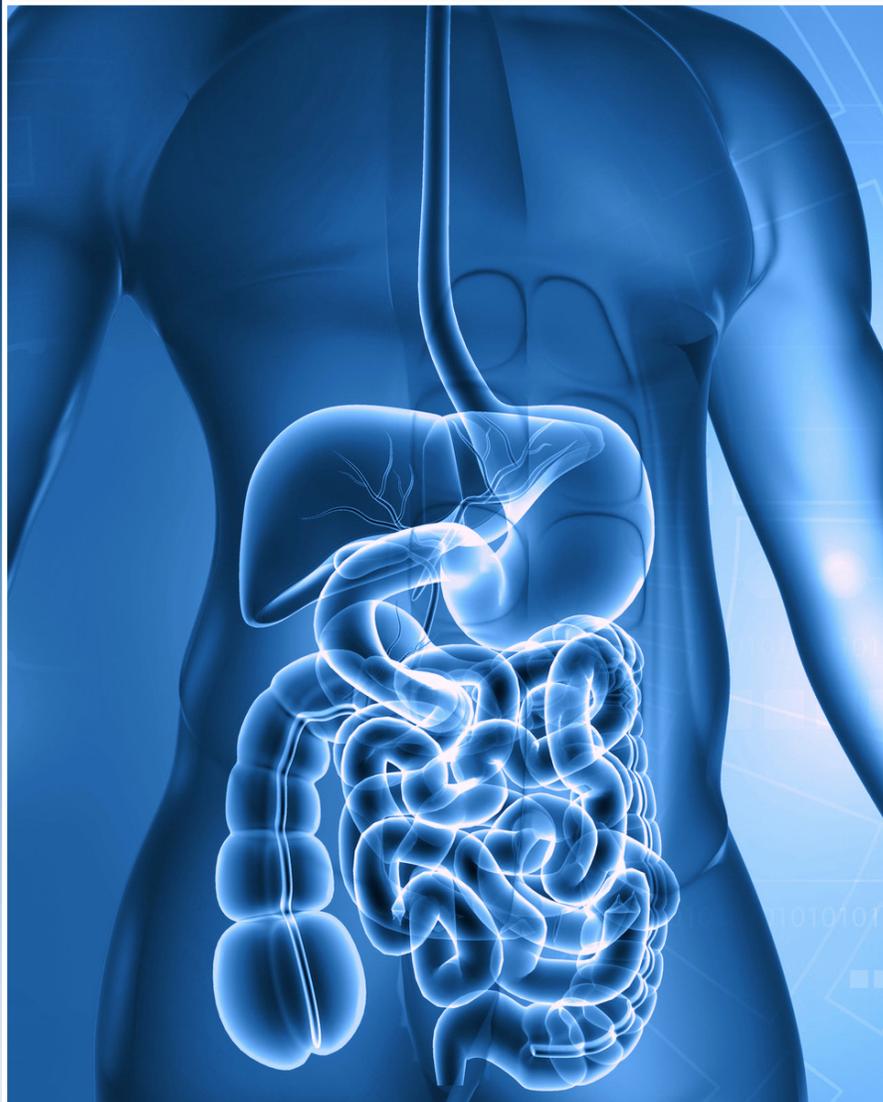


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SPECIAL SECTION: PART I

UPDATES *in* INFLAMMATORY BOWEL DISEASES

GUEST EDITORS: ABBAS H. RUPAWALA, MD; JASON M. SHAPIRO, MD; SAMIR A. SHAH, MD



A.H. Rupawala, MD



J.M. Shapiro, MD



S.A. Shah, MD



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## Introduction: Updates in Inflammatory Bowel Diseases

ABBAS H. RUPAWALA, MD; JASON M. SHAPIRO, MD; SAMIR A. SHAH, MD  
GUEST EDITORS

Inflammatory Bowel Diseases (IBD), including Crohn's disease (CD), ulcerative colitis (UC) and IBD unspecified (IBDU), are chronic immune-mediated diseases affecting the luminal gastrointestinal system. The incidence of IBD is rising worldwide, particularly in developing countries. In the United States (US) in 2015 an estimated 3 million adults (1.3% of the US adult population) lived with a diagnosis of IBD. This estimate did not include pediatric patients.<sup>1</sup> Over the last 20 years, there have been significant advances in our understanding of the etiopathogenesis of IBD, discovery of newer agents for management of these diseases, and a paradigm shift in the approach to managing them. In this issue and the following issue of the *Rhode Island Medical Journal*, we present updates on a wide range of topics related to care of patients with IBD written by experts in adult and pediatric gastroenterology, colorectal surgery, and other fields from within the state. We are also fortunate to have contributions from national and international experts on many of these topics from across the country. Each topic covers clinically relevant information that should serve as a quick reference guide for busy clinicians in the inpatient and outpatient settings. Given the number of topics to be covered, we have split them over two consecutive issues. The editors include Dr. Samir A. Shah, who is a leading expert on IBD in Rhode Island, Chief of Gastroenterology at The Miriam Hospital, and Immediate Past President of the American College of Gastroenterology; Dr. Jason M. Shapiro, Director of the Pediatric IBD Center at Hasbro Children's Hospital and Director of Research in the Division of Pediatric Gastroenterology, Nutrition and Liver Diseases; and Dr. Abbas H. Rupawala, previously Co-Director of the IBD Center at Brown Medicine and now Director of the IBD Center at the University of Massachusetts Medical Center.

### PREVENTIVE CARE AND HEALTH MAINTENANCE IN PATIENTS WITH IBD

Patients with IBD will often need treatment with immunosuppressive medications that carry an increased risk of infections and malignancies. Therefore, health maintenance with specific focus on vaccination and cancer surveillance is of paramount importance, particularly as our patients live longer with these conditions and may remain on treatment for prolonged periods of time. These concepts have been

succinctly covered in this topic by Dr. Daniela Fluxa and Dr. Breton Roussel, both trainees in gastroenterology, and Dr. Jana Alhashash. The senior author on this topic, Dr. Francis Farraye, is an internationally renowned expert on this topic and is also the lead author of the American College of Gastroenterology's (ACG) clinical guidelines on preventive care in IBD.

### EXTRAIESTINAL MANIFESTATIONS OF IBD

Patients with IBD are at increased risk of developing other autoimmune diseases.<sup>2</sup> However, more commonly, they will exhibit symptoms related to other organ systems, typically involving the joints, skin and eyes. Many of these patients benefit from multidisciplinary care at the Rhode Island Hospital Center for Skin and Musculoskeletal Diseases. Some extraintestinal symptoms may parallel disease activity of IBD while others may manifest independently of the bowel inflammation activity. Furthermore, patients with IBD are at risk of several complications affecting every organ system. Dr. Sean Fine, Director of the IBD Center at Brown Medicine/Brown Physicians, Inc., has provided a comprehensive summary of the extraintestinal manifestations of IBD and their management.

### CLOSTRIDIODES DIFFICILE AND FMT IN PATIENTS WITH IBD

Over the last decade there has been an epidemic of *Clostridioides difficile* infection (CDI), in part due to the rampant use of antibiotics that has led to significant interest and education in antibiotic stewardship. It was also, in large part, due to the emergence of a hypervirulent strain of *C. difficile* characterized as North American pulsed-field type 1, restriction-endonuclease analysis group type BI, and PCR ribotype 027. Patients with IBD seem to have increased risk of CDI even in absence of antibiotic use, in part due to the dysbiotic gut microbiome, and are at higher risk of adverse outcomes. Furthermore, fecal microbial transplant has emerged as a promising treatment modality in multiply recurrent CDI. However, given the effect of microbiome perturbations on the course of IBD, FMT requires special consideration in this patient population, particularly as we explore FMT as an emerging therapeutic modality for this condition. Dr.

Sohum Patwa, resident in internal medicine at Rhode Island Hospital (RIH), and Dr. Christopher Ward, former chief resident at RIH and currently a gastroenterology fellow at the Lahey Clinic, accompany Dr. Colleen Kelly, an associate professor of medicine at Brown, world-renowned expert in FMT and lead author of the recent ACG guidelines on management of CDI, discuss the features of CDI in IBD patients and the nuances of FMT in this population.

**TREAT-TO-TARGET: THE ERA OF BIOLOGICS IN IBD MANAGEMENT**

One of the major paradigm changes in the management of IBD over the last decade is the shift of goals of treatment from improvement in symptoms alone to healing gut inflammation. This concept is inspired from care of patients with rheumatoid arthritis, where the focus of treatment has evolved to healing joint inflammation with the goal of preventing long-term joint damage and preserving organ function. This concept is discussed at length in the manuscript written Dr. Daniel Marino and lead editor Dr. Samir A. Shah. We are also fortunate to have input from renowned faculty across United States, including Dr. Siddharth Singh of the University of California San Diego, Dr. Jason Hou of the Baylor College of Medicine, Dr. Corey Siegel of Dartmouth-Hitchcock Medical Center, and Dr. Gil Melmed of Cedars-Sinai Medical Center. They also review the efforts of IBD Qorus, a nationwide quality improvement initiative aimed at improving care of patients with IBD. IBD Qorus now includes over 50 sites across the US that work in a collaborative fashion to improve care of IBD patients in a variety of different areas; their most recent focus is improving adoption of a treat-to-target approach in the care of IBD patients.

**PART II**

In the upcoming issue, we will cover the following topics:

- Lessons from the Ocean State Crohn’s and Colitis Area Registry (OSCCAR)
- Surgical Advances in IBD
- Management of the Hospitalized Patient with Acute Colitis
- Reproductive Issues in Women with IBD
- Nutritional Therapy in Inflammatory Bowel Disease
- Pediatric IBD
- COVID-19 and IBD: Lessons from SECURE-IBD

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**Guest Editors**

- Abbas H. Rupawala, MD, Division of Gastroenterology, UMass Chan Medical School, Worcester, Massachusetts.
- Jason M. Shapiro, MD, Division of Gastroenterology, Nutrition and Liver Diseases, Hasbro Children’s Hospital, Providence, Rhode Island.
- Samir A. Shah, MD, Chief of Gastroenterology, The Miriam Hospital, Providence, Rhode Island; Gastroenterology Associates, Inc., 44 West River Street, Providence, Rhode Island.

