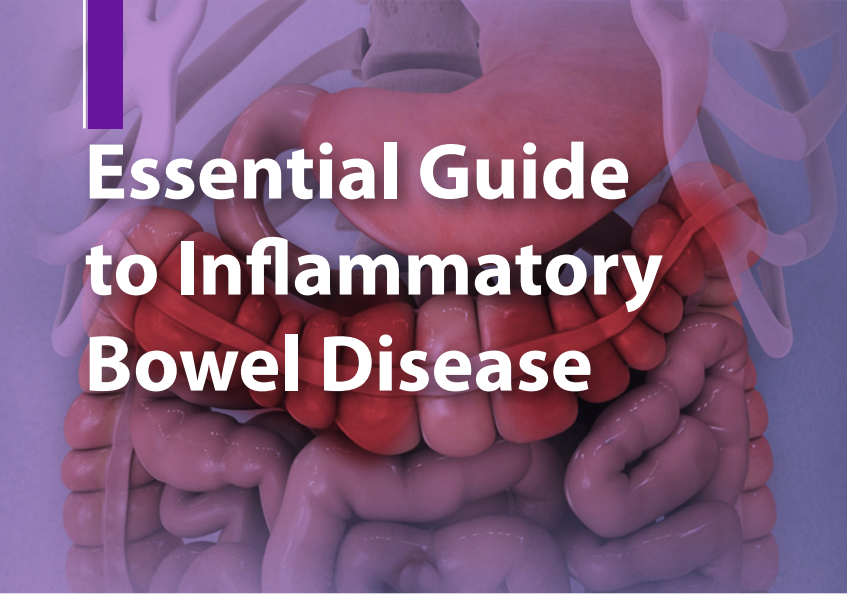

Essential Guide to Inflammatory Bowel Disease

Edited by
Majid Almadi, MSc, MBA, FRCPC
Fahad Alsohaibani, MEd, MBA, FRCPC

First Edition

Alsohaibani , Fahad Ibrahim Saleh
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Preface

Inflammatory Bowel Disease (IBD) has emerged as one of the most challenging chronic conditions in modern medicine. It is a disorder that affects not only the digestive system, but also the physical, emotional, and social well-being of millions worldwide. Despite remarkable advances in research and treatment, patients and caregivers often face uncertainty and overwhelming amounts of information when navigating this complex condition.

This book, Essential Guide to Inflammatory Bowel Disease, was written by experts in IBD to provide a practical, accessible, comprehensive, and state-of-the art resource for healthcare professionals. It brings together up-to-date knowledge on the nature of IBD, its causes, diagnosis, treatment options, and long-term management strategies that will help GI trainees and practicing gastroenterologists strengthen their clinical knowledge in IBD. Equally important, it explores the human side of living with IBD by addressing diet, lifestyle, mental health, and the support systems that are crucial to thriving with such chronic illness.

We would like to extend our deepest gratitude to all of our invited authors whose expertise, insights, and dedication have enriched this book. Each chapter, idea, and perspective shared reflects a collective effort that has made this work possible. Your commitment to advancing knowledge and supporting this endeavor is sincerely appreciated, and this book stands as a testament to your invaluable contributions.

Sincerely,

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Introduction:

Fahad Alsohaibani & Christopher Ma

Inflammatory bowel disease (IBD) comprises a group of chronic, immune-mediated inflammatory disorders of the gastrointestinal tract, principally Crohn's disease (CD) and ulcerative colitis (UC). These conditions are characterized by a relapsing–remitting disease course and heterogeneous clinical presentations, ranging from mild mucosal inflammation to severe, progressive disease complicated by strictures, fistulas, and systemic involvement. IBD has emerged as a global health concern, with rapidly rising incidence and prevalence in newly industrialized regions, including the Middle East, Asia, and South America.

The global burden of IBD is substantial and continues to grow. Patients often experience lifelong disease requiring continuous medical care, with significant impacts on physical health, psychological well-being, social functioning, and quality of life. From a healthcare systems perspective, IBD is associated with high rates of outpatient visits, hospitalizations, surgical interventions, and escalating healthcare costs. Despite improvements in disease control over recent decades, IBD remains a leading cause of gastrointestinal morbidity among young and working-age adults, emphasizing the need for sustained advances in care delivery and disease modification.

