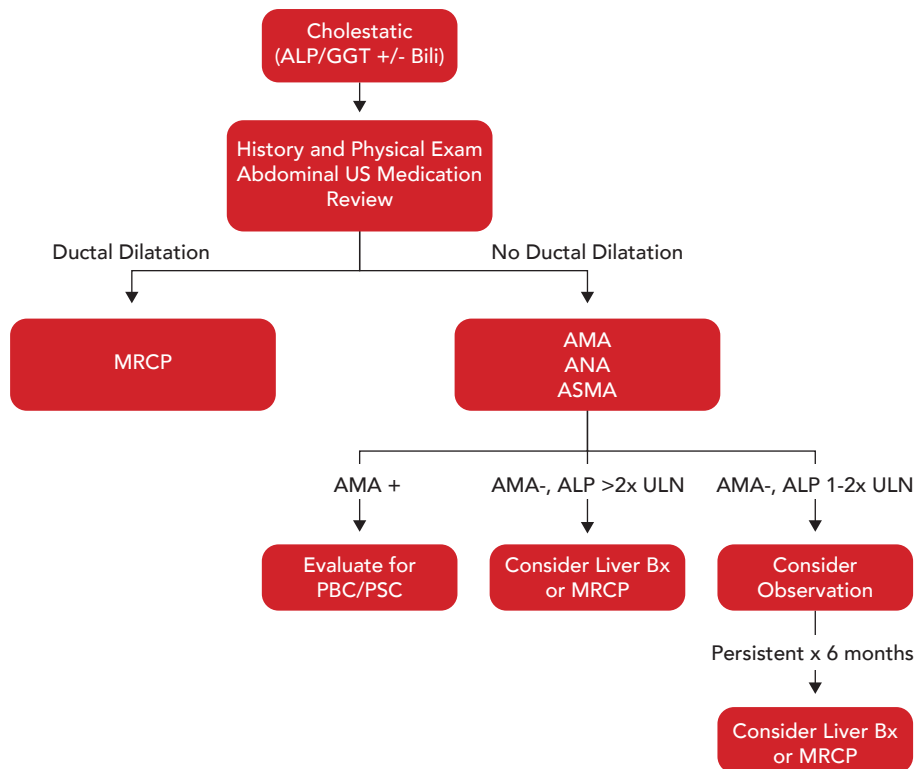


Figure 3. Approach to Patients with chronic Cholestatic Liver Enzymes: Adapted from 2017 AGA guidelines⁵

ALP: Alkaline Phosphatase, AMA: Antimitochondrial antibody, ANA: Antinuclear antibody, ASMA: Anti-Smooth Antibody, GGT: Gamma-Glutamyl Transferase, MRCP: Magnetic Resonance Cholangiopancreatography, PBC: Primary Biliary Cholangitis, PSC: Primary Sclerosing Cholangitis.

during prolonged fasting states, including total parenteral nutrition.^{32,33} Evaluation with abdominal ultrasound is needed in patients experiencing biliary-type pain, and for those with cholestatic liver injury. Among patients with IBD who develop cholelithiasis, approximately 20% are symptomatic and require surgical intervention.³³

Medication-related hepatotoxicity

Medications used to treat IBD are potentially hepatotoxic and can cause reactivation of viral hepatitis. All patients with IBD should undergo screening for hepatitis B surface antigen (HBsAg), hepatitis B antibody (HBsAb), and hepatitis B core antigen (HBcAg) before initiating treatment with immunosuppression therapies to prevent hepatitis B reactivation (HBVr). Those with negative serology test results should receive vaccination as recommended by the National Advisory Committee on Immunizations (NACI) and Canadian Association for the Study of the Liver (CASL) guidelines.³⁴

Those with HBcAg-positive findings, with or without the presence of HBsAg, should be referred to hepatology for expert opinion. Depending on the serology pattern, antiviral therapy might be required.³⁴⁻³⁶ Screening for hepatitis C antibodies should also be routinely obtained before biologic therapy.³⁷

DILI can occur within days to months and can be seen in hepatocellular, cholestatic or mixed patterns and range from asymptomatic to fulminant liver failure.³⁵ When DILI is suspected, physicians should exclude other potential

aetiologies and withdraw the offending agent. If the agent is not a well-known hepatotoxic medication, physicians may refer to LiverTox, a web-based compendium of DILI.^{38,39} In addition, validated scales such as the Roussel Uclaf Causality Assessment Method (RUCAM) can be used to quantitatively assess causality in suspected cases of DILI.⁴⁰ Commonly used medications in the treatment of IBD and their potential hepatotoxicity are described below.

Thiopurine therapy is a well known cause of DILI, which is reported to occur in 3.7 to 13.3% of patients, with adverse effects ranging from hepatocellular, cholestatic, or mixed hepatitis to vascular endothelial lesions such as nodular regenerative hyperplasia.⁴¹⁻⁴⁴ Thiopurine S-methyltransferase (TPMT) enzyme plays an important role in the metabolism of 6-methyl-mercaptopurine (6-MMP), which has been associated with hepatotoxicity when present at higher levels. ELEs usually occur in the first 3 months of therapy with thiopurines. These ELE are often asymptomatic; thus, liver enzymes should be regularly monitored.³⁵ After the occurrence of ELE, thiopurines can be restarted at a lower dose under close monitoring and after discussion with carefully selected patients.

Treatment with sulfasalazine and its therapeutically active derivative 5-Aminosalicylic Acid (5-ASA) is a rare cause of DILI with an incidence of 3.1 cases per million prescriptions and between 0% and 4% incidence of DILI respectively.^{35,45,46} DILI due to sulfasalazine can be identified as hepatocellular, cholestatic or mixed injury, and

by fever, rash, lymphadenopathy or hepatomegaly. The mechanism is likely related to a hypersensitivity reaction. Patients who experience a DILI to these medications should not be rechallenged.

Methotrexate therapy has well-known hepatotoxic effects. DILI as a result of methotrexate therapy can be identified as hepatocellular injury, which is mild and self-limiting. Chronic use of methotrexate can lead to hepatic steatosis, fibrosis, and cirrhosis. A meta-analysis that included patients with IBD reported an incidence of hepatotoxicity of 0.9 per 100 person-months, with a discontinuation rate of 0.8 per 100 person-months.⁴⁷ Patients treated with methotrexate should be screened every 2 weeks for the first 2 months and every 3 months thereafter.³⁵

The use of anti-TNF inhibitors, especially infliximab, can cause different types of liver injury which are often mild and transient. Infliximab also induces autoantibodies which can remain asymptomatic except in rare instances of a lupus-like syndrome or drug-induced AIH.³⁵ Adalimumab is less commonly associated with hepatotoxicity.³⁵

Biologic agents such as vedolizumab, ustekinumab, and tofacitinib, are uncommon causes of clinically apparent liver injury. ELEs are typically mild and transient. Persistent ELE might require drug discontinuation, though quite rare.^{35,48,49}

Conclusion

ELEs are often seen in patients with IBD at a higher prevalence than in the general population. These liver abnormalities may occur at any stage of their disease and can be either transient or persistent in nature. Being able to identify and diagnose these associations between ELEs and IBD early in their clinical course has important prognostic implications.

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COLORECTAL NEOPLASIA SURVEILLANCE IN INFLAMMATORY BOWEL DISEASE: UPDATES AND PRACTICAL APPROACHES

Background

Performing colorectal neoplasia surveillance in persons with inflammatory bowel disease (IBD) that is both clinically effective and cost effective is among the greatest challenges facing endoscopists who care for this population. While heightened colorectal cancer (CRC) risk has long been recognized among persons with IBD, this risk has been declining over time, with recent reports suggesting no more than a 1.5–2-fold higher risk compared to age and sex matched members of the general population.^{1–4} Nonetheless, given that CRC still occurs at a higher rate in this population, current surveillance strategies are inadequate for some persons. Conversely, 80–90% of persons with IBD had no neoplastic lesions identified during colonoscopy surveillance,⁵ suggesting that many persons with IBD are unnecessarily exposed to the risks of colonoscopy, with society bearing these excess costs.