**Correspondence**

Abbas H. Rupawala, MD  
[Abbas.rupawala@umassmed.edu](mailto:Abbas.rupawala@umassmed.edu)

# Preventive Care and Health Maintenance in Patients with Inflammatory Bowel Disease

DANIELA FLUXA, MD; BRETON ROUSSEL, MD; JANA G. HASHASH, MD, MSc; FRANCIS A. FARRAYE, MD, MSc

## ABSTRACT

Health maintenance in patients with inflammatory bowel disease (IBD) is essential. In order to achieve clinical and endoscopic remission, many patients will require treatment with steroids, immunomodulators, biologics or small molecules, which place them at a higher risk of serious infections as well as certain malignancies. Some of these adverse events are preventable through vaccination and adherence to cancer screening guidelines, making preventive care and health maintenance in this patient population crucial. Gastroenterologists should take a proactive role in health care maintenance and collaborate with the patient's primary care provider. The aim of this article is to review and provide guidance on preventive care and health maintenance in patients with IBD, including vaccinations, cancer screening, bone health, nutrition, and mental health assessment as well as smoking cessation.

**KEYWORDS:** health maintenance; inflammatory bowel disease (IBD); preventive medicine; screening

## INTRODUCTION

Inflammatory bowel disease (IBD) consists of a spectrum of diseases including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis. These are chronic inflammatory conditions of the bowel that may affect patients of any age range with a peak incidence during the second to fourth decade of life.<sup>1</sup> It has been estimated that the number of people worldwide living with IBD had increased from 3.7 million to more than 6.8 million between 1990 and 2017, with nearly a quarter of these patients living in the United States.<sup>1</sup> IBD is a complex condition and many patients with IBD will require immunosuppressing therapies with corticosteroids, immunomodulators, small molecules and/or biologic agents. For this reason, many patients with IBD are at an increased risk of infections, malignancy and other complications.<sup>2</sup> Up-to-date health maintenance is paramount in patients with IBD as a means of limiting morbidity from the disease itself and its treatment. Data suggests that patients with IBD do not receive adequate preventive care as compared to the general population,<sup>3</sup> and even though health

maintenance guidelines from different GI societies are available, adherence to preventive care recommendations, especially vaccination, remain low.<sup>4</sup> Moreover, many patients with IBD consider their gastroenterologist as their primary care provider (PCP).<sup>2</sup> For these reasons, it is imperative that gastroenterologists take a proactive role in health maintenance in these patients. It is of equal importance to partner with PCPs in optimizing health maintenance. The intent of this article is to review and provide guidance on preventive care and health maintenance in patients with IBD, including vaccinations, cancer screening, bone health, nutrition, and mental health assessment as well as smoking cessation.

## VACCINES

Patients with IBD are susceptible to acquiring infections for two reasons: immunological disorder caused by the disease itself, as well as treatment side effects.<sup>5</sup> Over the last two decades, the advent of new biologic agents and small molecules revolutionized the treatment of IBD. These medications are proven to be beneficial in controlling disease activity but may also place the patient at a higher risk for serious and/or opportunistic infections, a number of which are vaccine preventable.<sup>6</sup> In general, patients with IBD are recommended to follow standard, age-appropriate immunization schedules, with immunizations occurring ideally prior to initiation of immunosuppressive therapy, as some of these therapies may blunt vaccine response.<sup>3</sup> Special consideration must be kept for live-attenuated vaccines, which are contraindicated in immunosuppressed patients, particularly those who are moderately-severely immunosuppressed. Patients with IBD are considered to be moderately-severely immunosuppressed if taking any of the following medications: systemic steroids with doses of  $\geq 20$  mg for  $\geq 2$  weeks, methotrexate (MTX)  $> 20$  mg per week or  $> 0.4$  mg/kg/week, azathioprine (AZA)  $> 3$  mg/kg/day, 6-mercaptopurine (6-MP)  $> 1.5$  mg/kg/day, cyclosporine, biologic agents (except for vedolizumab) and small molecules.<sup>7</sup> Of note, significant protein calorie malnutrition is also linked with immunosuppression.<sup>8</sup> Low dose immunosuppression includes receiving treatment with topical steroids (oral budesonide  $> 6$  mg/day) and those on lower doses of systemic steroids, MTX, AZA and 6-MP.<sup>7</sup> In contrast to patients who are moderately-severely immunosuppressed, certain live vaccines may be safe

during low-dose immunosuppression or in patients on certain biologic agents; however, the decision to administer any live vaccine should be considered on a case-by-case basis.<sup>7,8</sup> Examples of commonly used live-attenuated vaccines include measles-mumps-rubella (MMR) vaccine, varicella (VAR) vaccine, nasal influenza and the live herpes zoster vaccine (no longer available in the United States). Other live vaccines include yellow fever, cholera and one of the existing typhoid vaccines which are usually administered for travel purposes.<sup>2</sup> Otherwise, all adult patients with IBD may receive non-live vaccines including inactivated influenza vaccine, pneumococcal vaccines, hepatitis A and B vaccine, tetanus-diphtheria and pertussis (Tdap), human papillomavirus (HPV) vaccine, meningococcal vaccine, inactivated recombinant herpes zoster vaccine and adenovirus, subunit or messenger RNA (mRNA) vaccines directed against coronavirus virus disease (COVID-19).<sup>2</sup> Current vaccination recommendations in adult patients with IBD are summarized in **Table 1**, see **Appendix**. Given COVID-19 vaccinations are dynamically changing as the pandemic evolves, would recommend visiting the Center for Disease Control and Prevention websites for updated information. Pediatric recommendations on regards to COVID-19 vaccination are also available in these websites: (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html> and <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html>).

Regarding optimal timing for vaccination, the Infectious Diseases Society of America (IDSA) guidelines recommend that the administration of live vaccines should occur at least 4 weeks prior to initiating immunosuppression and should be avoided within 2 weeks of initiation of immunosuppression.<sup>9</sup> On the other hand, if a live vaccine is required and the patient has discontinued immunosuppressive therapy, it is recommended to at least wait for 1–6 months (five times the elimination half-life of a drug) prior to the live vaccine administration,<sup>7</sup> or if there is no detectable drug in the system for medications in which there are options to measure. For inactivated vaccines, the IDSA recommends administration at least 2 weeks prior to initiating immunosuppression.<sup>9</sup>

Employing a “cocoon strategy”, vaccinating household and close contacts is also an important approach. Healthy immunocompetent individuals who live in a household with immunocompromised patients should receive inactivated vaccines as per their age-appropriate schedules, and the following live vaccines based on the Centers for Disease Control and Prevention (CDC) annual schedule: MMR vaccine, rotavirus vaccine in infants 2–7 months (immunocompromised patients should avoid handling diapers of vaccinated infants for 4 weeks following vaccination), VAR vaccine, and in cases when the inactive zoster vaccine is not available, the live zoster vaccine is recommended. Immunocompromised patients should avoid individuals who develop skin lesions after receiving the VAR or the live zoster vaccines until the

lesion disappear.<sup>9</sup> Household and close contacts may also receive the following live vaccines for travel: yellow fever and oral typhoid vaccine, while the oral polio vaccine should not be administered under any circumstances.<sup>9</sup>

**CANCER SCREENING**

**Colon Cancer**

Colonoscopy remains the primary modality used for colorectal cancer and dysplasia surveillance in patients with IBD. Two-step modalities such as fecal immunochemical test (FIT) or multi-targeted stool DNA tests (like Cologard™) are not appropriate for CRC surveillance in the IBD population.<sup>10</sup> The interval of screening and/or surveillance differs based on the duration and extent of disease. Dysplasia surveillance using high-definition colonoscopy should begin 8 years after disease diagnosis in patients with UC with involvement extending proximal to the rectum, or in patients with CD who have more than 1/3 of the colon involved.<sup>11–13</sup> Subsequent surveillance colonoscopies should be completed every 1-5 years following a negative colonoscopy based on additional patient risk factors for developing dysplasia or clinical features that could potentially obscure the detection of dysplasia (**Table 2**).<sup>12</sup> A personal history of dysplasia, adenomatous polyps, primary sclerosing cholangitis, family history of CRC, degree and extent of colonic inflammation, extensive pseudopolyps all inform increased frequency of surveillance. Patients with primary sclerosing cholangitis (PSC) should undergo a colonoscopy at time of

**Table 2.** Interval of time to next colonoscopy following a colonoscopy negative for dysplasia

1 year	2–3 years	5 years
Ongoing moderate or severe inflammation	Mild inflammation	Continuous disease remission with mucosal healing on colonoscopy and one of the following: No dysplasia on ≥2 consecutive colonoscopy Minimal historic colonic involvement i.e. <1/3 of the total colon
PSC	Family history of CRC but no first degree relative <50 years	
Family history of CRC in first degree relative diagnosed age <50 years	Endoscopic evidence of prior severe colitis such as scarring or moderate polyposis	
Extensive pseudopolyps	History of invisible dysplasia or high-risk visible dysplasia* diagnosed > 5 years prior	
History of invisible dysplasia or high-risk visible dysplasia* in last 5 years	History of lower risk visible dysplasia diagnosed in the last 5 years	

\*High risk visible dysplasia: >2cm, lateral spreading, irregular boarder, local recurrence, incomplete prior resection.

Table published in the 2021 AGA Clinical Practice Update on Endoscopic Surveillance of Colonic Dysplasia (12).

diagnosis and then annually. Chromoendoscopy during surveillance can be used at the discretion and expertise of the endoscopist with the potential of increasing detection of subtle lesions.

**Cervical Cancer**

Women with IBD on immunosuppressants are at an increased risk of developing cervical cancer or high-grade dysplasia.<sup>14</sup> For this reason, the American College of Obstetrics and Gynecology and American College of Gastroenterology (ACG) recommend an increased frequency of cervical cancer screening with annual cytology.<sup>8,15</sup> Furthermore, the increased risk of cervical dysplasia and malignancy emphasizes the importance of vaccination for HPV when indicated.

**Skin Cancer**

Both melanoma, and non-melanoma skin cancers (NMSC) are observed more frequently in patients with IBD. Immunosuppression with either immunomodulators or biologics confer additional risk. For patients taking chronic thiopurines for longer than 1 year, the risk of developing NMSC was at least four times that of matched healthy controls.<sup>16</sup> This association applies to both current and prior exposure to thiopurines.<sup>17</sup> Similarly, there is a higher risk of being diagnosed with melanoma (OR 1.88, 95% CI 1.08-3.29) in patients with a history of IBD, and particularly in patients treated with biologic therapy.<sup>18,19</sup> Primary prevention through behavioral modification such as sun avoidance and sunscreen use should be discussed with all patients with IBD. Furthermore, all patients with IBD should be referred for skin exam with a dermatologist.<sup>8</sup> Given the durability of risk despite cessation of immunomodulators, annual skin exams should be continued lifelong in select patients as directed by dermatology.