IBD arise from a complex interplay between genetic susceptibility, environmental exposures, the intestinal microbiome, and dysregulated immune responses. Genome-wide association studies have identified hundreds of genetic loci associated with IBD, implicating pathways involved in innate and adaptive immunity, epithelial barrier function, and host–microbial interactions. Environmental factors, including diet, antibiotic exposure, smoking, and urbanization, further modulate disease risk and phenotype, while alterations in gut microbial composition and function play a central role in disease initiation and perpetuation.

Advances in disease pathophysiology have directly influenced clinical management strategies. Traditional symptom-based approaches have given way to treat-to-target paradigms, emphasizing objective markers of inflammation and long-term outcomes rather than short-term symptom control alone. International consensus initiatives, including STRIDE-II recommendations, have established therapeutic targets such as clinical remission, biomarker normalization, endoscopic healing, and prevention of disease-related complications as central goals of IBD care. These strategies aim to alter the natural history of disease by min-

Introduction:

imizing cumulative inflammatory burden and structural bowel damage. The therapeutic landscape of IBD has expanded dramatically over the past two decades. In addition to conventional therapies such as corticosteroids, immunomodulators, and aminosalicylates, the introduction of biologic agents and small-molecule therapies has revolutionized disease management. Tumor necrosis factor (TNF) antagonists, integrin inhibitors, interleukin inhibitors, Janus kinase inhibitors, and sphingosine-1-phosphate receptor modulators have provided effective treatment options across a broad spectrum of disease severity. However, therapeutic decision-making has become increasingly complex, necessitating individualized treatment selection based on disease phenotype, prognostic risk, comorbidities, safety considerations, and patient preferences. Despite these advances, primary non-response, secondary loss of response, and treatment-related adverse events remain significant clinical challenges.

IBD also represents a major cause of gastrointestinal hospitalization and surgery, particularly in patients with acute severe disease or complex complications. Hospitalized patients with IBD are at increased risk for infections, thromboembolic events, malnutrition, and corticosteroid-related morbidity, and often require coordinated multidisciplinary care team. Optimizing inpatient management through early recognition of disease severity, timely escalation of therapy, and adherence to evidence-based protocols is critical to improving short- and long-term outcomes.

As the field of IBD continues to evolve rapidly, the main goal remains the same: to improve patient outcomes through earlier diagnosis, personalized therapy, sustained disease control, and prevention of long-term complications. By combining scientific advances with real-world clinical insights, this book aims to support evidence-based, patient-centered, and multidisciplinary care for individuals living with inflammatory bowel disease.

This book is designed to serve as a comprehensive and practical resource for clinicians, trainees, and allied healthcare professionals involved in the care of patients with IBD. It integrates foundational concepts in disease biology with contemporary clinical practice, addressing the full spectrum of care—from epidemiology, diagnosis, and risk stratification to outpatient and inpatient management, advanced medical therapies, surgical considerations, and long-term monitoring. Special emphasis is placed on emerging therapies, evolving treatment paradigms, quality-of-care metrics, and the management of IBD in special populations.

Chapter 1: Epidemiology and disease burden

Majid Almadi

Introduction

Inflammatory bowel disease (IBD) is an immune mediated disorder that affects the intestine and has extra intestinal manifestations as well. The first description of ulcerative colitis was in 1859 [1]. Cases resembling Crohn's disease have been described since 1612 but the classical publication describing Crohn's disease was in 1913 [1]. Management of patients with IBD has remarkably advanced from initial use of steroid, 5 ASA, and Azathioprine till the complete shift after the approval of first Anti-Tumor Necrosis Factor (TNF) (Infliximab) by the United States Food and Drug Authority (FDA) in 1998 [2]. Since then, there have been numerous medications, targeting various pathways have been introduced to market. IBD encompasses Crohn's disease, ulcerative colitis and indeterminant colitis. Ulcerative colitis is confined to the colon and might involve the most distal part of the small bowel (Backwash ileitis), while Crohn's disease can involve any part of the gastrointestinal tract. In a small proportion of IBD patients (5 to 15%) it is not clear whether the patient has Crohn's disease or ulcerative colitis and with time the disease might declare itself [3]. Also, the disease is characterized by periods of flares and remissions and there is an accumulative amount of bowel damage that happens with each flare. Multiple elements have been proposed as a cause for the development of IBD and these include factors like genetics, environmental exposures either early in life (breastfeeding and antibiotic exposure) or latter (medications, stress, smoking, infections) [4] (Figure 1). It is this interplay between genetics, environment and microbiome that cause the disease and is evident by the increasing incidence in areas where the disease was not prevalent in the past as well as the development of IBD in immigrant populations and with the industrialization of societies. Also, the direct (medical) and indirect (societal) costs associated with the disease or not insignificant and with the increased

therapeutic options have become an area of active research to achieve the best possible outcome with a reasonable amount of healthcare resources [5].