The purpose of colorectal neoplasia surveillance is to reduce the burden of CRC and CRC-related death in the IBD population. Societal guidelines recommend initiating colorectal neoplasia screening with colonoscopy in all persons with colorectal IBD involving at least the rectosigmoid (or at least 1/3 of the colorectum if accompanied by discontinuous inflammation) at 8–10 years following disease diagnosis and continuing lifelong surveillance every 1–5 years.^{6–8} Major factors influencing surveillance frequency include historical disease severity, extent of colorectal inflammation, chronic post-inflammatory changes, family history of CRC, history of colorectal neoplasm, primary sclerosing cholangitis, prior colonoscopy findings, and adequacy of prior surveillance (**Table 1**).^{6–8} All guidelines further recommend targeted sampling or resection of suspicious visible abnormalities, and some societies continue to recommend extensive non-targeted biopsies to detect

“invisible” neoplasia, particularly if other adjunctive optical modalities, such as dye-spray chromoendoscopy (DCE) or virtual chromoendoscopy (VCE), are not performed, or if the mucosa is poorly visualized, such as in areas of significant inflammation, post-inflammatory polyposis, or poor bowel preparation.^{6,9} Most societies now advocate for DCE or VCE as primary screening tools for IBD neoplasia surveillance or, at a minimum, as alternative modalities to traditional white light colonoscopy with non-targeted biopsies where resources and expertise exists.⁵⁻¹¹

However, there are no prospective studies demonstrating a reduction in the incidence of CRC or of death from CRC with current surveillance strategies in persons with IBD. Furthermore, observations from large retrospective studies are also conflicting.^{12,13} A Cochrane analysis of 3 studies in persons with UC did not find a significant mortality benefit for current surveillance strategies.¹⁴ Considering that IBD afflicts many persons at a young age, is rising in prevalence in Canada and globally,¹⁵ and requires intensive lifelong surveillance, the amount of endoscopy resources directed toward IBD surveillance is potentially enormous. Increasing demands on colonoscopy resources from expansion of population-based CRC screening programs and an aging population are likely to challenge the ability to continue to provide intensive surveillance to all persons with IBD. Optimizing delivery of limited colonoscopy resources will thus be essential to maintain effective CRC prevention programs in this population.

Current standards for neoplasia surveillance in IBD have been recently updated.^{6,7,10} Shah and Itzkowitz authored a comprehensive review that includes epidemiology, pathogenesis, and management of colorectal neoplasia, along with a chart that compares surveillance recommendations put forward by multiple societies.¹⁶ The present review will highlight new evidence influencing neoplasia surveillance and provide practical approaches for surveillance and management of neoplastic lesions in the IBD population.

Recent Data Influencing Neoplasia Surveillance Strategies

1. *Value of Negative Colonoscopy:* In a multi-centre study conducted across centres in North America and Europe that included 775 persons with long-standing IBD colitis without advanced neoplasia risk factors, Ten Hove et al. demonstrated that having 2 consecutive negative colonoscopies predicted a markedly reduced risk of developing high-grade neoplasia or CRC over a median of 6.1 years of follow-up.¹⁷ A negative colonoscopy was defined as a technically adequate procedure with no post-inflammatory polyps, strictures, active disease, or neoplasia. This observation has led to the American Gastroenterological Association advocating that persons with consecutive negative colonoscopies undergo a 5-year surveillance colonoscopy,⁶ in line with recommendations from multiple medical societies for persons without active

endoscopic or histologic inflammation and/or who have limited historical colitis extent.^{6,7}

2. *Importance of Cumulative Inflammatory Burden:* Choi and colleagues from St. Mark's Hospital in the U.K. conducted a retrospective single-centre study that included 987 persons with extensive UC between 2003 and 2012 who underwent surveillance colonoscopy every 1–2 years from 8–10 years after the onset of disease symptoms, which included 7516 colonoscopies and 13884 patient-years of follow-up, with segmental random biopsies and targeted biopsies from suspicious areas.¹⁸ They found that a cumulative inflammatory burden score, based on an average histologic inflammation severity score that included multiple surveillance episodes over several years, was significantly associated with future colorectal neoplasia development (hazard ratio [HR] 2.1 per 10-unit increase in cumulative inflammatory burden, 95% confidence interval [CI] 1.4–3.0).¹⁸ Age at colonoscopy, primary sclerosing cholangitis, colonic stricture, and tubular, featureless, or shortened colon were also predictors of future colorectal neoplasia risk, whereas inflammation severity based on the most recent colonoscopy alone was not. These findings were further validated by Yvellez and colleagues at the University of Chicago.¹⁹ While incorporating these findings accurately into clinical practice requires systematic endoscopic and histologic surveillance, clinicians could incorporate these findings into their decision making regarding timing of surveillance colonoscopy by estimating the historical inflammatory burden in their patient population over the preceding 5–10 years rather than focusing on findings from the most recent colonoscopy.
3. *Personalized Risk Model of Neoplasia Progression* In a multi-centre retrospective cohort of 246 persons with UC, Curtius and colleagues evaluated 17 clinicopathological variables for association with time-to-progression of low-grade dysplasia (LGD) to advanced neoplasia, defined as high grade neoplasia or CRC, among participants with UC who had LGD that was identified during index colonoscopy. They derived a model comprising 4 statistically significant variables: LGD >1 cm (HR 2.7; 95% CI 1.2–5.9), unresectable or incomplete endoscopic resection (HR 3.4; 95% CI 1.6–7.4), moderate/severe histological inflammation within 5 years of LGD diagnosis (HR 3.1; 95% CI 1.5–6.7) and multifocality (HR 2.9; 95% CI 1.3–6.2).²⁰ They went on to validate this model in a retrospective cohort from 3 centres comprising 198 persons with UC and demonstrated excellent discriminatory ability (area under the receiver operating characteristic curve=0.89) and calibration (Observed/Expected of 1.01 [95% CI 0.64–1.52]), and minimal prediction error (Brier score=0.068), for progression to advanced neoplasia over 3 years from the date of LGD diagnosis. While longer term follow-up data and validation in other jurisdictions is required, this group has developed a web-based tool to compute

personalized risk prediction for advanced neoplasia based on their model for use in clinical practice termed UC-CaRE (www.uc-care.uk).