**BONE HEALTH/OSTEOPENIA-OSTEOPOROSIS**

Patients with IBD are at increased risk of osteopenia, osteoporosis, and bone fractures due to multiple factors, including type of IBD, history of corticosteroid use, low body mass index, malnutrition, vitamin D deficiency, calcium malabsorption, underlying chronic inflammatory state, and immobilization.<sup>4,20</sup> Published literature indicates that the risk of osteoporosis is estimated to be 15–40%.<sup>4</sup> Recommendations on screening of osteopenia/osteoporosis and prevention in patients with IBD are detailed in **Table 3**.<sup>21</sup>

**NUTRITIONAL ASSESSMENT**

Iron deficiency anemia is observed in approximately 45% of patient with IBD and occurs through multiple mechanisms, including luminal blood loss and decreased iron absorption.<sup>22</sup>

**Table 3. Bone Health – Screening and prevention of osteopenia and osteoporosis\***

	Recommendation
Screening Dual energy X-ray absorptiometry (DEXA)	All IBD patients should be screened for osteoporosis if any of the following risk factors is present: <ul style="list-style-type: none"> <li>• Low BMI</li> <li>• &gt;3 months of cumulative steroid use</li> <li>• Postmenopausal</li> <li>• Hypogonadism</li> <li>• Tobacco use</li> </ul> If osteoporosis is noted the patient should be referred to endocrinology for evaluation of bisphosphonate therapy. Repeat in 5 years if initial screen is negative.
Prevention Vitamin D 25-OH level assessment	Serial monitoring of vitamin D levels, supplement if deficient (levels <20 consider vitamin D3 50,000 units weekly for 8 weeks followed by vitamin D3 2,000 units daily)
Calcium and Vitamin D supplementation	Co-prescription of calcium and vitamin D for all patient receiving a course of oral corticosteroids

\*Adapted from Health Maintenance Checklist for adults from the Crohn’s & Colitis Foundation (21) and Cornerstones Health IBD Checklist for monitoring and prevention (23).

The presence of inflammation may confound the interpretation of iron studies, and a ferritin cut-off of 100 ng/mL should be considered as the lower limit of normal in patients with active IBD. A consequence of impaired absorption, oral iron repletion may be ineffective and parenteral infusions are often necessary. Similarly, vitamin B12 deficiency is well described in patients with ileal CD or those with a history of prior ileal resection. Cornerstones Health recommends screening for iron deficiency in all patients with IBD and vitamin B12 deficiency in patients with ileal CD or history of ileal resection.<sup>23</sup> In patients at risk of B12 deficiency, methylmalonic acid (MMA) levels should be checked simultaneously and B12 replacement therapy considered in all patients with elevated MMA level for a goal B12 level of greater than 400 pg/mL and normalization of MMA. Parenteral replacement should be considered in patients with greater than 20 cm of terminal ileal resection.

**MENTAL HEALTH – DEPRESSION AND ANXIETY SCREENING**

Depression and anxiety are common disorders in patients with IBD with pooled mean rates almost twice as high when compared to healthy controls.<sup>24</sup> While anxiety has been associated with decreased compliance to medications, increased risk of surgery and lower quality of life, depression has been linked with pain, IBD flare and lesser response to IBD treatment in some studies.<sup>25</sup> Furthermore, depression severity has been associated with suicidal ideation in this patient population.<sup>26</sup> Therefore, screening of these conditions is critical as they may cause significant morbidity. The Crohn’s & Colitis Foundation health maintenance checklist

recommends all patients with IBD should be screened at baseline and on a yearly basis for depression and anxiety.<sup>21</sup> Patients who are found to have anxiety or depression should be referred to their primary care physician or mental health for further evaluation and management.

In addition, fatigue has also been related to psychosocial factors, including depression and sleep disturbances.<sup>27</sup> Therefore, evaluation of fatigue, sleep quality and management of sleep disorders are equally important.

### TOBACCO USE/SMOKING CESSATION

Smoking and tobacco use remain a significant health risk for any patient with IBD. Multiple studies suggest that active tobacco use is associated with an increased risk for the development of CD and for disease specific complications such as progression, need for surgery, and surgical complications.<sup>28,29</sup> Although there are data demonstrating decreased disease activity in patients with UC, tobacco should not be recommended because the overwhelming detriments of smoking on extra-intestinal health outweigh any benefits.

Despite clear evidence for the negative effects of smoking, up to 20% of patients with CD and 60% of patients with UC reported believing that smoking was either neutral or beneficial for their disease activity.<sup>30</sup> Furthermore, 21% of patients with CD and 44% of patients with UC within the same cohort were never asked about their smoking status.<sup>30</sup> Society guidelines emphasize the need to screen for tobacco use at every encounter.<sup>8,23</sup> For those patients who engage in cessation planning, the alliance between the gastroenterologist and PCP is critical to coordinate adjunctive therapies and optimize success.

### CONCLUSION

Healthcare maintenance remains a crucial issue in the care of patients with IBD. Despite their importance, many physicians do not address these factors due to lack of knowledge, time constraints, or because they do not feel that this is their responsibility. Checklists are now available to help gastroenterologists and PCPs ensure that their patients with IBD are receiving appropriate vaccinations and other screenings.

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**Authors**

Daniela Fluxa, MD, Division of Gastroenterology, Mayo Clinic, Jacksonville, FL.  
 Breton Roussel, MD, Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, RI.  
 Jana G. Hashash, MD, MSc, Inflammatory Bowel Disease Center, Division of Gastroenterology, Mayo Clinic, Jacksonville, FL.  
 Francis A. Farraye, MD, MSc, Inflammatory Bowel Disease Center, Division of Gastroenterology, Mayo Clinic, Jacksonville, FL.

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**Correspondence**

Francis A. Farraye, MD, MSc  
 4500 San Pablo Rd S, Jacksonville, FL, 32224  
 904-953-0729  
 Fax 904-953-6225  
[Farraye.Francis@mayo.edu](mailto:Farraye.Francis@mayo.edu)

# Extraintestinal Manifestations of Inflammatory Bowel Disease

SEAN FINE, MD, MS

## ABSTRACT

Inflammatory bowel disease (IBD) is primarily a disease of the digestive tract system, though it may affect other organ systems outside of the intestines. Extraintestinal manifestations (EIMs) can occur in up to one third of patients with Crohn's disease or ulcerative colitis. The most common EIMs involve dermatologic and musculoskeletal manifestations. EIMs may either parallel intestinal inflammation or be completely independent of disease activity. Physicians should be aware of EIMs and think systematically when evaluating patients with IBD, as nearly every organ can be involved, and a multidisciplinary treatment approach should be undertaken to improve outcomes and quality of life.

**KEYWORDS:** inflammatory bowel disease; extra intestinal manifestations; Crohn's disease; ulcerative colitis

## INTRODUCTION

Inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic immune-mediated diseases of the gastrointestinal tract. The chronic inflammation is a result of a dysregulated immune response that leads to tissue inflammation and destruction. However, IBD should not solely be regarded as an intestinal disorder, but rather a systemic disease given that a significant number of patients will develop extraintestinal manifestations (EIMs). Between 25-40% of patients with IBD<sup>1</sup> will develop EIMs and the presence of one confers the risk to develop subsequent EIMs. Rarely, up to five organ systems have been reported to be impacted at one time. Most patients who develop EIMs will do so after a diagnosis of IBD has been established. However, about 25% of patients will be diagnosed with an EIM initially, prior to uncovering a diagnosis of IBD. In a large IBD cohort study, the most common EIMs diagnosed prior to the onset of IBD included peripheral arthritis or axial arthritis, uveitis, and primary sclerosing cholangitis (PSC).<sup>2</sup> Risk factors that have been strongly correlated with the development of EIMs include cigarette smoking, colonic disease, and perianal CD.<sup>3</sup> Extraintestinal symptoms may involve virtually any organ system with a potential for a profound impact on the patient's quality of life, in some instances more so than bowel disease. The most affected systems

are the skin, musculoskeletal, and eyes, but several other organs may also be affected, including the kidneys, blood, and hepatobiliary.

The pathogenesis of EIMs in IBD is not clearly elucidated. The European Crohn's and Colitis Foundation working group has defined the mechanism for EIMs to better standardize for scientific discovery and research as the following: "An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."<sup>4</sup> Genetics, environmental triggers, and the intestinal microbiota have been postulated as potential culprits for the development of EIMs. Studies have demonstrated overlaps between genetic risk loci for IBD and EIMs and found a concordance for EIMs in parent-offspring pairs and sibling-pairs of 70% and 84% respectively.<sup>5</sup> The most well-known genetic risk factor for central arthritis (Ankylosing spondylitis) in association with IBD is HLA-B27 positivity. Tobacco use has been shown to be associated with a higher risk for development of both skin and joint EIMs.<sup>6</sup> The role of the intestinal microbiota in the pathogenesis of IBD is well established as an undesired and overacted immune response is directed at the intestinal flora. One of the hypothesized processes in which the microbiota plays a role in the development of EIMs is in part through molecular mimicry. Cross-reactivity of the immune system against other extra-intestinal sites occurs due to gut microbiota antigens sharing similar epitopes present on cells in organs. Another potential etiology of inflammation developing beyond the intestine may be attributed to loss of the intestinal barrier integrity, which then allows for bacterial flora and its components to translocate to distant sites and lead to an inflammatory response. The importance of the colonic microbiota in inflammation is seen in the findings that patients with IBD that involves inflammation of the colon develop EIMs at a higher rate compared to those with isolated small bowel disease.