Improved diagnostics, therapeutics, and updated management targets have improved patients' survival and quality of life. In addition to this, due to decreased mortality and the ageing of populations this has contributed to the increased prevalence of the disease [6].
The prevalence of IBD has increased over the years mostly in industrialized countries and is most prevalent in North America and Europe and is least prevalent in Sub-Saharan Africa (Figure 2). Although IBD is not very prevalent, it remains a cause of significant morbidity or mortality in a younger population, effects their quality of life, is associated with an increase in the sum of the years of life lost (YLL) due to premature mortality, in years lived with a disability (YLD) as well as an increase in disability-adjusted life years (DALYs) [7] (Figure 3). As expected, due to the higher prevalence of IBD in North America and Europe, these areas have the highest burden related to disease associated life years, but in terms of years of life lost areas with a low sociodemographic index (SDI) like the geographical area of Sub-Saharan Africa are disproportionally affected. This might reflect limited access to care and diagnostic and therapeutic interventions. The disease effects both males and females in almost identical proportions [8,9]. Also, the age distribution that both diseases effect is almost similar with a tendency for UC to effect those above the age of 40 years more frequently compared to Crohn's disease.

The disease distribution for both diseases and the behavior of Crohn's disease and severity of ulcerative colitis vary. There is also a risk of developing Crohn's disease or ulcerative colitis based on the family history of IBD and the risk is highest in first degree relatives and higher with multiple relatives affected [10] as is shown in Figure 4. The relative risks associated with

developing both Crohn's disease and ulcerative colitis from some environmental exposures [11] is shown in Figure 5.

Figure 1. Various factors that have been associated with inflammatory bowel disorder. (Adapted from Ananthakrishnan A.N.[4])

Figure 2. Prevalence per 100,000 population of inflammatory bowel disease by geographic region (adapted from Piovani D. et al. [7]).

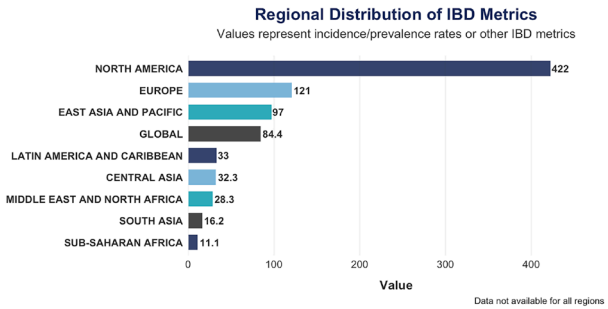


Figure 3. The burden of IBD on populations in terms of Disease Associated Life Years (DALYs), Years Lived with a Disability (YLD), and Years of Life Lost (YLL) by geographic region (adapted from Piovani D. et al. [7]).

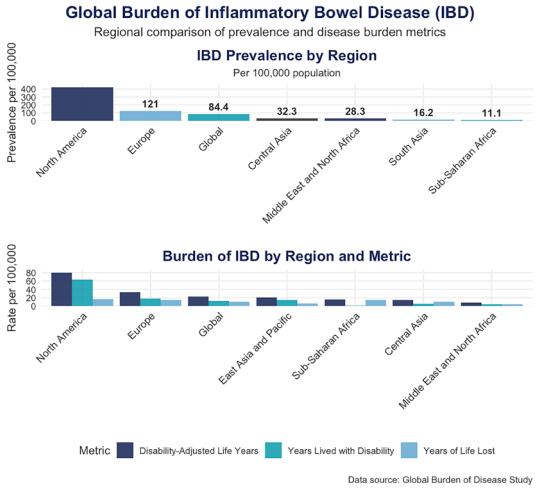


Figure 4. Heat map of the 10-year risk of developing Crohn's disease and ulcerative colitis based on the family history and the current age of the individual (Adapted from Moller FT et al. [10]).