4. **Virtual Chromoendoscopy as a Surveillance Tool:** Pancolonic DCE has shown a benefit over both standard definition and high definition white light endoscopy for the detection of colorectal neoplastic lesions in persons with IBD,²¹ and has been recommended as the preferred modality for colorectal neoplasia surveillance in this setting by multiple societies.⁵⁻¹⁰ Conversely, VCE technologies, including Olympus' narrow-band imaging and Pentax' *iscan*, had failed to show similar benefits in comparison to white light endoscopy for neoplasia detection.²² However, several recent randomized controlled trials have shown that pancolonic narrow band imaging performed similarly to DCE for neoplasia detection in persons with IBD.²²⁻²⁴ Based on these data, several societies now support VCE as an alternate strategy to DCE for colonoscopy surveillance in persons with IBD,^{6,11} especially considering the limitations for adoption of DCE in many centres, including inadequate endoscopist training, cost of supplies, and added procedural time. VCE technologies are now routinely available with easy-to-use "flick of a button" formats that are offered in the latest generation endoscopes and can be readily applied during colonoscopy without additional resources or procedure time. Improved brightness and sophistication of VCE technologies have made them more suitable for routine use. Importantly, both DCE and VCE require meticulous bowel preparation for optimal visibility and neither modality is a substitute for careful inspection for visible abnormalities. Furthermore, DCE remains the preferred strategy to unmask suspicious lesions that are poorly delineated during white light endoscopy.⁶
5. **Serrated Epithelial Change:** While tubular, tubulovillous, and serrated adenomas are well recognized pathological entities in persons with and without IBD, serrated epithelial change (SEC) is a less commonly recognized histologic finding that is most often encountered in nontargeted biopsies of persons with long-standing colitis in their fifth to sixth decade of life.²⁵⁻²⁷ SEC is distinct from other serrated colorectal lesions in persons with IBD, including characteristic histologic findings of disorganized crypt architecture, irregular serrations, and goblet cell-rich epithelium.²⁸ Several studies have reported a higher incidence of colorectal neoplasia among persons identified as having SEC.^{27,29} Although the clinical implications, and appropriate diagnosis, and management of SEC are still being defined, a reasonable approach for the clinician would be to endoscopically resect visible circumscribed SEC, and to consider more frequent endoscopic surveillance with targeted and non-targeted sampling in those with widespread SEC.

Practical Approach to Neoplasia Detection, Surveillance, and Management

A putative framework for IBD neoplasia surveillance and management is outlined in **Figure 1**.

1. **Optimized Neoplasia Detection:** Routine surveillance should ideally be conducted with high-definition white light colonoscopy in combination with pancolonic DCE or newer generation VCE. Where resources and/or expertise for chromoendoscopy are not available, or when inflammation or suboptimal bowel preparation limit application of DCE or VCE, a suitable alternate strategy is high-definition colonoscopy in combination with widespread non-targeted biopsies (30-40) throughout the colorectum. Extensive non-targeted biopsies of non-suspicious mucosa should always be obtained in persons with major risk features, such as primary sclerosing cholangitis, mild chronic inflammation, or diffuse post-inflammatory changes (i.e., extensive post-inflammatory polyposis, extensive scarring or foreshortening, or diffuse SEC). Localized non-targeted biopsies should be routinely obtained from areas previously harbouring invisible or high-risk visible neoplasia. In the absence of widespread non-targeted biopsies, 1-2 non-targeted biopsies should be obtained per colonic segment to assess for microscopic inflammation, as this may influence treatment and future neoplasia surveillance. If adequate neoplasia surveillance is not possible because of the presence of significant inflammation, repeat surveillance should be performed following a period of optimized medical therapy.
2. **Surveillance Intervals:** Colonoscopy surveillance frequency should generally be between 1 and 5 years, guided by the risk factors stated previously (**Table 1**). However, as proposed by the American College of Gastroenterology,¹⁰ a rational approach to surveillance frequency should be based on a combination of risk factors and findings from previous colonoscopy. It is the opinion of the author that surveillance frequency should also consider risk factors for CRC that are established in the general population as well as IBD-specific factors recognized more recently to predict neoplasia risk, including consecutive negative colonoscopies, cumulative inflammatory burden, and SEC.
3. **Neoplasia Management:** Persons with pathologically-confirmed neoplastic lesions that are not completely resectable owing to their location or morphology, or because they harbour features of submucosal fibrosis or invasion should be referred for surgery. Persons with high-risk neoplastic lesions that are completely resected and do not harbour features of invasive cancer, but that are either large (i.e., >2 cm), harbour high-grade neoplasia, have highly complex morphology (i.e., laterally spreading tumours with indistinct borders), or are locally recurrent, may be appropriate for either intensified endoscopic surveillance (i.e., every 3-6 months until 2 consecutive

≤ 1 year	≤ 2-3 years	≤ 4-5 years
Macroscopic and/or microscopic moderate to severe colorectal inflammation or extensive mild inflammation (optimize medical therapy) Poor bowel preparation Primary sclerosing cholangitis First degree relative diagnosed with CRC before age 50 or multiple first-degree relatives diagnosed with CRC Extensive/severe post-inflammatory polyposis, scarring or serrated epithelial change History of invisible neoplasia or higher-risk visible neoplasia (high-grade, multifocal, complex morphology, recurrent) within previous 5 years	Macroscopic and/or microscopic limited mild inflammation (optimize medical therapy) First degree relative diagnosed with CRC after age 50 or multiple second-degree relatives diagnosed with CRC Limited/moderate post-inflammatory polyposis, scarring or serrated epithelial change History of invisible neoplasia or higher-risk visible neoplasia (high-grade, multifocal, complex morphology, recurrent) > 5 years ago Low-risk visible neoplasia (single tubular or serrated adenoma, fully resected) within previous 5 years No features meeting criteria for earlier surveillance	Absence of inflammation (endoscopic and histologic) and neoplasia in current examination AND either of: Similar findings on prior colonoscopy Limited historical colitis extent (< 1/3 of colorectum) AND No features meeting criteria for earlier surveillance

Table 1. Recommended timing of the next surveillance exam where no neoplasia are found at the present colonoscopy*; Adapted from Murthy et al, 2021⁶

*Exact timing should also consider other factors, such as age, sex, body mass index, co-morbidities, smoking history, and cumulative inflammatory burden over the preceding 5 to 10 years

Abbreviations: CRC, colorectal cancer

negative colonoscopies) or surgery. In such situations, clinicians should have a risk-benefit discussion with the patient that considers their ability to comply with IBD treatment and endoscopic surveillance as well as factors that may impact surgical risk, such as age, body mass, and comorbid conditions. Persons with lower-risk resectable visible neoplastic lesions are appropriate for continued endoscopic surveillance, with the surveillance intervals dictated by factors such as neoplasia size, number, grade, and resection completeness, wherein shorter intervals (i.e., 3–6 months) are suggested for high-grade or incompletely resected lesions. Where uncertainty exists, referral to an expert centre for a second opinion is appropriate. Additionally, clinicians may consider using the UC-CaRE model to guide timing of surveillance colonoscopy in persons with low-grade neoplastic findings.

Persons with invisible or poorly delineated neoplastic lesions identified during white light endoscopy should be referred for DCE, conducted by an experienced endoscopist, to unmask any potentially resectable lesions. During DCE, non-targeted biopsies of the areas

of abnormality identified during white light endoscopy should be performed, in addition to targeted sampling and/or resection. If a fully resectable lesion is identified and removed, or, if no neoplastic lesions are identified during DCE, continued intensified endoscopic surveillance every 3–12 months, guided by other risk factors, until 2 consecutive high-quality exams in which no neoplastic lesions are detected is appropriate. Conversely, the persistence of unresectable high-grade or multifocal neoplasia during DCE should prompt surgery. Unifocal invisible LGD remains an area of uncertainty, wherein the risks and benefits of intensified surveillance versus surgery should be personalized following a discussion with the patient.