It is important to differentiate EIMs from extraintestinal complications. EIMs are immune-mediated conditions which echo the immunologic mechanisms of inflammation in bowel disease, whereas extraintestinal complications (Table 1, see Appendix) arise from secondary processes that are direct

**Table 2.** Extra-Intestinal Manifestations and Association with Bowel Disease Activity

EIM	Parallels Bowel Disease Activity	Unclear Association With Disease Activity	Independent of Bowel Disease Activity	Therapy
<b>Oral</b> • Aphthous Stomatitis • Pyostomatitis Vegetans	✓ ✓			Treatment of intestinal inflammation
<b>Ocular</b> • Episcleritis • Scleritis • Uveitis	✓		✓ ✓	Refer to Table 3
<b>Musculoskeletal</b> Peripheral Arthritis • Type 1 (<5 joints) • Type 2 (≥5 joints)  Axial Arthritis • Ankylosing Spondylitis • Sacroiliitis	✓		✓  ✓ ✓	Treatment of intestinal inflammation  COX-2 inhibitors Sulfasalazine (notably in UC)  Anti-TNF
<b>Dermatologic</b> • Erythema Nodosum  • Pyoderma Gangrenosum  • Sweet's Syndrome  • Bowel associated dermatosis and arthritis syndrome (BADAS)	✓   ✓ ✓	✓		Treatment of intestinal inflammation  <b>Local</b> • Wound care, Topical steroids, topical calcineurin inhibitors <b>Extensive</b> • Systemic steroids, systemic cyclosporine, Anti-TNF <sup>30</sup> , methotrexate, azathioprine, Dapsone <sup>31</sup> , minocycline, IVIG <sup>32</sup>  Treatment of intestinal inflammation  Short course of systemic steroids if needed
<b>Hepatobiliary</b> • Primary sclerosing cholangitis			✓	Close monitoring and surveillance given strong malignancy association (cholangiocarcinoma, HCC, colon cancer, gallbladder cancer) Liver Transplantation for cirrhosis

or indirect sequela of bowel damage (anemia, nephrolithiasis, Vitamin B12 deficiency) or related to medications used to manage the disease.<sup>7</sup> EIMs can manifest in parallel with IBD disease activity or be completely independent (Table 2), sometimes being even more difficult to manage and treat than the bowel disease itself. Patient awareness through education and a multidisciplinary team approach are important key factors for early identification and treatment of EIMs that can lead to symptom resolution and improving quality of life.

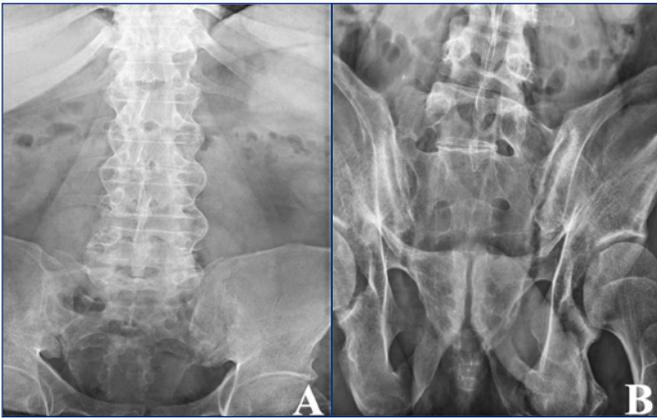
**MUSCULOSKELETAL**

Musculoskeletal symptoms represent the most common EIMs in IBD and are termed “seronegative spondyloarthropathies.” Peripheral small and large joints as well as axial joints may be affected in up to 40% of patients with IBD.<sup>8</sup> Musculoskeletal EIMs can precede, occur concurrently, or develop following the diagnosis of IBD, often by as many as 10 years.<sup>9</sup> Males and females are equally affected, but patients with colonic disease are more impacted than those

with isolated small-bowel disease.

Peripheral arthritis is a migratory arthritis that shows little to no joint deformity, but inflammation may last up to several weeks. Peripheral arthropathy is divided into two types: type 1 and type 2. Type 1 is pauciarticular (typically involving fewer than 5 joints), seronegative, asymmetric and will often parallel disease activity. Joints that may be affected include the knees (most common), shoulders, hips, wrist, ankles, and elbows. Type 2 is polyarticular (involving 5 or more joints), symmetric, is independent of bowel disease, and typically affects the metacarpophalangeal joint. Type 2 is associated with an increased risk of uveitis.<sup>10</sup> The diagnosis of type 1 and type 2 is based on clinical suspicion, as imaging is unrevealing due to the lack of joint destruction. Treatment for type 1 is based on addressing bowel disease whereas type 2 is more directed at symptoms with rest, intra-articular steroid injections, physiotherapy, or sulfasalazine. The selective COX-2 inhibitor, celecoxib, has been demonstrated to be a potential treatment option and used with caution in patients with IBD since it is not been found to be associated with inducing flares.<sup>11,12</sup>

Figure 1. (A) Ankylosing Spondylitis. (B) Sacroiliitis.



Axial arthropathies occur less frequently than peripheral arthritis and includes both ankylosing spondylitis and sacroiliitis. These inflammatory joint processes affect males more than females and do not parallel bowel inflammation. Ankylosing spondylitis classically presents with a stooped posture and worsening back pain/stiffness in the morning or at night and is improved with physical activity. Physical exam may reveal limited spinal flexion and X-ray imaging of the lumbar spine will show a “bamboo spine” that represents complete fusion of the bones (Figure 1A). Nearly all patients with IBD who have the genetic mutation in HLA-B27 will develop ankylosing spondylitis. IBD-associated sacroiliitis (Figure 1B) is most often bilateral in nature and can be either symptomatic or asymptomatic. Asymptomatic sacroiliitis can be seen in up to 50% of patients with CD.<sup>5</sup> Spinal and axial disease are treated similarly to other spondyloarthropathies. Patients should be given a formal exercise plan and work closely with physical therapy to prevent deformities. Therapeutic agents that may also be used in axial arthritis include sulfasalazine, immunomodulators (methotrexate and azathioprine), and anti-tumor necrosis factor (TNF) therapy.

**DERMATOLOGIC**

Cutaneous EIMs may occur in up to 15% of patients with IBD and require dermatologic evaluation to confirm and assist in management.<sup>13</sup> The two most common skin findings in IBD are erythema nodosum (EN) and pyoderma gangrenosum (PG). EN often appears on the extensor surfaces of the lower extremities, commonly the anterior tibial area, and is characterized by red raised tender nodules about 1–5 cm in diameter (Figure 2A). Although lesions may not be easily visible, physical exam will reveal tender palpable areas. Diagnosis is based on clinical judgement and skin biopsies are not necessary to make a diagnosis but would reveal inflammation of subcutaneous fat (panniculitis). EN shows a preponderance in females to males, associated with eye and joint involvement, and has a higher prevalence in CD than UC.<sup>14</sup> The development of lesions parallels disease activity and thus treatment is aimed at addressing the ongoing bowel inflammation. Importantly, EN has been shown in a retrospective study to carry a 6-fold risk of development IBD within 3 years of presentation so this physical exam finding should prompt clinicians to always have a high index of suspicion for IBD.<sup>15</sup> PG can be a debilitating skin disorder that occurs in about 5% of patients with IBD and is characterized by a discrete ulcer with a necrotic base, irregular violaceous edges, and purulent material which is sterile on culture. PG usually occurs on the lower extremities (Figure 2B) but may occur anywhere on the body notably, adjacent to a postsurgical stoma on the abdominal wall.<sup>16</sup> These ulcers can range in size from a few centimeters to an entire limb. PG exhibits pathergy, a significant physiologic response to minor trauma or injury. Therefore, biopsy of the lesion should be avoided and the diagnosis is made clinically. It affects women more than men and it is unclear if PG has an association with clinical intestinal disease activity but in some instances may resolve with treatment of IBD. Mild cases may be treated with topical or local therapy that consists of steroid injections and moist dressings, but often

Figure 2. (A) Erythema Nodosum on lower extremities of a patient with IBD. (B) Pyoderma Gangrenosum. (C) Bowel associated dermatosis-arthritis syndrome (BADAS).

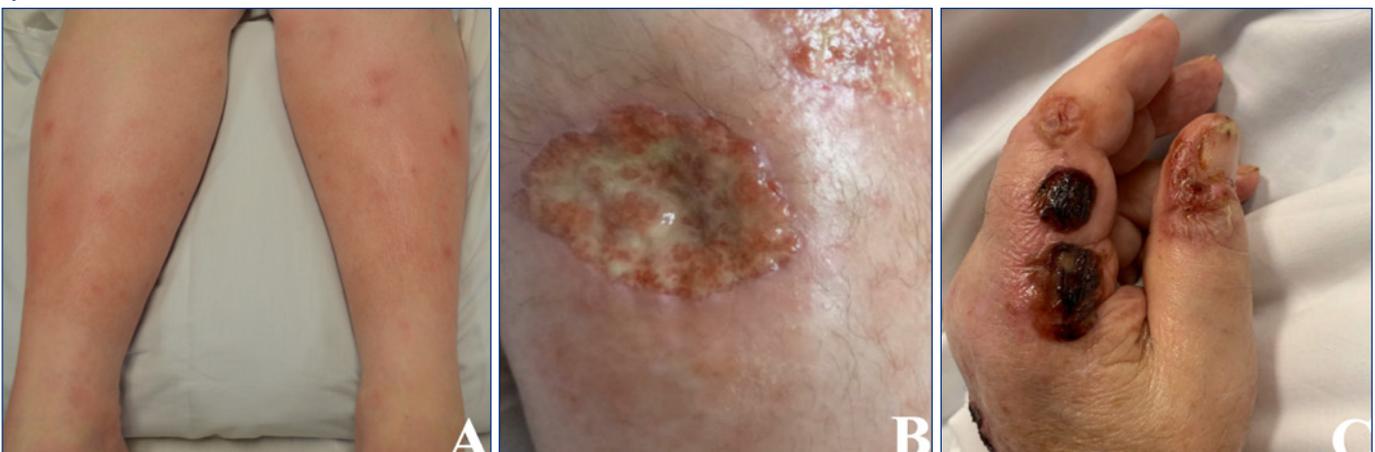
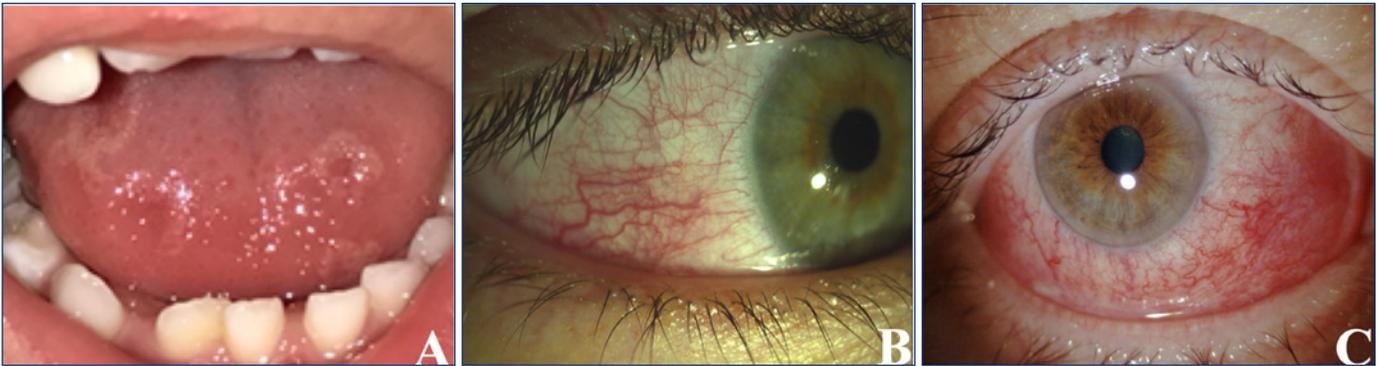


Figure 3. (A) Aphthous Stomatitis. (B) Episcleritis. (C) Scleritis.



systemic agents are needed that include dapsone, corticosteroids, and anti-tumor necrosis factor (TNF) therapy as well as involvement of a vascular surgeon specialist.