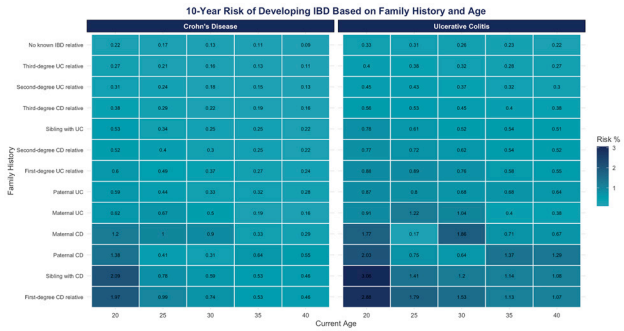
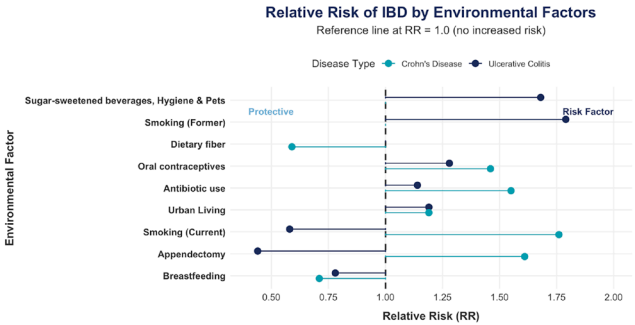


Figure 5. Relative risks of developing ulcerative colitis or Crohn's disease based on environmental factors (Adapted from Piovani D et al. [11]).



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Abdulaziz Alshahrani

Introduction

Inflammatory bowel disease (IBD) etiology involves an interaction between genetic predisposition, immune system dysregulation, gut microbiota dysbiosis, and environmental triggers [1]. The intestinal mucosa consists of epithelial cells, goblet cells, Paneth cells, stroma, and immune cells. Furthermore, the intestinal epithelium includes epithelial cells closely bound by tight junctions. The intestine is structured with a villi and invaginations called crypts of Lieberkühn. The goblet and Paneth cells produce mucus and antimicrobial peptides respectively, thus limiting the spread of luminal microorganisms [2].

Immune system dysregulation

The mucosal immune system is the most extensive part of the immune system. intestinal immune cells are involved in a highly balanced immune response aimed at controlling pathogen invasion, while stopping an excessive immune response against innocuous food antigens and commensal microbes that could risk unintentional tissue injury (Figure1).
The immune system can be classified into innate and adaptive immunity. Innate immunity that is composed of myeloid cells, initiates rapid responses to conserved structural motifs on microorganisms. Innate immune cells (IIC) express pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) and Nod-like receptors (NLR), allowing them to distinguish pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). IIC provide host defense and inflammation by generating cytokines and chemokines, triggering the complement cascade and phagocytosis, or stimulating adaptive immunity by presenting antigens. IIC include neutrophils, monocytes, macrophages, and dendritic cells (DCs) [3,4].

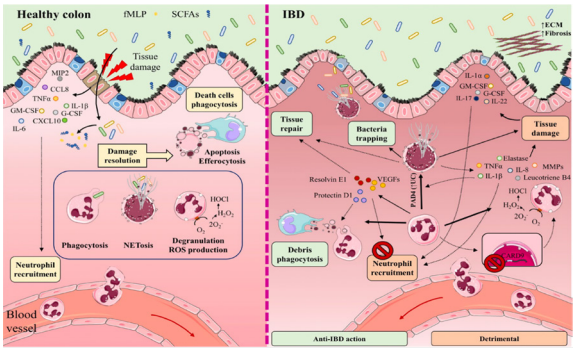


Figure 1 damage to the intestinal barrier triggers the recruitment of neutrophils from the circulation to the inflamed tissue along a chemotactic gradient formed by cytokines (IL-1β, IL-6, TNF-α), chemokines (CCL8, CXCL10, MIP-2), and growth factors (GM-CSF, G-CSF). Used with permission from Gonzalez-Granado J.M. [International Journal of Molecular Sciences, 2023, 24,1526:(3).

Neutrophils are the most numerous immune cells in the human circulation and are quickly recruited to sites of infection or inflammation [5]. It plays a role in intestinal homeostasis and inflammation, playing an essential role in gut defense but also being an important mediator of tissue damage in the inflamed mucosa upon excessive recruitment.