Limitations and Future Directions

There are a number of shortcomings to the current approach to neoplasia surveillance in persons with IBD that will need to be addressed in the coming years, including: (i) absence of personalized risk stratification models to guide timing of screening and surveillance that consider the collective predictive value of multiple risk factors and protective factors toward CRC risk; (ii) failure

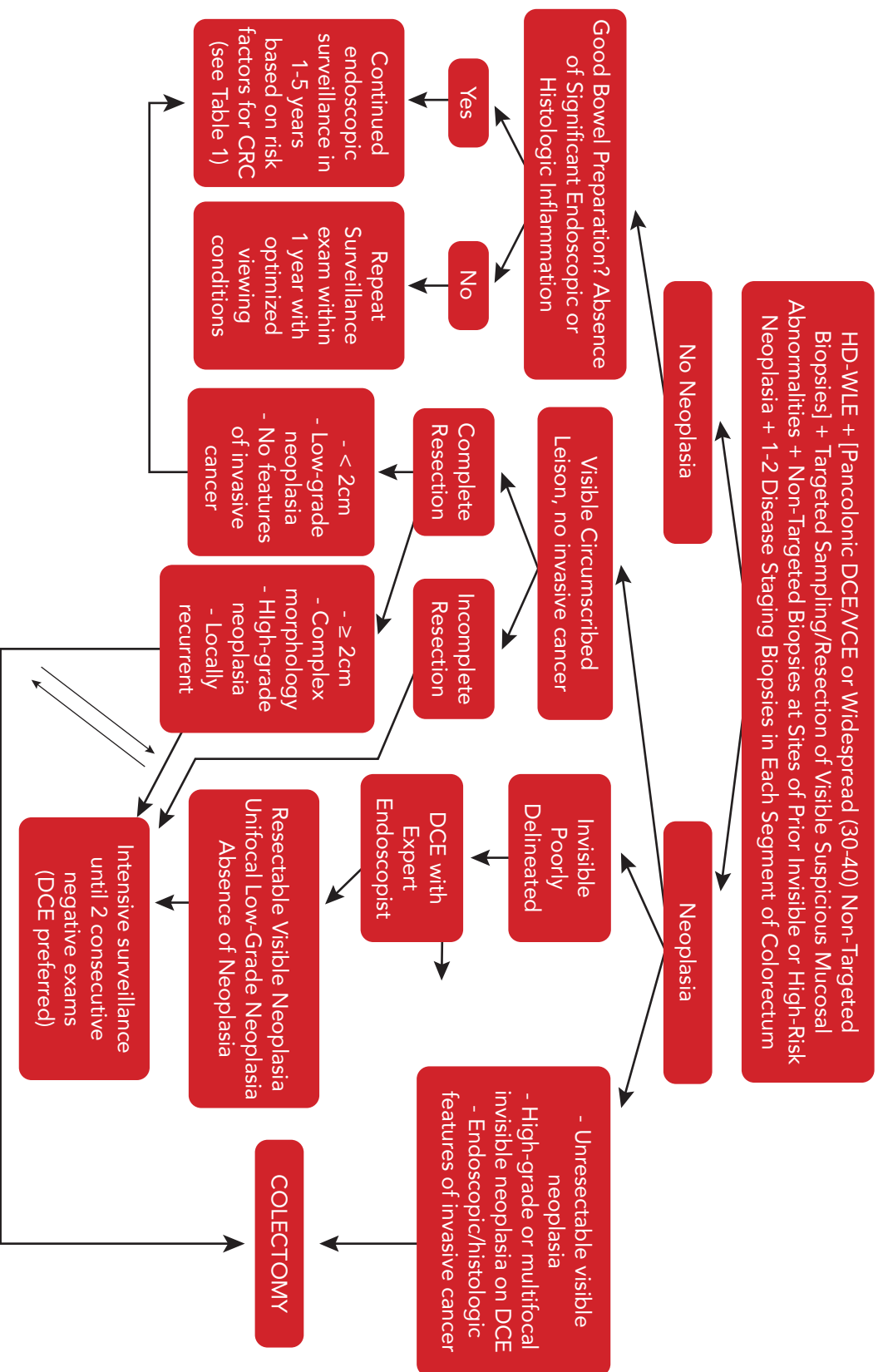


Figure 1. Putative Framework for Colorectal Neoplasia Detection and Management in Persons with IBD Undergoing Surveillance Colonoscopy; courtesy of Sanjay Murthy, MD, MSc (Epid), FRCPC
CRC, colorectal cancer; HD-WLE, high-definition white light endoscopy; DCE, Dye-spray chromoendoscopy; VCE, virtual chromoendoscopy

to consider factors such as patient age, sex, body mass index, comorbidities, immunosuppression, smoking history, and prior colonoscopy exposure in current surveillance algorithms; (iii) limited ability to accurately assess the cumulative lifetime contributions of inflammatory burden and neoplastic findings toward CRC risk; (iv) failure to adequately address the importance of traditional neoplastic lesions, such as adenomas and serrated lesions, particularly those outside of the colitis field, toward overall CRC risk and screening/surveillance requirements; (v) absence of a standardized definition of “advanced neoplasia” that considers lesion size, number, morphology, histology, and resectability, as well as limited ability to stratify persons at high risk of harbouring advanced neoplasia for intensive surveillance; and (vi) absence of convincing data regarding the utility of adjunctive modalities, including DCE, VCE, and non-targeted biopsies, in the context of the latest generation endoscopes and practice standards.

Ongoing clinical trials

Multiple Canadian studies are currently being conducted to address some of these important limitations. The IBD-Dysplasia trial is a multi-centre non-inferiority randomized controlled trial designed to assess the utility of widespread non-targeted biopsies as an adjunct to high-definition white light endoscopy for colorectal neoplasia detection in persons with colorectal IBD. This trial started in 2020 and, with more than 40% of participants already recruited, aims to be completed by 2025. Predict IBD Neoplasia is a multi-centre study that aims to develop a multivariable colorectal neoplasia prediction model to guide timing of surveillance colonoscopy in persons with colorectal IBD. This study began in 2022 and aims to be completed by 2027.

Summary

Despite data suggesting a declining risk of CRC and the lack of prospective studies demonstrating a reduction in the incidence of CRC or of death from CRC with current surveillance strategies in persons with IBD, surveillance continues to play an important clinical role for endoscopists who care for this population. Numerous factors may influence colorectal neoplasia risk, with newly recognized factors including cumulative inflammatory burden, sequential normal colonoscopies and SEC. Surveillance frequency and neoplasia detection modalities should be personalized, incorporating the collective contribution of all risk factors and protective factors. A framework for IBD neoplasia surveillance and management is presented here, accepting that many limitations to optimal screening and surveillance strategies in persons with IBD still exist. Ongoing clinical trials are underway in Canada, the results of which hope to address some of these shortcomings.

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MANAGEMENT OF CLOSTRIDIODES DIFFICILE IN IBD PATIENTS

Introduction

Clostridioides difficile (*C. difficile*) is an anaerobic, spore-forming, Gram-positive bacterium. *C. difficile* is the most frequently reported nosocomial pathogen.¹ *C. difficile* is also the most commonly identified pathogen associated with antibiotic-associated diarrhea, responsible for up to 30% of antibiotic-associated diarrhea.² Spores are transmitted via the fecal-oral route, and acquisition of *C. difficile* in the healthcare setting is generally by contaminated hands or surfaces. *C. difficile* has two monoglycosyltransferase virulence factors that are responsible for damage to the intestinal mucosa, enterotoxin A (TcdA) and cytotoxin B (TcdB). These two enzymes enter intestinal epithelium through receptor-mediated endocytosis and irreversibly inactivate Rho GTPases. This ultimately disrupts the cytoskeleton and tight junctions, resulting in a loss of parenchymal polarity and eventual apoptosis.

A population-based study from Manitoba reported that individuals with inflammatory bowel disease (IBD) have a 4.8-fold increased risk of laboratory confirmed *C. difficile*

infection (CDI) compared to individuals without IBD, with no difference in rates between those with ulcerative colitis (UC) or Crohn's disease (CD).³ Among individuals with IBD, exposure to corticosteroids; use of anti-TNF agents; use of metronidazole; hospitalizations; numerous ambulatory care visits; shorter duration of IBD; and numerous comorbidities are associated with an increased risk of CDI.³ The risk of CDI is increased among individuals of all ages with IBD. The incidence rate of hospitalization with CDI in a Canadian multi-provincial population-based incident cohort of children with IBD was reported to be 49.06 (95% CI 39.40-61.08) per 10,000 person-years and was nearly 70-fold that of age- and sex-matched children without IBD.⁴ The reasons why IBD patients are more susceptible to CDI are not fully understood, but some possible factors include: frequent use of antibiotics and immunosuppressive drugs; increased exposure to healthcare settings where *C. difficile* is prevalent; altered gut microbiota; compromised mucosal barrier function due to inflammation; and genetic susceptibility.