Acute febrile neutrophilic dermatosis, Sweet’s syndrome, is a rare EIM characterized by sudden onset tender erythematous papules and plaques on the upper extremities, trunk and face in association with fever and leukocytosis. Most cases occur in females, parallel intestinal disease activity, and are associated with other EIMs like arthritis. Treatment recommendations include topical or systemic steroids as well as adequate treatment of the IBD. Bowel associated dermatosis-arthritis syndrome (BADAS) is another rare neutrophilic dermatosis manifestation that was initially described in patients who had undergone ileojejunum bowel surgery but can also occur in patients with IBD. It presents with constitutional symptoms that include fever, arthritis, and arthralgias that precede an inflammatory skin eruption. Skin findings are characterized by erythematous macules that evolve into purpuric papules and vesiculopustular lesions on the upper extremities and trunk (Figure 2C). The pathophysiology is thought to involve immune complex creation in response to antigens from intestinal bacterial overgrowth that then deposit in the skin and synovium.<sup>17,18</sup> Therapy for BADAS syndrome should focus on addressing the underlying intestinal inflammation in patients with IBD.

**ORAL AND OCULAR**

Oral lesions are common in patients with IBD but are found more often in patients with CD rather than UC, more prevalent in children compared to adults, and are found more commonly in men than women.<sup>19</sup> The classic oral lesion associated with IBD is aphthous stomatitis, commonly referred to as a “canker sore”, presents as a shallow painful ulceration with a central fibrinous exudate and an erythematous boarder and can lead to symptoms of dysphagia or odynophagia. The lesions are commonly located along the buccal and labial folds but may also be present on the tongue (Figure 3A) or in the oropharynx. In a small number of patients, this may be the initial clinical exam finding

on presentation , but most often are diagnosed after intestinal involvement has occurred.<sup>20</sup> Aphthous stomatitis is common in the general population as well as other immune mediated diseases, but this finding is reported in up to 25% patients CD and 10% with UC.<sup>21</sup> The presence of aphthous stomatitis becomes more severe with active bowel disease. Treatment mainly consists of topical steroids and anesthetics as well as addressing bowel disease with anti-inflammatory medications.

Pyostomatitis vegetans (PV) is a much less common occurrence but is an important oral manifestation of IBD for providers to be aware of. PV is commonly associated with UC but may also present in patients with CD. Intestinal manifestations will often predate PV development and patients will present with numerous tender miliary sterile pustular eruptions anywhere on the oral mucosa in a linear arrangement that may resemble “snail tracks.” Similarly, treatment of this presentation is achieved by addressing the bowel inflammation as well as topical steroids and antiseptic mouthwashes.

Ocular manifestations in IBD occur in 0.3–5%<sup>9</sup> of patients and often associated with concomitant musculoskeletal manifestations. The ocular findings in patients with IBD that practitioners may encounter include episcleritis, scleritis, and uveitis. Being able to differentiate amongst these is of vital importance to early identify, appropriately treat, and prevent long-term patient morbidity (Table 3). Episcleritis is defined by hyperemia of the episcleral, which is the vascular plexus and fibrous tissue layer between the conjunctiva and sclera. It is a relatively benign manifestation and has no effect on vision. Eye exam reveals sectoral or diffuse patches of redness secondary to the inflamed superficial episcleral vessels (Figure 3B). Episcleritis often parallels bowel disease activity. Scleritis is a more pressing inflammation that affects the deeper layers of the eye, “the white of the eye”, and if not identified early can lead to visual impairment. Patients often have significant pain, classically deep boring pain that awakens the patient from sleep.<sup>22</sup> One key exam feature to differentiate episcleritis from scleritis is the deep episcleral vascular plexus does not blanch when topical phenylephrine

**Table 3.** Clinical Differences Between Episcleritis, Scleritis, Uveitis

	Symptoms	Urgency Level	Diagnosis/Treatment
Episcleritis	Redness, burning, itching (Never any vision changes, photophobia, or change in pupillary response to light)	Non-Urgent	Redness within white patches of sclera.  Blood vessels blanch when phenylephrine drops applied <ul style="list-style-type: none"> <li>• Treat underlying IBD</li> <li>• Cool compress and/or topical steroids</li> </ul>
Scleritis	Redness, eye pain with associated tenderness to palpation, deep boring pain that awakens patient from sleep	Urgent	No blanching of blood vessels when phenylephrine drops applied  Violaceous hue <ul style="list-style-type: none"> <li>• Systemic steroids or immunosuppression</li> </ul>
Uveitis	Redness, eye pain, blurred vision, photophobia	Urgent	Requires slit lamp exam <ul style="list-style-type: none"> <li>• Topical and systemic steroids</li> <li>• Severe/refractory cases may require systemic immunosuppression</li> </ul>

is applied. In scleritis, the sclera may have a bluish hue that is representative of thinning of the sclera (**Figure 3C**). Uveitis is inflammation of the middle chamber of the eye (iris, ciliary body, and choroid) and occurs independently of bowel disease activity, but often in association with other EIMs. Patients will often present with ocular pain, headache, and blurred vision. Urgent ophthalmic exam via slit-lamp reveals the presence of perilimibic edema and inflammatory flare in the anterior chamber.<sup>22</sup> Once identified, prompt initiation of topical and systemic steroids is vital and patients may require systemic immunosuppression with anti-tumor necrosis factor (TNF) therapy.

**HEPATOPANCREATOBILIARY**

Up to 50% of patients with IBD will experience hepatopancreatobiliary manifestations and complications during their disease course that may include gallstones, portal vein thrombosis, autoimmune hepatitis, autoimmune pancreatitis (Type 2), and primary sclerosing cholangitis (PSC). PSC is a chronic cholestatic liver disease that is characterized by fibrosis of the intrahepatic and extrahepatic bile ducts. Workup for PSC should be pursued in patients with IBD in the setting of elevated alkaline phosphatase or gamma-glutamyl transferase serum levels. Radiographic images will demonstrate multifocal bile duct strictures and segmental dilation, classically described as “beads on a string.” PSC is strongly linked to UC where at least 75% of patients with PSC have coexisting UC.<sup>9</sup> Overall, a small number of patients with IBD will have PSC, 5% of UC patients and 2% of patients with CD (mainly colonic). Risk factors for the development of PSC in patients with UC are pancolitis, history of appendectomy, and male gender.<sup>23</sup> There is a strong association (10-fold risk) for the development of colorectal dysplasia/and or cancer in patients with PSC and therefore patients should undergo initial colonoscopy at the time of diagnosis and then yearly thereafter. Gallbladder polyps in association with PSC have a high malignant potential and therefore screening by yearly ultrasound and if found should

undergo treatment with cholecystectomy. Other potential complications that may arise from PSC include the development of acute bouts of acute cholangitis, cholangiocarcinoma, progression to liver fibrosis/cirrhosis, and acute decompensation requiring liver transplant.<sup>24,25</sup> There are currently no recommended treatments for PSC and addressing the underlying bowel inflammation does not affect progression of PSC; however, management of patients requires a multidisciplinary team approach.

**RENAL**

Nephrolithiasis is prevalent at a higher rate in patients with IBD compared to the general population and represents an extraintestinal complication of IBD.<sup>26</sup> Renal stone formation can ultimately lead to repeated episodes of abdominal pain, chronic interstitial nephritis and, consequently, chronic kidney disease. One particular type of stone formation is closely associated with CD and an intact colon. Calcium-oxalate stones form due to depletion of bile acid salts secondary to inflamed or resected ileum. Bile acid salts are required for fat absorption; however, when inadequate amounts are present, fat can no longer be absorbed. This leads to calcium preferentially binding to fat rather than oxalate. Oxalate is then able to be easily reabsorbed by the colon and ends up in the urinary tract, leading to stone formation.

**HEMATOLOGIC**

Patients with IBD are at an increased risk for venous thromboembolism (VTE) such as deep vein thrombosis, portal vein thrombosis, and pulmonary embolus. The etiology is multifactorial in nature stemming from active inflammation, nutritional deficiencies, and hospitalizations/surgeries that lead to immobility. The risk for VTE in patients with IBD is 3-fold higher than the general population.<sup>27</sup> Several IBD-phenotype risk factors have been reported to be independent risk factors for VTE that include fistulizing disease, colonic involvement in CD, and extensive disease in patients with

UC.<sup>28</sup> The highest risk factor for VTE is in patients who are hospitalized with acute severe colitis.<sup>29</sup> Prevention of VTE is critical in IBD patients who are hospitalized and providers should order the appropriate prophylactic medications even in most settings of patient-reported gastrointestinal bleeding in order to prevent this complication.

## CONCLUSION

EIMs are common in both CD and UC and may have profound impacts on patients. While some EIMs may parallel bowel disease activity, others have an independent disease course that requires lifelong management and monitoring. It is important for providers in all specialties to have an awareness of the prevalence and clinical presentations of EIMs to best identify and implement therapeutic treatments to improve the quality of life for patients with IBD.

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**Author**

Sean Fine, MD, MS, Department of Medicine, Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, Rhode Island.

**Correspondence**

Sean Fine MD, MS  
 Director, Center for Inflammatory Bowel Disease  
 Brown Medicine  
 375 Wampanoag Trail  
 Riverside RI, 02915  
 401-649-4030  
 Fax 401-649-4031  
[sean\\_fine@brown.edu](mailto:sean_fine@brown.edu)

# FMT: What's Next?

## A Narrative Review of Fecal Microbiota Transplantation in *Clostridioides difficile* Infection and Inflammatory Bowel Disease

SOHUM A. PATWA, MD; CHRISTOPHER WARD, MD; COLLEEN R. KELLY, MD, FACG

### ABSTRACT

Fecal microbiota transplantation (FMT) is an increasingly employed treatment option for *Clostridioides difficile* infection (CDI), with growing data supporting its safety and effectiveness in patients with concurrent inflammatory bowel disease (IBD). Given that alterations in the gut microbiome are associated with both ulcerative colitis (UC) and Crohn's disease (CD), the use of FMT for the treatment of IBD itself is another area of active investigation. In this narrative review, we highlight the evidence for use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone, and provide insight into the future of microbiome therapeutics.