Intestinal macrophages, which restrain their robust proinflammatory potential through a natural resistance to producing inflammatory mediators in response to pattern-recognition molecules, while also retaining several of their homeostatic abilities, including phagocytosing bacteria, preserving Tregs and maintaining tolerance, and promoting epithelial cell renewal [6]. In the intestinal microenvironment, macrophages adapt their functions to the context. homeostasis, the intestinal microbiota inhibits the migra-

tion of antigen-loaded CX3CR1 high intestinal macrophages to mesenteric lymph nodes, thereby also inhibiting antigen presentation to T cells, and effectively sustaining tolerance towards commensal bacteria. The etiology of IBD remains unknown, but IBD appears to be sustained in genetically susceptible individuals by an impaired immune response against intestinal microorganisms. This abnormal immune response is associated with dysregulation of both innate and adaptive immune responses. IBD is characterized by penetration of the epithelial barrier of the intestine, and non-resolving mucosal damage is a major component of the disease [7]. While generally unknown, the cause of this damage could be related to an infectious agent [8], a chemical compound [1], or a metabolic alteration probably related to diet-mediated dysbiosis [9]. Unsuccessful resolution of inflammation is supported by disruption of tolerance towards commensal microorganisms or autologous signals of tissue damage [10].

Genetic predisposition

Comparison of first-degree relatives of IBD patients with the general population reveals a heritable risk of CD and UC [11]. Genome wide association studies (GWAS) have identified more than 240 risk variants associated with IBD. These variants are found in genes related to bacteria recognition (e.g., NOD2), autophagy (e.g., ATG16L1 and IRGM), regulation of epithelial barrier (e.g., ECM1), and innate and adaptive immunity (e.g., IL-23R, IL-10, ITGAL, and ICAM1 variants) [12]. Based on that, it has been possible to uncover fundamental molecular features underlying the disease and to identify genes and signaling pathways that represent potential therapeutic targets or biomarkers. However, only a small percentage of the disease variance in CD and UC can be linked to recognized IBD risk loci [13]. To resolve this limitation, new techniques have allowed the study of single-cell-specific

transcriptional profiles. For example, single-cell RNA sequencing (scRNA-seq) and high-dimensional protein analyses, such as mass cytometry and multichannel spectral cytometry, have defined IBD-linked profiles and detected cell sub-populations that are elevated or diminished in IBD, particularly populations of fibroblasts, epithelial cells, and immune cells [14].

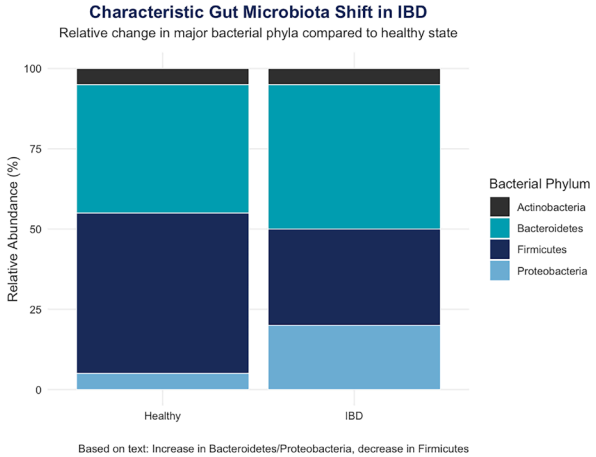
Intestinal microbial dysbiosis

The gut microbiota is an important physical, chemical, and immunological interface between the environment and host; thus, any dysregulation or breakdown of this barrier can contribute to disease states (Figure 2). For example, altered physical epithelial barrier function, a thinner mucus layer, and altered responses to endoplasmic reticulum stress (via mutations in MUC19, ITLN1, FUT2, and XBP1) have all been identified as risk factors for IBD [15]. Currently, the pathogenesis of human IBD is believed to involve inappropriate activation of the immune system when genetically susceptible individuals are exposed to gut antigens, such as microbiome components [16]. Although alterations in the gut microbiome have been proposed to be critical in IBD pathogenesis, it is not yet clear how this process occurs and whether dysbiosis is a central cause or a common consequence of the disease [17]. In healthy individuals, 99% of gut bacterial are Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria.