Among patients with IBD, CDI is associated with worse clinical outcomes compared to individuals without IBD, including increased emergency room visits, longer hospitalizations, higher rates of colectomy, and increased mortality.^{3,5-7} CDI may mimic an IBD flare and can precipitate an IBD flare. Given the clinical overlap between CDI and IBD exacerbations (e.g., increased frequency of loose stools, abdominal pain), it is difficult to differentiate CDI versus colonic colonization in patients with active IBD who test positive for *C. difficile*.⁸ *C. difficile* colonization occurs in up to 15% of healthy adults and more than 20% of hospitalized adults.⁹ In a prospective study, *C. difficile* colonization was higher among IBD patients (8.2%) in remission with no recent hospitalizations or recent exposure to corticosteroids, immunomodulators or antibiotics compared to healthy controls (1.0%).¹⁰

Diagnosing *Clostridioides difficile* Infection

Testing and treatment for *C. difficile* colonization is not recommended. Rather, testing for *C. difficile* should occur in patients where there is clinical suspicion for CDI (e.g., frequent and loose stools, abdominal pain, leukocytosis). Therefore, anyone with known IBD presenting with an acute flare associated with diarrhea should undergo testing for *C. difficile*.¹¹ All diagnostic tests have been validated for use on unformed stool only; as a result, most laboratories will not process formed stool.

The Infectious Disease Society of America (IDSA) and the American College of Gastroenterology (ACG) recommend multistep testing algorithms to diagnose CDI.^{11,12} However, use of a multistep testing algorithm can fail to differentiate symptomatic CDI from asymptomatic colonization among individuals with IBD with symptoms due to IBD.¹³

Commercially available tests include nucleic acid amplification tests (NAAT), enzyme immunoassays (EIA), toxigenic culture, and next-generation sequencing (NGS). NAAT is a PCR that tests for the presence of toxin genes A and B. NAAT is regarded to have excellent sensitivity (up to 100%), but a specificity of 87% with a positive-predictive value of 45%,¹⁴ therefore, there is risk of overdiagnosis in the setting of colonization. The EIAs test for the presence of toxin in stool and are regarded to have lower sensitivity but improved specificity compared to NAAT. Ultrasensitive protein-based stool tests have been developed that have improved diagnostic accuracy for CDI; however, they are not yet commercially available.¹⁵ Certain laboratories may use EIA to detect stool glutamate dehydrogenase (GDH). However, this enzyme is produced by both toxigenic and nontoxigenic strains of *C. difficile*, therefore, a second confirmatory test is required.

Due to the issues with differentiating CDI vs colonization, a multistep algorithm is recommended by the ACG,¹¹ first using a highly sensitive NAAT or GDH test, followed by a more specific toxin EIA if the first test is positive. If both tests are positive, a diagnosis of CDI is reliably made. A problem arises when there is discordance between two tests. As toxin EIA is less sensitive, GDH positive,

toxin negative can result in a false negative, where a CDI exists. The ACG guideline points out “Because no test is perfect, the diagnosis and decision to treat is a clinical one. Treatment should not be withheld when there is high clinical suspicion, based on laboratory testing alone”. Therefore, a positive GDH with a negative EIA toxin test requires treatment in selected cases with severe symptoms and a high index of suspicion for CDI in IBD patients.

Treatment of *Clostridioides difficile* Infection

Following the diagnosis of a CDI in an individual with IBD involves treating the infection with antibiotics and optimizing management of the patient’s immunosuppression.⁷ The IDSA and ACG consider vancomycin or fidaxomicin as first-line antibiotics for non-severe or severe diseases (white blood count $\geq 15,000$ cells/mL or serum creatinine $>1.5\times$ above baseline).^{11,12} Vancomycin is dosed at 125 mg orally four times/day for 10 days, and fidaxomicin is dosed at 200 mg orally twice daily for 10 days. Vancomycin is generally preferred as the first-line antibiotic as fidaxomicin is much more expensive. However, fidaxomicin is associated with lower rates of CDI relapse and some cost-effectiveness analyses do favour fidaxomicin over vancomycin.^{16,17}

There are limited data and randomized, controlled trials concerning treatment-specific regimens for CDI in individuals with IBD. In general, metronidazole is not recommended as monotherapy, and a prolonged course of vancomycin (14 days instead of 10 days) is favoured.¹¹ Fidaxomicin is also deemed a reasonable option. In the setting of a suspected or confirmed IBD flare with concurrent CDI, immunosuppressive therapy should not be held; conversely escalation of immunotherapy should be considered in those with no symptomatic improvement after three days of CDI treatment.

For fulminant CDI, defined as the presence of hypotension or shock, ileus, or megacolon, vancomycin 500 mg four times daily (orally or by nasogastric tube) is recommended. Vancomycin can be administered rectally as an enema if enteral administration is contraindicated and, in such cases, intravenous metronidazole 500 mg every eight hours should be added in addition to rectal vancomycin.^{11,12}

C. difficile infection recurrence is defined as an episode of CDI occurring within 12 weeks of a previous CDI. For the first recurrent CDI, it is recommended that the treatment regimen be modified from the first, as follows: (1) vancomycin 125 mg orally four times daily for 10 days if metronidazole was used for the initial episode; (2) pulsed vancomycin plus taper (125 mg orally four times daily for 10-14 days, followed by twice daily for one week, then once daily for one week, then every two or three days for two to eight weeks if standard vancomycin dosing was used for the initial CDI; or (3) fidaxomicin 200 mg orally twice daily for 10 days if standard vancomycin dosing was used for the initial CDI.^{11,12} For a second recurrence or any subsequent recurrence thereafter, vancomycin pulse

and taper or standard fidaxomicin are recommended, as outlined above. Standard 10-day dosing of vancomycin followed by rifaximin 400 mg three times daily for 20 days is also an option. However, all of these treatment regimens for the second CDI and recurrence thereafter is based on low quality of evidence and therefore is backed by weak strength of recommendation (**Table 1**).¹²

Other options for the treatment of CDI recurrence include bezlotoxumab, a monoclonal antibody targeting cytotoxin B (TcdB), and fecal microbiota transplantation (FMT). The ACG recommends reserving bezlotoxumab for individuals experiencing at least their second episode of CDI in the past six months, in those aged 65 or over, along with an additional risk factor, i.e., immunocompromised or severe CDI.¹¹

FMT has been shown to be beneficial in preventing CDI recurrence in IBD patients.¹¹ The ACG recommends that FMT be considered for patients with severe or fulminant CDI that is refractory to antibiotics, or for patients experiencing their second or further recurrence of CDI. It can be considered in IBD patients with their first CDI recurrence.¹¹ FMT is administered through a colonoscopy and should be combined with an antibiotic regimen as described above. Toxic megacolon is not considered an absolute contraindication to the administration of a FMT.¹¹ The colonoscope should be carefully advanced beyond

the splenic flexure, and FMT repeated every 3-5 days until pseudomembrane resolution or discharge from hospital. Vowst™ is an orally administered fecal microbiota product that is FDA approved but not yet available in Canada. It is a capsule composed of purified Firmicutes spores from healthy donors, and is approved for CDI recurrence that is unresponsive to antibiotics.¹⁸

Additional Considerations

Probiotics are not recommended for the prevention of CDI or recurrent CDI due to a lack of conclusive evidence; this has been previously reviewed in detail.¹¹ Follow-up testing or so-called test of cures should not be done where there has been adequate treatment and symptom resolution as there can be clinically irrelevant toxin shedding for up to four weeks postinfection. Furthermore, there is insufficient evidence to suggest that proton pump inhibitors (PPIs) should be discontinued as a measure for preventing CDI.^{11,12} *C. difficile* enteritis and pouchitis are rarely reported entities; however, *C. difficile* testing can be considered in IBD patients who have undergone colectomy and are unresponsive to conventional treatment for their underlying IBD.