**KEYWORDS:** fecal microbiota transplantation; *Clostridioides difficile* infection; inflammatory bowel disease

In addition to being effective for the treatment of CDI in patients with IBD, FMT may also be effective in the treatment of IBD itself, as several RCTs have shown promising results.<sup>9-12</sup> However, FMT for this indication is still considered investigational and only permissible within clinical trials being performed under an investigational new drug application (IND).<sup>13</sup>

The process of FMT includes donor selection, serological and stool screening for transmissible infections, anaerobic or aerobic preparation and processing of fecal material, and homogenization of stool to a form which can be administered to the recipient (**Figure 1**).<sup>11,14</sup> Delivery of FMT through colonoscopy or capsules appears to be most effective<sup>15,16</sup> though enema delivery may be considered in some circumstances.<sup>8</sup>

In this narrative review, we discuss the evidence surrounding use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone. Additionally, we provide insight into future investigations around microbiota therapeutics for these indications.

### INTRODUCTION

The normal gastrointestinal microbiome contains a delicate and diverse balance of bacteria and other microorganisms which are increasingly recognized to play a major role in health and disease. Fecal microbiota transplantation (FMT) is a powerful therapeutic option in conditions caused by an imbalance in the microbiota, or dysbiosis, such as *Clostridioides difficile* infection (CDI). FMT aims to restore gut homeostasis through the reintroduction of the community of organisms contained in the fecal material of healthy donors.

The use of FMT in Western medicine was first described in 1958 for the treatment of pseudomembranous enterocolitis.<sup>1</sup> It remained rarely utilized until the early 2000s, when the rates of multiply recurrent CDI, refractory to standard antibiotic therapies, sharply increased.<sup>2</sup> After a number of cohort studies and randomized-controlled trials (RCTs) demonstrating high efficacy,<sup>3-7</sup> FMT is now considered a standard treatment option for CDI. The American College of Gastroenterology (ACG) 2021 guidelines on the treatment of CDI recommended the consideration of FMT for patients after a second or further episode of recurrent CDI and for patients with acute, severe and/or fulminant CDI that is refractory to antibiotic therapy, especially when patients are poor surgical candidates.<sup>8</sup>

**Figure 1.** Preparation of donor stool in saline.



**FECAL MICROBIOTA TRANSPLANTATION FOR CLOSTRIDIODES DIFFICILE INFECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE**

In patients with IBD, many variables can predispose to *C. difficile* colonization and infection, including increased exposure to antimicrobials, immunosuppression, and altered (reduced, less diverse) fecal microbiota.<sup>17</sup> Patients with IBD tend to suffer from more severe CDI owing to an increased prevalence of virulent and refractory *C. difficile* strains in this population.<sup>17</sup> Patients with IBD who contract CDI are at increased risk of IBD flare, hospitalization, *C. difficile* carriage, recurrence, and death.<sup>17,18</sup>

The most recent evidence on the use of FMT in patients with IBD is gathered in a meta-analysis from Tariq et al,<sup>18</sup> who reviewed 25 observational studies addressing the use of FMT for recurrent *C. difficile* infections in both the adult and pediatric IBD populations. Of the 25 studies included in this meta-analysis, one was a prospective study, the remainder were retrospective. In their analysis, single (i.e., one-dose) FMT was associated with a pooled CDI cure rate of 78% in both the adult and pediatric populations. The definition of cure rate varied by study, ranging from clinical resolution to clinical remission to endoscopic resolution.<sup>18</sup> In studies reporting single and multiple FMTs combined, the pooled cure rate was 88% in the adult population and 77% in the pediatric population, a difference that was significant in the adult population.

Based on early case reports, there was concern that altering the microbiome of the recipient through FMT could lead to worsened IBD symptoms or negatively impact the trajectory of the underlying disease process.<sup>19</sup> In their meta-analysis, Tariq et al found that after FMT, a pooled 26.8% of adult patients experienced an IBD flare, which was defined in most studies as escalation of therapy and/or worsening symptoms. Conversely, the authors of seven studies in this meta-analysis noted that a pooled 33.8% patients had an improvement in IBD symptoms after FMT. This improvement may reflect the notion that FMT may treat underlying IBD symptoms – a concept addressed in later sections of this review.

A systematic review analyzing side effects of FMT for the treatment of CDI (without underlying IBD) found that amongst 1089 patients, most common adverse events included abdominal discomfort, fever, and nausea.<sup>19</sup> Serious adverse events (SAEs) included severe infection (2.5%) and death (3.5%), though the authors of this review acknowledged that many of the studies suffered from small sample sizes.<sup>19</sup> Tariq et al noted that the most common adverse events (AEs) after FMT were fever and diarrhea, with isolated reports of abdominal pain, small bowel obstruction, cytomegalovirus colitis, pancreatitis, and upper respiratory tract infection.<sup>17,18,20</sup> The pooled rate in the adult population of undergoing colectomy after FMT was reported as 7.3%,

with authors citing worsening IBD symptoms and increased colon cancer risk in the setting of primary sclerosing cholangitis as the indications for colectomy. Eight deaths were reported in this meta-analysis, one of which was due to aspiration during anesthesia, and seven of which were unrelated to FMT.<sup>18</sup> Tariq et al found variables that may be associated with failure of FMT included severity of CDI, low serum albumin, proton pump inhibitor use, and hypertension. There was insufficient data to carry out a meta-analysis on this subject.<sup>18</sup>

The prospective study by Allegretti et al<sup>21</sup> referenced in the meta-analysis is the largest to date on the subject of CDI and IBD outcomes. In this study, the authors enrolled 50 patients with IBD [15 with Crohn’s disease (CD) and 35 with ulcerative colitis (UC)] and a history of two or more confirmed episodes of CDI within the past year. All patients in the study underwent single FMT delivered via colonoscopy. The primary outcome assessed was FMT failure by week 8 (diarrhea and positive *C. difficile* stool testing). If FMT failure occurred, patients underwent a second FMT; *C. difficile* colonization (no diarrhea but polymerase chain reaction positive for *C. difficile*) was a secondary outcome. The authors found that 89.8% of patients achieved cure after a single FMT. All four of the patients who initially failed FMT underwent a subsequent FMT, resulting in clinical cure by the eighth week. 91.8% of the patients enrolled were found to have decolonized *C. difficile* by one-week post-FMT. The authors found that two SAEs occurred, both of which were determined to be unrelated to the treatment, and FMT was otherwise well tolerated. A secondary analysis of the patients in this prospective study found that 62% of those enrolled with UC experienced an improvement in clinical severity and disease activity rating scores, 29.4% experienced no change, and 4% had a flare.<sup>22</sup> 73.3% of patients with CD experienced improvement, and 26.6% had no change in disease activity. None of the patients with CD experienced a disease flare.

The most recent ACG guidelines note that in patients with IBD who develop recurrent CDI, FMT should be considered,<sup>8</sup> though the quality of evidence is considered very low. Early evidence on the role of FMT in the treatment of CDI in those with concurrent IBD is promising.

**FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF ULCERATIVE COLITIS**

Recently there has been more research into the role of FMT in the primary treatment of IBD. This research is based on knowledge that the pathophysiology of IBD involves altered intestinal microbiota.<sup>23</sup>

A meta-analysis of four RCTs investigating the role of FMT in the treatment of UC found a pooled rate for clinical remission of 42.1% in the treatment group and 22.6% in the placebo group,<sup>24</sup> with most assessing clinical remission a

few weeks to months after delivery of FMT. In one of these RCTs, 42% of patients studied had achieved clinical and endoscopic remission 12 months post-FMT.<sup>11</sup>

There is no clear consensus on dosing of FMT in the IBD population. Paramsothy et al conducted their RCT using intensive dosing (40 infusions of stool blended in saline initially delivered directly to the terminal ileum or cecum via colonoscopy and later self-administered via enema over 8 weeks).<sup>10</sup> Others used lower intensity FMT in their RCTs (6 doses of stool blended in water delivered by once weekly retention enemas over 6 weeks<sup>12</sup> or 3 doses of stool blended in saline and glycerol initially delivered directly to the right colon via colonoscopy and later administered via enema over 1 week<sup>11</sup>). It does, however, seem clear that lower dosing employed for the treatment of CDI may not suffice for the primary treatment of IBD, which may require multiple doses for effect.

In an RCT analyzing the safety and tolerability of FMT in the UC population, the side effects most associated with FMT delivered via frozen oral capsule were nausea, fever, and a flare of disease requiring steroid taper.<sup>25</sup> Delayed side effects have been seen. In another RCT testing the effect of FMT on UC, low-dose FMT delivered colonoscopically and via enema was associated with at least one AE in 51% of participants at 12 months, including worsening colitis requiring colectomy in 13% of patients.<sup>11</sup> Notably, 12-month data were considered observational by the authors, as 97% of the control group had crossed over to the treatment group. Two other RCTs on the matter found no significant difference in AEs between treatment and control groups at the 8-week mark.<sup>10,12</sup>

Pouchitis is inflammation of the ileal pouch, a condition affecting patients with UC who have undergone proctocolectomy. FMT in the management of pouchitis has also been investigated. In a systematic review of four studies (one RCT, one prospective trial, and two cohort studies) by Kayal et al,<sup>26</sup> rates of clinical response and remission varied, and FMT in pouchitis was found to be generally safe but ineffective. The authors note that it was difficult to analyze these studies in aggregate given the differing characteristics of the four studies.

### FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF CROHN'S DISEASE

Evidence for the use of FMT in the treatment of CD is less robust, though early results were promising. A recent systematic review by Fehily et al analyzed 2 RCTs and 13 cohort studies on this topic, finding that FMT may be an effective treatment option for CD; however, large RCTs are lacking.