Firmicutes and Bacteroidetes account for approximately 90% of the total microbiome composition. These phyla are critically important in maintaining gut homeostasis and produce short-chain fatty acids (SCFAs), especially butyrate and propionate, from the fermentation of dietary components such as indigestible fibers. SCFAs are important energy sources for colonic mucosa cells but have also been shown to play

key roles in regulating immune homeostasis [18]. Dysbiosis is defined as an alteration in gut microbiota composition and diversity and a shift in the balance between commensal and potentially pathogenic microorganisms [19]. Several pieces of evidence support the role of the microbiome and dysbiosis in IBD development. For example, experimental mice subjected to germ free conditions develop attenuated colitis.

Figure 2: The role of gut dysbiosis in the pathogenesis of IBD. Gut microbiota reflect an interaction of host genetics with dynamic exposure to innumerable stimuli from the exposome.



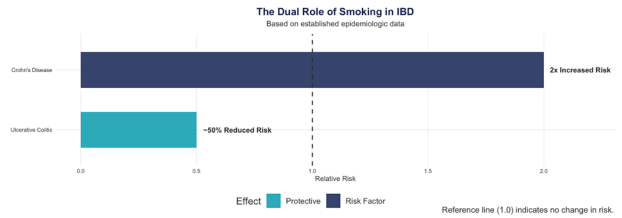
Environmental triggers

Epidemiologic data suggest a strong role of the environment [20]. Disease concordance in monozygotic twins approaches 50% at best, with many studies suggesting that the estimates may be lower. The risk of IBD in the immigrant population resembles that of country of residence rather than the country

of origin [21].
Also, countries that have witnessed a rapidly changing environment and lifestyle have seen an increase in the incidence of IBD over the past few decades at a rate of change that outpaces what could be attributed solely to genetics [22]. Many environmental triggers for IBD include smoking, Vitamin D deficiency, medications including antibiotics, stress, diet, and air pollution.

Smoking remains the most widely studied and replicated environmental trigger for CD and UC (Figure 3). The first described protective association between UC and smoking was in 1982, subsequent studies confirmed the inverse effect of current smoking on the development of UC, lower rate of relapse, and reduced need for colectomy in current smokers [23]. However, cessation of smoking is associated with an increase in risk of UC within 2–5 years of cessation. On the other hand, smoking increases the risk of developing CD two-fold [24], increases risk of disease flares, need for steroids and is associated with a higher rate of post-operative disease recurrence [25]. Despite strong epidemiologic data, the mechanism how smoking impacts IBD remains unclear as does the reason for its protective effect in UC but deleterious impact on CD.

Figure 3: The Dual Role of Smoking in IBD.



Many studies suggest that the role of vitamin D is variable and associated with a diverse spectrum of IBD. A deficiency of vitamin D could be a consequence of IBD itself with reduced physical activity, sunlight exposure, malnutrition, inadequate dietary intake of vitamin D, or lower bioavailability, all contributing to the deficiency [26]. However, vitamin D deficiency is common even in newly diagnosed IBD patients suggesting that low vitamin D itself can contribute to increased risk of IBD [27]. Medications adverse effects like aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are well recognized. However, while their potential effect in triggering onset or relapse of IBD has been clinical suspected, limited high quality evidence is available to support this. Most studies where case-controls where confounding by indication is a possibility, identifying use of aspirin or NSAIDs to treat pre-diagnosis symptoms of CD and UC, and differentiating NSAID enteritis or colitis from true idiopathic IBD have been difficult to achieve. high dose, prolonged duration, and frequent use of NSAIDs was associated with an increased risk of CD and UC [28]. Antibiotics probably influence the risk of developing disease through their effect on the microbiome. Whether early life flora acquired during birth and infancy is critical, or whether an individual at risk for IBD remains susceptible to dynamic changes in flora associated with dietary patterns or other lifestyle factors [29]. Stress is thought to play a role in the pathogenesis of CD and UC, and to mediate disease flares [30]. Mood components of perceived stress including depression and anxiety may play a role in mediating or exacerbating disease related to stress [31]. A prospective study using the Nurses' Health Study found that both recent and remote depressive symptoms were associated with increased risk of CD but not UC [32]. The effect of recent depressive symptoms within 4 years of diagnosis was more prominent than that of remote depression. There is limited high-quality data on whether interventions to treat

depression or stress can modify its effect on disease. One of the environmental triggers most reported by patients, but one where there is a significant gap in data is diet [33]. Most prior studies have been limited by factors including retrospective ascertainment of diet, allowing for both recall bias as well as modifications in diet that may have occurred since the onset of disease symptoms, and the small number of incident cases limiting power. There are far fewer data examining the role of diet in triggering disease flare. In a survey of 244 IBD patients in France, over half the participants reported belief that diet played a role in disease relapse [34]. However, the spectrum of foods that patients reported excluding to prevent relapse was distributed among the different food groups, suggesting that there may not be uniform dietary triggers to relapses.