Treatment	Dosing regimen
First CDI episode	
1. Vancomycin	125 mg orally four times daily for 14 days
2. Fidaxomicin	200 mg orally twice daily for 10 days
First CDI Recurrence (episode of CDI occurring within 12 weeks of a previous CDI)	
1. Vancomycin	pulsed + taper (125 mg orally qid for 14 days, followed by bid for one week, then once daily for one week, then every two or three days for two to eight weeks if standard vancomycin dosing was used for initial CDI)
2. Fidaxomicin	200 mg orally bid for 10 days
Second CDI Recurrence (or any subsequent recurrence thereafter)*	
1. Vancomycin	pulsed + taper (125 mg orally qid for 14 days, followed by bid for one week, then once daily for one week, then every two or three days for two to eight weeks)
2. Fidaxomicin	200 mg orally bid for 10 days
3. Vancomycin + rifaximin	Standard 14-day dosing (vancomycin) followed by 400 mg tid for 20 days (rifaximin)

Table 1. First line drug regimens for the management of CDI in IBD; courtesy of Harminder Singh, MD and Jeffery M. Venner, MD

* Low strength of evidence for these treatment regimens.

Clinical Pearls

- ✓ *C. difficile* occurs much more commonly among people with IBD
- ✓ *C. difficile* Infection is associated with worse outcomes among people with IBD
- ✓ Individuals with colonic IBD with flare symptoms should be evaluated for *C. difficile* infection
- ✓ Vancomycin is the drug of choice for treating the first episode of *C. difficile* infection
- ✓ Metronidazole should no longer be used to treat *C. difficile* Infections among those with IBD
- ✓ Multistep testing algorithms (i.e., include both a highly sensitive and a highly specific assay) should be used to diagnose CDI. However, as noted by the ACG, clinicians should also be aware that "Because no test is perfect, the diagnosis and decision to treat is a clinical one. Treatment should not be withheld when there is high clinical suspicion based on laboratory testing alone".

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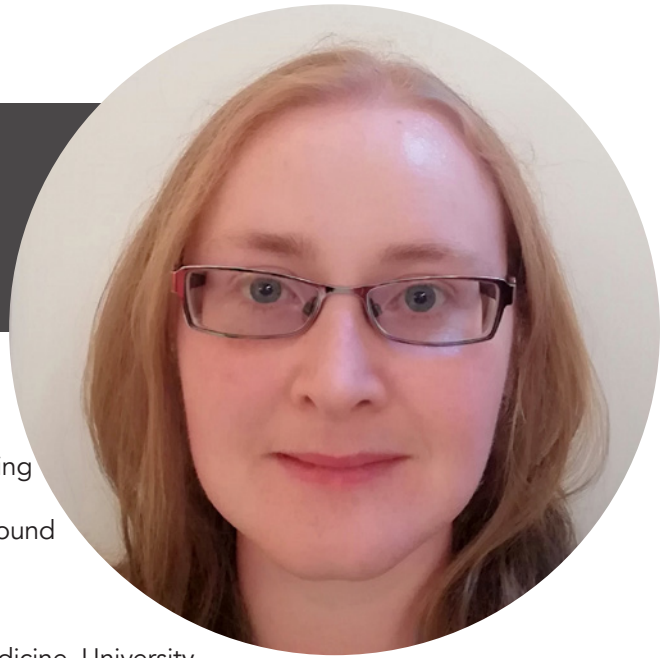
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TODAY AND TOMORROW: THE USE OF BIOMARKERS IN INFLAMMATORY BOWEL DISEASE

Introduction

Biomarkers play important roles in clinical care for people with inflammatory bowel diseases (IBD) (**Box 1**). Biomarkers are also central to the development of new therapies and as endpoints in their evaluation.

The recommendations from the STRIDE-II study emphasize the central role of clinical indices and biomarkers such as fecal calprotectin (FC) and C-reactive protein (CRP) in the management of Crohn's disease (CD) and ulcerative colitis (UC).¹

This review will focus on the established roles for FC and CRP, emerging roles for alternative and composite biomarkers, limitations of current biomarkers, and unmet needs in the field. This is an evolving area, with recent clinical practice guidelines from the American Gastroenterological Association in UC. In addition, updates are expected from the European Crohn's and Colitis Organisation on their multi-society guideline for IBD monitoring.²

Established roles for biomarkers

There are several roles for biomarkers in clinical care for IBD including diagnosis, assessing disease activity, monitoring therapeutic response, predicting disease recurrence, and mucosal healing. The best-established biomarkers are FC and CRP.

Fecal calprotectin – the cornerstone inflammatory bowel disease biomarker

FC is the cornerstone biomarker in IBD (**Box 2**).

Calprotectin is a soluble cytosolic calcium- and zinc-binding protein, which is produced mainly by neutrophils and granulocytes at sites of inflammation, and to a lesser extent by monocytes, macrophages, and epithelial cells.

FC can be used during diagnosis to help distinguish non-inflammatory conditions from IBD in patients with gastrointestinal (GI) symptoms. Repeated FC testing is more accurate in identifying patients who warrant endoscopic evaluation compared to a single measurement.³ FC can also be used to assess and monitor disease activity and response to therapy, and to predict relapse and post-operative recurrence.⁴ FC may also have a role in risk-stratifying patients who do not have early post-operative recurrence on their initial colonoscopy. Patients with advanced post-operative recurrence (Rutgeerts i3/i4) were identified by two consecutive FC values >250 µg/g, at 4-month intervals over a 2-year period, with 100 % sensitivity and 60% specificity. However, 25% of patients with FC values <250 µg/g were found to have Rutgeerts i2 recurrence at the end of the study period, demonstrating the limitations of this biomarker.⁵

FC is a useful marker in UC and in CD regardless of disease location, including small bowel CD, though it may be less useful in isolated proctitis.^{2,6} FC can also be a useful marker in patients with pouchitis, perianal disease, and potentially in patients with an ostomy.⁴ Overall, FC measurement can help to inform the timing and choice of disease assessment by endoscopy and/or by imaging, and potentially avoid unnecessary colonoscopy/sigmoidoscopy in some patients.

Key limitations in clinical practice are patient adherence with monitoring, equitable access to assays without additional costs to patients, and timely availability of results that integrate with electronic patient records. There are also numerous GI and non-GI factors that can impact results (**Box 2**).

Most manufacturers recommend an FC threshold of 50 µg/g to define normal and abnormal values, although, in practice, the cutoff value depends on the desired outcome. Suggested threshold values are described in **Box 2**.

Practical recommendations for optimal collection, storage, and analysis of stools were proposed in a recent international consensus, in particular⁷:

- <7 days and ideally ≤3 days stool storage at room temperature prior to analysis,
- non-liquid stools provide more precise measurements,
- discontinuation of non-steroidal anti-inflammatory drugs (NSAID)s for ≥2 weeks before measurement.

Patients should be given written information on how to collect a stool sample, when and how to submit it, and ideally a pre-made testing kit (most provincial laboratory services provide this information).