In one of the RCTs analyzed in this systematic review, the authors investigated the use of FMT in the treatment of CD over 24 weeks, with the primary outcome of colonization of donor fecal microbiota and with clinical parameters as

secondary outcomes. In this RCT, a significant difference was found between the FMT and placebo groups in the reduction in CD severity index at the 6-week time point after FMT.<sup>9</sup> Of the 17 patients analyzed, 44% of patients in the placebo group had clinical remission (defined as a score of <5 on the Harvey-Bradshaw Index, a calculator assessing CD severity) at 10 weeks, which dropped to 33.3% at 24 weeks. In the FMT group, 87.5% and 50.0% of patients experienced clinical remission at 10 weeks and 24 weeks, respectively. These, however, were not statistically significant differences. AEs were reported in both treatment and placebo groups, including disease flare; however, the authors did not consider these phenomena to be related to FMT itself.<sup>9</sup>

### PATIENT PERCEPTIONS ON FECAL MICROBIOTA TRANSPLANTATION

Patient perceptions of FMT may vary, but most patients are amenable to the procedure after counseling and education. Authors of a 2017 study conducted surveys of FMT perceptions amongst 267 patients in gastroenterology waiting rooms.<sup>27</sup> The authors found that those with a university degree were likelier to agree to FMT as compared to those without (p=0.04), suggesting that health literacy may play a role in the acceptance of FMT, and 77% of those surveyed were willing to undergo the procedure if indicated, with respondents' greatest concerns being lack of hygiene (22%) and risk of disease transmission (30%).

Sentiments on hygiene were echoed in a survey of 95 patients medically managed for UC who were surveyed regarding preferences and concerns surrounding FMT in the management of their IBD.<sup>28</sup> In this study, 46% of patients surveyed were willing to undergo the procedure, with 41% citing infection, 24% citing cleanliness, and 18% citing potential to worsen UC as their main concerns regarding FMT.

Patients who have undergone FMT appear to be satisfied with the procedure. In a survey of 54 patients who underwent FMT for recurrent CDI, 96% were willing to recommend FMT to others, and 94% were satisfied with the outcome.<sup>29</sup>

As the concept of FMT has made its way into the public domain, do-it-yourself (DIY) FMT has emerged – a phenomenon in which the public accesses and administers FMT for various conditions. In a 2019 survey of 84 people who had administered FMT to themselves or others, 43% had performed more than 10 FMTs, with 87% of those surveyed using techniques garnered through the internet.<sup>30</sup> 92% of these patients surveyed had acquired the DIY stool from a donor known to them. Conditions DIY FMT was used to treat included IBD (35%), IBS (29%), and CDI (26%). Notably, 86% of those with CDI felt that FMT improved their condition, and 90% of those with IBD reported improvement. Some of the reasons cited in this survey for implementing DIY FMT included lack of efficacy of other treatments (64%) or lack of access to physicians offering FMT (33%).

**CONCLUSION AND FUTURE DIRECTIONS**

FMT is now well-established as an effective intervention in the fight against CDI. In patients with recurrent CDI in the setting of underlying IBD, there is mounting evidence for its high effectiveness and safety. The evidence for FMT as a therapeutic for IBD itself is in its infancy, though with notable potential (Table 1). As FMT continues to gain acceptance, improving access to FMT for both patients and physicians will be necessary.

**Table 1.** Relative Approximation of the Strength of Evidence for the use of FMT

Condition Treated with FMT	Strength
CDI	+++++
CDI in patients with IBD	+++
Ulcerative Colitis	++
Crohn's Disease	+

Directions for future studies include determining optimal strength, dose, processing conditions, and duration of FMT in the treatment of IBD. Further research is necessary to determine whether the effects of FMT on the treatment of IBD are sustained, or if recurrent FMT is necessary. Future studies will ideally risk stratify patients and provide predictions for which patients with IBD will benefit most from treatment with FMT.

Additionally, the role of individualizing FMT, perhaps by manipulating microbiota, needs further investigation. Live biotherapeutic products (consortia of bacteria or other microorganisms) are an exciting new frontier in the management of CDI and possibly other conditions. This is a topic under active investigation, and may represent a future where the standard of care for IBD extends beyond conventional immunosuppressant therapies.

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### Disclaimer

The views, expressed herein, are those of the authors and do not necessarily reflect the views of the Warren Alpert Medical School of Brown University, Department of Medicine at Alpert Medical School, or Lifespan.

### Authors

Sohum A. Patwa, MD, Resident Physician, Department of Internal Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Christopher Ward, MD, Chief Resident, Department of Internal Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Colleen R. Kelly, MD, FACG, Associate Professor, Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, RI.

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CRK is a consultant for Sebelo Pharmaceuticals.

### Correspondence

Sohum A. Patwa, MD  
 593 Eddy Street, Providence, RI 02903  
[sohum.a.patwa@gmail.com](mailto:sohum.a.patwa@gmail.com)

# Treat-to-Target: The Era of Targeted Immunosuppressive Agents in IBD Management

DANIEL MARINO, MD, MBA; SIDDHARTH SINGH, MD, MS; JASON HOU, MD, MS; COREY SIEGEL, MD; GIL MELMED, MD; SAMIR A. SHAH, MD

## ABSTRACT

With the advent of biologic agents, the treatment of patients with Inflammatory Bowel Diseases (IBD) has changed from managing symptoms to achieving remission of disease. Disease remission is associated with better outcomes than symptomatic care alone. The Treat-to-Target paradigm provides targets that serve as surrogates for achieving disease remission. The most important target is endoscopic mucosal healing and other targets include symptomatic response, symptomatic remission, biomarker normalization, and normalization of patient's quality of life. Targets are reached via utilization of biologic medications that may be modified or substituted as goals are not met. IBD Qorus represents a national collaborative of academic IBD centers and private gastroenterology practices using the Treat-to-Target approach and patient-centered communication methods to provide better care for all patient's suffering from IBD.

**KEYWORDS:** IBD; Crohn's Disease; Ulcerative Colitis; Treat-to-Target; QORUS

Management of patients with Inflammatory Bowel Disease (IBD) underwent a paradigm shift from managing symptoms to a focus on achieving remission, also known as the Treat-to-Target (TTT) approach. TTT was borrowed from rheumatologists and adopted by gastroenterologists to focus on achieving remission of IBD as defined by surrogate markers, chief among them is mucosal healing, and creating goals (targets) that physicians and patients could work together to achieve. This guidance was proposed in the Selecting Therapeutic Targets in IBD program, STRIDE and STRIDE II initiatives by the International Organization for the Study of IBD via systemic review and expert consensus.<sup>1,2</sup> This method replaces older strategies that focused primarily on controlling symptoms which have not proven to be effective in altering a patient's disease course. The main goal, or treatment target, of TTT is endoscopic mucosal healing and other targets that are also regularly monitored, which include symptomatic response, inflammatory biomarkers, and overall patient well-being.

Treat-to-Target utilizes the principle that a symptomatic response to treatment does not always result in a decrease in

mucosal inflammation<sup>3</sup>; ongoing inflammation may result in complications of IBD such as neoplasia, abscess, and strictures. Mucosal inflammation is quantified endoscopically by mucosal healing, the gold standard outcome for all IBD treatment modalities, as mucosal healing predicts sustained clinical remission and resection-free patient survival.<sup>4</sup> The CALM trial showed that treatment escalation of biologic therapy via symptoms alone led to less mucosal healing when compared to objective measurements, thus providing the foundation for the TTT approach.<sup>5</sup> Furthermore, because assessment of mucosal healing via endoscopy is invasive and expensive, other objective therapeutic targets were needed so surrogate markers of inflammation such as laboratory data were included as targets.

For primary care providers, TTT is likened to monitoring patients with diabetes' hemoglobin A1c every three to six months and using various tools such as insulin and insulin secretagogues to achieve the goal <7%. While microvascular damage to kidneys, eyes, and peripheral nerves may be present in patients with A1c >7%, they are often asymptomatic. Similarly for patients with IBD, significantly active inflammation may be present while the patient is clinically asymptomatic, thus clinicians should consider changing therapies to achieve treatment targets.

For patients, TTT can be likened to car maintenance. While the check engine light may not be on, and the car is seemingly running smoothly, there still may be hidden problems. By having yearly visits with diagnostic maintenance tests, drivers can determine if there is any significant damage occurring to the car and attempt any measures to alleviate or stop the damage.

The goals for the TTT are achieved primarily through biologic medications, small molecule inhibitors, aminosalicylic acid agents, and immunomodulators in both ulcerative colitis (UC) and Crohn's Disease (CD). **Table 1** shows medications that are commonly used in achieving these targets. Generally, these medications are started at the lowest effective dose and up titrated as needed to achieve TTT goals. Another biologic was approved for Crohn's in late June, 2022: Rizankinumab, a monoclonal antibody targeting IL-23. Several other anti-IL23 inhibitors will become available in the next few years. **Table 2** shows a general timeline for achieving the specific targets as defined by the STRIDE-II team.<sup>2</sup>

**Table 1.** Common Medications used in the treatment of IBD

Generic Name	Trade Name(s)	Disease Treated	Major Side Effects	Clinical Pearls
<b>Anti-tumor necrosis factor agents</b>				
Infliximab	Remicade, Inflectra, Renflexis, Ixifi, Avsola	CD and UC	Increased risk of bacterial and atypical infections, possibly lymphomas and non-melanoma skin cancer, and worsening congestive heart failure.	Contraindicated in patients with NYHA Class III or IV heart failure
Adalimumab	Humira, Amjevita, Cyltezo	CD and UC		
Golimumab	Simponi	UC		
Certolizumab	Cimzia	CD		
<b>Anti-Integrin Inhibitors</b>				
Vedolizumab	Entyvio	CD and UC	No significant increased risk of infections.	Increased risk of Progressive Multifocal Leukoencephalopathy if infected with JC virus (Natalizumab only).
Natalizumab	Tysabri	CD		
<b>Interleukin-12/23 Inhibitors</b>				
Ustekinumab	Stelara	CD and UC	Increased risk of infection and possibly non-melanoma skin cancer	
<b>5-Aminosalicylic Agents</b>				
Mesalamine	Asacol, Pentasa, Delzicol, Lialda	CD and UC	Allergic reactions, paradoxical diarrhea, and pancreatitis.	
<b>Antimetabolites</b>				
6MP/Azathioprine		CD and UC	Bone marrow suppression, hepatotoxicity, pancreatitis, lymphoma	Test for Thiopurine Methyltransferase before use to prevent severe bone marrow aplasia
<b>Jak Inhibitors</b>				
Tofacitinib	Xeljanz	UC	Increased risk of infection, lymphoma, thrombosis, and cardiac events	
Upadacitinib	Rinvoq	UC	Increased risk of infection, theoretical risk of perforation	
<b>Sphingosine 1 Phosphate Receptor Modulator</b>				
Ozanimod	Zeposia	UC	Dose dependent decreases in heart rate, increased risk hypertension, associated with increased risk hepatotoxicity, increased risk of infection	