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Nahla Azzam

Introduction

Crohn's disease (CD) and Ulcerative Colitis (UC) share several clinical features and overlapping treatment strategies, yet each present with distinct pathological and phenotypic characteristics. This section provides an overview of their classification, clinical presentation, and specific phenotypes.

Classification of Crohn's disease

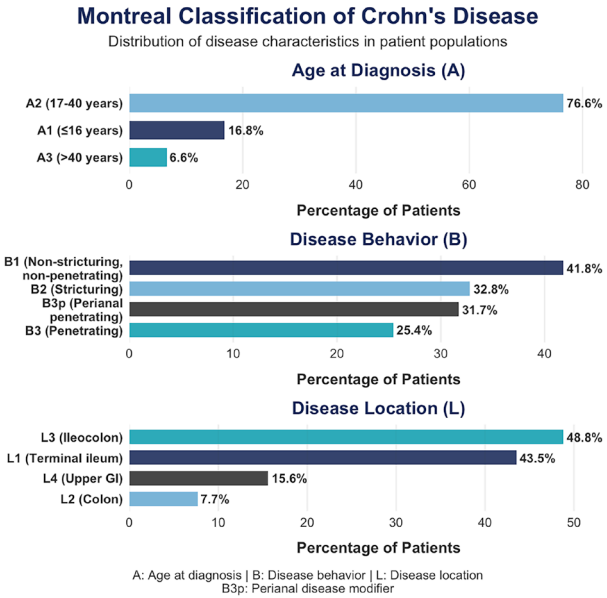
CD is classified using the Montreal classification system, which considers age at diagnosis, disease location, and behavior (Figure 1). This system helps improve diagnostic precision and guides individualized management strategies [1].

Age at diagnosis
- A1: ≤16 years
- A2: 17–40 years
- A3: >40 years

Location of disease
- L1: Terminal ileum
- L2: Colon
- L3: Ileocolon
- L4: Upper GI (may coexist with L1–L3)

Disease behavior
- B1: Non-stricturing, non-penetrating
- B2: Stricturing
- B3: Penetrating
- Perianal modifier (p)

Figure 1. The phenotype of Crohn's disease in Saudi Arabia as per Montreal Classification for Age (A), Behavior (B), and Location (L) (adapted from Aljebreen A. M. et al.[2]).



Clinical presentation of Crohn's disease

Clinical evaluation has always been fundamental in diagnosing diseases, and this holds especially true in IBD. CD presents with a wide range of intestinal and extraintestinal symptoms, reflecting its complex and systemic nature. Understanding the phenotypic classification helps clinicians tailor treatment and improve patient outcomes. Early recognition of these features remains critical to effective long-term disease management.

Gastrointestinal symptoms

Abdominal pain and diarrhea
Abdominal pain, particularly in the lower right quadrant, in patients with ileal involvement, is a common early symptom (80-85%). It may be accompanied by bloating, flatulence, and distension. Diarrhea is another hallmark symptom often non-bloody (65%), but can be bloody depending on disease location. Visible blood in the stool is less frequent than in UC but not uncommon [3].

Oral manifestations
Recurrent aphthous ulcers may appear, though their direct association with CD remains debated, as they are also common in the general population. Other findings may include nodular swelling, a cobblestone appearance in the oral mucosa, granulomatous ulcers, or pyostomatitis vegetans. Medications used in CD, including sulfasalazine, corticosteroids, and immunosuppressive therapy can lead to oral side effects such as lichenoid reactions, or oral fungal infections like candidiasis. Anemia-related signs such as pallor, angular cheilitis, and glossitis could develop due to malabsorption.

Systemic Symptoms

Growth delay in children
Is a notable concern in pediatric CD. It may be the presenting sign, particularly during puberty, with up to 30% of affected children showing delayed growth.

Fever and weight loss
Fever, when present, usually indicates complications like abscesses or infections, however fever could be a manifestation of the disease activity. Weight loss is common, especially in adults, due to decreased food intake and malabsorption.

Patients may avoid eating to reduce symptoms. Extensive small bowel involvement may impair absorption of key nutrients, exacerbating weight loss [4].