FC measurement can also be performed as a point of care test or by the patient at home. There are several commercially available home-testing kits. These kits use a lateral flow-based testing method rather than ELISA, along with software to allow mobile devices to read the measurement.⁸ The benefits of home FC-testing include a more rapid result and potentially earlier changes in management of the disease. Patients using home-based FC testing kits had a significantly higher use of medical therapy than did those using standard care.⁹ However, adherence to home testing in this study was only 29%, with lower adherence seen amongst male patients. Furthermore, the accuracy of home-based testing kits can vary considerably compared to ELISA-based testing kits. For instance, when comparing three commercial kits with the laboratory performed ELISA method, the agreement was over 75% for FC measurements <500 µg/g. The rate of agreement between home kits and the ELISA method had

reduced to 19–37% for FC measurements >500 µg/g. The type of mobile device used may also impact the reliability and accuracy of measurements.⁸ These factors should be taken into consideration when interpreting results of home-based FC testing.

C reactive protein

CRP is produced by hepatocytes during an acute-phase response and has a half-life around 19 hours; therefore, it changes more rapidly with changes in disease activity than that of the other serum biomarkers.¹⁰ CRP is usually elevated in active CD and less frequently elevated in UC, apart from acute severe UC (ASUC). Although the erythrocyte sedimentation rate (ESR) is altered in both CD and UC, it is less responsive to changes in activity, and is affected by several physiological factors, such as age, sex, pregnancy, hemocrit levels, and erythrocyte size. Unlike FC, elevated CRP values are not specific to GI inflammation and can be elevated in association with a rising body mass index, though obesity also increases the risk of CD and UC.¹¹

Both CRP and ESR lack specificity and accuracy in diagnosis, though CRP has a useful negative predictive value in the context of IBD, with a probability ≤1% in a meta-analysis of 12 prospective diagnostic cohort studies.¹² CRP shows at best a weak to moderate correlation with endoscopic disease activity, and is especially poor for ulcerative proctitis, and has a limited role in predicting risk of relapse.^{13,14} Furthermore, the accuracy in predicting post-operative recurrence in CD is low.¹⁵ CRP is most useful with severe disease and penetrating/fistulizing complications, at baseline, and to monitor response to therapy. In ASUC, CRP guides therapy escalation. The Oxford Criteria includes CRP and stool frequency and can be used to predict the rate of in-hospital colectomy in patients unresponsive to intravenous steroids, albeit with less accuracy since the introduction of rescue therapy.^{16,17}

A CRP value of <5 mg/L was used alongside FC in the CALM trial as a treatment target in CD to optimize adalimumab or combination therapy to achieve tight disease control, with deep remission linked to better medium-term patient outcomes.^{18,19} This treatment strategy was also shown to be cost effective in Canada.²⁰ Most decisions to escalate therapy in the CALM trial were driven by biomarkers rather than clinical assessment, particularly by FC values ≥250 µg/g at weeks 12 and 24 rather than by CRP or FC+CRP combination therapy.²¹ In the STARDUST trial, biomarker targets of FC ≤250 µg/g and CRP ≤10mg/L were used to optimize ustekinumab dosing in CD.²² Only 30% of patients achieved biomarker targets for FC and CRP, despite 78% of patients achieving clinical remission and >30% showing biomarker response, with no significant benefit over standard of care in endoscopic improvement at 48 weeks.

Bottom line – biomarkers cannot (yet) replace endoscopy

A systematic review and external validation study that looked at non-invasive models to identify patients with

endoscopic activity of CD found that 7 of 27 identified diagnostic models could predict endoscopic endpoints in CD, and that 4 of these models showed a benefit similar to FC and CRP, which showed positive predictive values of ≥90% for mucosal disease activity.²³ However, only the Utrecht Activity Index (UAI) and TAILORIX models were able to reliably predict endoscopic healing, and 1 in 5 patients were misclassified using FC cut-off values of <100 and ≥250 µg/g.^{23,24} Ileocolonoscopy remains the gold-standard to evaluate disease activity in adults with CD. FC has utility in UC, although biomarkers may be suboptimal in confirming endoscopic healing and evaluating mild symptoms; furthermore, it is not known whether a biomarker or endoscopic strategy is superior for long-term monitoring.² In addition, biomarkers have no role in detecting dysplasia, surveillance, or excluding cytomegalovirus colitis and infection, which require endoscopy and/or microbiological evaluation.²

Emerging biomarkers and novel roles

Despite advances in therapeutics, there remains a distinct gap between our treatment goals and actual results. Biomarkers that perform beyond the established roles in diagnosis and disease activity monitoring are essential in bridging that gap. Areas where biomarkers may be particularly important include the prediction of disease course, disease phenotype, and the choice of advanced therapy.

Composite biomarkers

There is interest in developing and integrating different biomarkers into a single readout to better predict endoscopic healing and to guide decision making in research and clinical practice.²⁵ Dragoni et al. reviewed the use of panels of blood, fecal biomarkers, and drug levels, that have the potential to replace single biomarker approaches in the future.²⁶ This approach may be particularly helpful to reduce the ambiguous “grey zone” associated with biomarker readouts.¹⁰

Better utilization of readily available biomarkers is one potential strategy. The CALM trial showed that measurements of FC and CRP together were superior to FC alone in CD, though the majority of treatment escalations were driven by FC.¹⁸ The UAI included platelet count and mean corpuscular volume alongside FC, CRP, and stool frequency, although it may offer limited benefit beyond FC and/or CRP.^{23,24} In pediatric CD, the composite Mucosal Inflammation Noninvasive index (MINI) score (comprising FC, ESR, CRP and pediatric CD activity index) can predict mucosal healing in lieu of ileocolonoscopy and/or magnetic resonance enterography.²⁷ The added benefit over FC alone was particularly seen for FC concentrations 100–599 µg/g. The Portuguese DIRECT study derived risk matrices to predict CD progression, comprising the degree of elevation in FC and CRP and the presence and persistence of anemia across single or multiple visits.²⁸ Another example of potential composite biomarkers is a combination of a fecal immunochemical test (FIT) and FC, which were superior to predict clinical

relapse over 12 months in UC and might have the ability to better predict endoscopic healing.²⁹

Putative and future biomarkers

The pursuit of an ideal biomarker continues, with many candidates studied including fecal and tissue markers of intestinal inflammation, fecal volatile organic metabolites, and urinary prostaglandins.^{30,31} Serum/plasma assays for epigenetic biomarkers, especially microRNAs, glycoprotein biomarkers, and leucine-rich alpha-2-glycoprotein, amongst others, are under review.^{10,15,32}

Lactoferrin and calgranulin C (S100A12) are fecal biomarkers similar to FC. They have not demonstrated additional utility, share similar limitations as FC and are not typically used in practice. In UC, FIT has a high positive likelihood ratio and moderate negative likelihood ratio for predicting endoscopic healing.³³ In addition, FIT is less accurate than FC although it may be equivalent in predicting endoscopic disease activity, and agnostic for disease extent.^{29,34}

Other potential biomarkers include widely available laboratory results which could be seamlessly integrated into clinical practice. For instance, the platelet-to-lymphocyte ratio index showed an area under the curve (AUC) of 0.87–0.91 for moderate/severe activity and an AUC of 0.74 for mucosal healing in isolated small bowel CD against capsule endoscopy, which was superior to FC and CRP.³⁵ Neutrophil-to-lymphocyte ratio also shows promise as a biomarker of endoscopic activity and response to biologic therapy.³⁶

Susceptibility, diagnosis and predicting disease course

Genetic susceptibility plays an important role in the development of IBD, with over 230 risk alleles identified.³⁷ The NOD-2 gene is recognized as a major susceptibility gene, and over 50 genes have been associated with very early onset IBD.^{38,39}

In terms of predicting the development of IBD, serological markers such as atypical perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) may have a role. A study of Israeli military recruits detected ASCA in approximately 30% of patients before the clinical diagnosis of CD with a mean interval between detection and diagnosis of 38 months. In addition, pANCA was found in 25% of patients subsequently diagnosed with UC.⁴⁰ The cohort in this study was small, therefore conclusions should be limited accordingly.