**Table 2.** Summary of Short-Term, Intermediate, and Long-Term Targets

Short-Term (within 3 months)	Intermediate Targets (within 6 months)	Long-Term targets (6–9 months)
1. Symptomatic response - CD=50% reduction in PRO2 abdominal pain and stool frequency - UC=50% reduction in PRO2 rectal bleeding and stool frequency	1. Symptomatic remission - CD=50% reduction in PRO2 abdominal pain </=1 and stool frequency </= 3 - UC= PRO2 rectal bleeding score of 0 and stool frequency of 0  2. Normalization of biomarkers - Fecal calprotectin generally preferred over CRP	1. Endoscopic Healing - Endoscopic remission is preferred  2. Normalized Quality of Life

**TREATMENT TARGETS**

While not the most important marker for disease progression, symptomatic response is an important patient-centric target for both physicians and patients in the management of IBD. Patients often value symptomatic response above other targets, while mucosal inflammation leading to long-term problems may still be present despite clinical remission. The REACT trial showed that treating to a target of clinical remission generally results in lower rates of surgery, hospitalization, and disease-related complications.<sup>6</sup> The patient-reported outcomes (PRO2) score quantifies and standardizes symptoms of IBD and includes daily stool frequency and abdominal pain for CD and normal stool frequency and absence of rectal bleeding for

**Table 3.** Simplified PRO2 Score for Crohn's Disease

	Day 1	Day 2	...	Day 7	Average	Weighing Factor	Total
# Liquid or Very Soft Stools						X2	
Abdominal Pain (3=severe, 2=moderate, 1=mild, 0=none)						X5	
						Pro2 Total=	

**Table 4.** Simplified PRO2 Score for Ulcerative Colitis

Perceived Stool Frequency	Normal=0	1-2 more stools than normal=1	3-4 more stools than normal=2	5+ more stools than normal=3
Perceived Severity of Rectal Bleeding	No blood=0	Streaks of blood for over half the time=1	Obvious blood=2	Blood passed without stool=3

UC (Tables 3 and 4). Symptomatic response is divided into clinical response, a short-term target, and clinical remission, an intermediate target. Clinical response for CD is defined as a 50% reduction in PRO2 abdominal pain and stool frequency and for UC a 50% reduction in PRO2 rectal bleeding and stool frequency by 50%. Clinical remission for CD is defined as PRO2 abdominal pain  $\leq 1$  and stool frequency  $\leq 3$  and for UC a PRO2 rectal bleeding score of 0 and stool frequency of 0. If clinical response or remission cannot be achieved within 1–2 months for clinical response or 3–6 month for clinical remission, treatment modification should be considered. Given there is a closer correlation between symptomatic response and mucosal healing in UC compared with CD,<sup>7</sup> clinical response is considered a more important target in UC. In addition to symptomatic response, there is also a focus on steroid-free symptomatic remission, decrease in emergency department visits/hospitalization, and other patient-centered goals such as desire for pregnancy.

Endoscopic healing is the most important target in the TTT approach, which is generally defined as no macroscopic injury on direct mucosal imaging via colonoscopy. Mucosal inflammation is associated with poor long-term outcomes, including increased risk of bowel damage and other complications.<sup>4,8</sup> While endoscopic healing is considered a long-term goal, endoscopic response to treatment can be used to evaluate intermittent responsiveness to treatment in the short term. Generally, a significant decrease in inflammation on colonoscopy is considered endoscopic response, while near complete resolution of inflammation is considered healing. Colonoscopy should be considered six to nine months after starting therapy for CD and three to six months after starting therapy for UC. Sigmoidoscopy can take the

place of colonoscopy for UC. Capsule endoscopy or balloon enteroscopy should be considered for CD depending on the anatomic disease location and phenotype.

Histologic healing is not currently a target in the TTT protocol. While histologic remission may result in fewer long-term complications and lower cancer risk in UC,<sup>9</sup> trying to achieve histologic remission has several drawbacks. Sample error can occur in CD depending on biopsy site, inter-reader reliability can vary among pathologists in both diseases, and most importantly, histologic remission is difficult to achieve with an estimated 10% of patients with CD<sup>10</sup> and 33% of patients with UC<sup>11</sup> achieving histologic response despite long-term treatment.

Cross sectional imaging is not a treatment target currently but is a useful adjunct in monitoring disease in IBD. For CD, imaging can find proximal lesions in the small bowel that are not seen on colonoscopy and determine full thickness healing, which may not always correlate with mucosal healing. Popular in Europe and other countries, point-of-care small bowel ultrasound may represent an efficient way to examine for CD or UC flare. Findings that are concerning include increased bowel wall thickness, increased blood flow to segments of bowel, bowel hypomotility, hypoechogenic bowel wall pattern, and lymphadenopathy.<sup>12,13</sup> Diagnosis of IBD associated complications such as strictures or fistulas with ultrasound and usage of contrast enhanced ultrasound and elastography represent future directions for managing IBD with ultrasound.

Fecal calprotectin (FC) and C-Reactive protein (CRP) are two important markers of inflammation for patients with IBD as they are objective, non-invasive, and inexpensive. Biomarkers are often obtained post induction, then every six to twelve months throughout the patient's disease. FC has been shown to predict clinical remission<sup>14</sup> and probability of relapse in patients with CD.<sup>15</sup> The goal for FC in patients with CD is variable, and generally levels greater than 150 ug/g are associated with inflammation. High CRP in patients with CD is associated with higher risk of relapse,<sup>16</sup> while normalization predicts long-term remission.<sup>17</sup> For UC, FC is more sensitive than CRP to predict endoscopic activity and is highly correlated with symptomatic and endoscopic disease.<sup>18</sup> Biomarkers like FC are important adjunctive markers of inflammation and in general correlate with endoscopic inflammation thus providing a noninvasive option. FC is more accurate for colonic inflammation compared with small bowel.<sup>19</sup> However, despite its better performance than CRP, it can have false negatives and/or positives.

To take a holistic approach to IBD care, quality of life and disability have been added as a long-term treatment target

for patients with IBD. While FC has moderate correlation with patient wellbeing,<sup>20</sup> earlier guidelines did not take patient's overall quality of life into account. Frequent assessments of patient's quality of life are now recommended to further elucidate what is important to the patient; thus, there should be a conscious effort to manage factors associated with poorer quality of life such as presence of a stoma, open instead of laparoscopic surgery, and mood disorders.<sup>21-23</sup> In situations where mucosal healing has been obtained, there are still opportunities for multidisciplinary care with psychiatry, psychology, physical therapy, and social workers in the pursuit of restoring an individual's quality of life and ensuring a reduction in disability.

### IBD QORUS

IBD Qorus was developed by the Crohn's & Colitis Foundation to help develop a therapeutic alliance between patients, providers, and researchers to improve the care of patients with IBD. The mission of the Crohn's & Colitis Foundation is to, "...find a cure for Crohn's disease and Ulcerative Colitis while doing everything we can to improve the daily quality of life for patients with inflammatory bowel disease."<sup>24</sup> IBD Qorus is an electronic platform that allows for collaboration between enrolled gastroenterology clinics and patients. Rhode Island-based GI Associates has been an active participant in IBD Qorus for many years. After a patient consents to participate in IBD Qorus, they are sent a survey before their next appointment. This patient-centered survey was designed to briefly address individual's symptoms and goals, focusing on what is most important for the patient during their visit. This survey is reviewed by the provider prior to the visit and again during the visit with the patient. By taking the time to complete a survey prior to their visit, patients and providers both come to the visit with clear goals in mind, thus facilitating improved shared decision-making. The end goal of this process is to shift the focus of the appointment away from the disease and towards the patient's quality of life. The survey also prompts physicians to consider when they should next check for mucosal healing, either via labs or endoscopy, thus also targeting the TTT principles. Furthermore, deidentified data from the surveys populate a database that allows researchers to determine trends in population health.

IBD Qorus utilizes the Institute for Healthcare Improvement Breakthrough Series to achieve quality improvement that can then be widely disseminated. The Breakthrough Series model utilizes Plan-Do-Study-Act (PDSA) cycles after initial in-person learning sessions where promising best practices are widely distributed, and future directions are proposed. There are monthly calls with IBD Qorus staff where PDSA progress and challenges are discussed and addressed jointly.

The data from pre-appointment surveys and PDSA cycles have been used to improve care of IBD patients. For example,

low-cost practice changes utilized in IBD Qorus have been shown to decrease unplanned healthcare utilization,<sup>25</sup> and decrease cost by an average of \$2,528 per patient.<sup>26</sup> Clinical care pathways for nutritional care<sup>27</sup> and anemia management<sup>28</sup> have also been developed through IBD Qorus. Data is synthesized into reports and sent back to providers who can find clinic-wide trends in data compared with other sites, which can help guide future site directed PDSA cycles. With more than 50 sites nationally, best practices can be shared and benchmarking for important quality issues like steroid use and hospitalization can be examined.

### CONCLUSION

The TTT approach represents a paradigm shift in improving the quality of care of IBD patients. The TTT approach focuses on endoscopic mucosal healing, inflammatory biomarkers, and overall patient well-being, and not just symptoms to keep IBD in remission. IBD Qorus is a growing network of patients and providers who use the TTT framework to share their experiences and data to further advance IBD care. Future studies are further evaluating clinical outcomes of changing biologic therapy in patients who are otherwise completely asymptomatic with active mucosal disease in efforts to further validate TTT.

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**Authors**

Daniel Marino, MD, MBA, Department of Internal Medicine, Rhode Island Hospital/Brown University, Providence RI.  
 Siddharth Singh, MD, MS, Division of Gastroenterology, University of California, San Diego, CA.  
 Jason Hou, MD, MS, Division of Gastroenterology, Baylor College of Medicine, Houston, TX.  
 Corey Siegel, MD, Chief, Division of Gastroenterology, Dartmouth Hitchcock Medical Center, Lebanon, NH.  
 Gil Melmed, MD, Division of Gastroenterology, Cedars Sinai Medical Center, Los Angeles, CA.  
 Samir A. Shah, MD, Gastroenterology Associates, Chief of Gastroenterology, Miriam Hospital, Providence, RI.

**Correspondence**

Samir A. Shah, MD  
 44 West River Street, Providence, RI 02904  
 Samir\_shah\_MD@brown.edu