More recently, anti- $\alpha\beta 6$ autoantibodies were found to be significantly higher amongst patients subsequently diagnosed with UC compared with healthy controls. These autoantibodies were detected up to 10 years before diagnosis and were associated with worse outcomes such as hospitalization, colectomy, and need for biologic therapy.⁴¹

Several serological markers have been identified in IBD patients and evaluated in distinguishing UC from CD. Most

notably, pANCA and ASCA have been studied.⁴² Atypical pANCA is found mainly in UC (50–67%) and to a lesser extent in CD. However, pANCAs are also present in other inflammatory conditions such as autoimmune hepatitis and primary sclerosing cholangitis. ASCAs are typically more common in CD (40–60%) although not exclusive to CD, having been detected in UC and disease controls.

The performance of these serological markers improves when used in combination. The pattern associated with CD is ASCA+/ANCA-, and for UC is ASCA-/ANCA+. When used in this manner, ASCA and pANCA affect the post-test probability of having CD or UC. The positive likelihood ratio of ASCA+/ANCA- ranges from 6.3–11, and that for ASCA-/ANCA+ ranges from 2.9–22 across various studies.^{43–47} An important caveat is that pANCAs are frequently detected in colonic CD as in UC, thus limiting its utility as a specific marker for CD in the scenario in which such a marker would be most useful.⁴⁸

pANCAs do not distinguish or predict disease location or phenotype.⁴⁵ However, ASCA has been associated with a more complex CD phenotype and with small bowel involvement.^{43,49,50} In a pediatric cohort, seropositivity to anti-Cbir1 (flagellin), anti-outer membrane protein C, ASCA, and pANCA was associated with a complex penetrating/stricturing phenotype, and the need for surgery while higher antibody sum, as a marker of immune reactivity, was associated with rapid disease progression.⁵¹

Personalized medicine

A key unmet need in IBD is the ability to reliably predict disease course at diagnosis, and the serological markers above demonstrate the ongoing interest in this goal. Another gap in knowledge is the ability to predict response to specific therapies. Precision medicine is an elusive goal in IBD given the complexity of the condition. With respect to predicting response to existing therapies, there have been some promising steps in recent years.

The PROFILE (PRedicting Outcomes For Crohn's disease using a moLecular biomarker) study is the first biomarker-stratified trial in IBD and has recently completed follow-up to week 48.⁵² PROFILE recruited 390 adults in the UK who were recently diagnosed with CD of at least moderate activity, and were naïve to immunomodulator and anti-TNF therapies. PROFILE utilizes a peripheral blood CD8+ T-cell transcriptomic signature early after diagnosis to classify patients into IBD^{hi} and IBD^{lo} to predict disease course and risk of complications. The analysis will also compare the relative benefit of treatment strategies in each biomarker subgroup to determine if this biomarker study can identify the most appropriate therapy.

Inflammatory modules associated with response and resistance to anti-TNF therapy have been identified.^{53,54} The glycoprotein 130 family of cytokine receptors were found to be upregulated in patients with CD refractory to anti-TNF therapy and related to particular NOD-2 gene variants.⁵⁵

Several strategies have been proposed to predict response to vedolizumab, including immunoglobulin glycosylation, mucosal vascular addressin cell adhesion molecule 1 (MadCAM1) non-expression in LP endothelial cells, and increased baseline colonic mucosal eosinophil counts.⁵⁶⁻⁵⁸ Battat et al found a trend toward more rapid increases in s- α 4 β 7 concentrations in patients treated with vedolizumab who achieved clinical remission and endoscopic remission. S-MadCAM-1 concentrations declined more rapidly in this group compared to non-responders.⁵⁹ In UC patients, increased density of mucosal eosinophils was a negative predictor of response to vedolizumab.⁵⁸

Microbiome diversity and more abundant populations of *Burkholderiales* species was associated with remission in patients treated with vedolizumab.⁶⁰ Microbial analysis and development of serum profiles reflecting microbial diversity have also been explored as a way to identify patients more likely to respond to anti-cytokine therapy rather than anti-integrin therapy.⁶¹ These profiles have yet to be used in clinical practice but incorporating multi-omic data, clinical data, and microbial signatures with machine learning models may enhance our ability to accurately predict therapeutic response in the future.

Conclusion

Biomarkers are a critical component to achieving high quality care for patients with IBD. Established biomarkers complement more invasive assessments and act as useful guides to therapy. Currently available biomarkers such as FC and CRP could potentially be exploited more to our advantage as composite biomarkers that can more accurately inform treatment goals such as endoscopic remission. However, in their present form, biomarkers cannot replace essential functions of endoscopic evaluation and fall short of predicting a response to a particular advanced therapy. Biomarker development is now focusing on disease prediction and on strategies to individualize therapy decisions. Future biomarkers are likely to incorporate data from clinical, immunologic, and microbial sources to provide a more nuanced approach to IBD therapy.

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According to the World Health Organization, a biomarker is described as follows: "Almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction."⁶²

- May include molecular, histologic, radiographic, or physiologic characteristics
- Not a measure of how an individual feels, functions or survives
- Includes the categories of susceptibility/risk, diagnostic, monitoring, prognostic, predictive, response, and safety biomarkers

Box 1. What is a Biomarker?; adapted from World Health Organization, 1993

Thresholds:

- FC <50 µg/g to distinguish between IBS and possible IBD, in settings in which patients with chronic GI symptoms are being evaluated, and a high negative predictive value is needed, though FC >250 µg/g can identify ~90% of new patients who were confirmed to have IBD
- FC <100-250 µg/g as therapeutic target in CD⁶³⁻⁶⁶
- FC <150 µg/g as therapeutic target in UC

Trends in an individual patient using the same quantitative assay and correlated with endoscopic assessment(s) are more important than an absolute binary cut-off. Exact cut-offs to distinguish between IBD and IBS or between active and inactive IBD do not exist in all scenarios.

Suggested frequency of endoscopic assessments

	Remission	Active/Treatment initiation
CD	6–12 monthly (not established for CD)	3 monthly
UC	6–12 monthly (3–6 monthly if FC >150 µg/g)	3–6 monthly

Levels of FC can be affected by:

- active IBD
- inactive IBD with anastomotic ulceration attributable to surgery-related factors and local ischemia (Rutgeert's score i2a)
- perianal disease, up to FC >1000 µg/g
- medications:
 - bowel preparation for colonoscopy, up to >1000 µg/g
 - NSAIDs and Aspirin, up to ~ 500 µg/g (including NSAID-induced enteropathy)
 - proton pump inhibitors, up to 150 µg/g
- non-IBD causes of intestinal inflammation:
 - bacterial and viral GI infections, up to ~ 1000 µg/g
 - microscopic colitis, up to ~ 500 µg/g
 - radiation proctitis, up to ~ 250 µg/g
- other GI factors:
 - colonic diverticular disease, up to 60 µg/g
 - colonic polyps (including IBD-associated inflammatory polyps), up to ~120 µg/g
 - colorectal cancer, up to ~130 µg/g
 - GI bleeding, up to ~500 µg/g
 - patients ultimately diagnosed with IBS, up to ~ 300 µg/g
- non-GI and lifestyle factors:
 - age <9 years, up to ~200 µg/g
 - age >65 years, up to ~120 µg/g
 - bariatric surgery, up to ~400 µg/g
 - obesity, up to 185 µg/g
 - physical inactivity, up to 60 µg/g
 - rheumatological diseases, up to ~500 µg/g

Box 2. Fecal Calprotectin; courtesy of Catherine R Rowan, MD and Richard J M Ingram, MD

CD, Crohn's disease; CRP, C reactive protein; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; UC, ulcerative colitis

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