Extraintestinal manifestations

These include arthritis, erythema nodosum (tender red nodules) and pyoderma gangrenosum (ulcerative lesions), uveitis, and episcleritis. (Covered in detail in Chapter 5).

Hepatobiliary
These include primary sclerosing cholangitis (less common in CD but can occur), especially in colonic CD.

Distinct phenotypes of Crohn's disease

Upper gastrointestinal CD
Including the esophagus, stomach, or duodenum is less common but clinically significant. Symptoms may include nausea, vomiting, epigastric pain, and dysphagia. The median prevalence of upper CD was found to be 8.7% (interquartile range, 4.74%-24.36%). Over one-third of patients are asymptomatic, and abdominal pain was the most frequently reported symptom in symptomatic patients (41%; range, 5%-93%) [5]. Diagnostic evaluation often requires upper endoscopy, and treatment strategies may need to be adjusted to address the unique challenges of upper gastrointestinal disease. Although isolated gastric involvement is rare, upper gastrointestinal symptoms can be found in 13–16% of CD patients, usually following the onset of lower gastrointestinal symptoms. It commonly affects younger, non-smoking patients, and more frequently present with concomitant ileal involvement and a stenosing behavior [6].

Perianal Crohn's Disease

Perianal involvement is among the most complex and debilitating manifestations of CD. Perianal fistulizing CD represents a particularly aggressive disease phenotype that carries substantial morbidity and markedly impairs quality of life. Its development reflects a multifactorial process involving genetic susceptibility, immune dysregulation, gut microbiome disturbances, and several poorly understood physiological and mechanical contributors. Patients may present with pain, itching, or discharge due to fistulas, fissures, abscesses, or skin tags; incontinence can also occur. A precise anatomical characterization and classification of the fistula supported by thorough clinical evaluation, endoscopic assessment, and advanced radiological imaging is essential before initiating treatment. Effective management often requires a multidisciplinary approach combining medical therapy and surgical interventions aimed at fistula healing and symptoms control [7].

Classification of Ulcerative Colitis

UC is classified based on the anatomical extent of colonic involvement, which guides both clinical decision-making and therapeutic strategies (Figure 2).

Age at diagnosis

- A1: ≤16 years
- A2: 17–40 years
- A3: >40 years

Disease extent

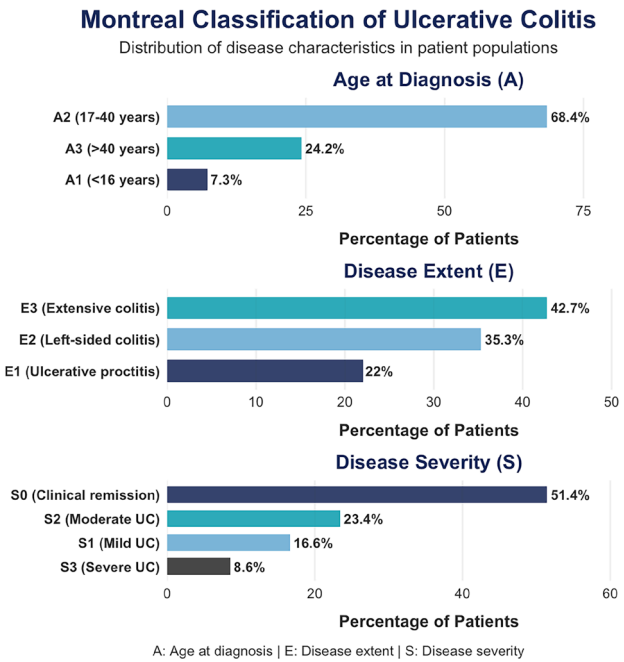
- E1 (Ulcerative Proctitis): Inflammation limited to the rectum
- E2 (Left-sided Colitis): Involvement distal to the splenic flexure (rectum, sigmoid, and descending colon)

• E3 (Extensive Colitis / Pancolitis): Inflammation extending proximal to the splenic flexure and potentially involving the entire colon

Disease severity

• S0: Clinical remission
• S1: Mild ulcerative colitis
• S2: Moderate ulcerative colitis
• S3: Severe ulcerative colitis

Figure 2. The phenotype of ulcerative colitis disease in Saudi Arabia as per Montreal Classification for Age (A), Extent (E), and Severity (S) (adapted from Alharbi O. et al.[8]).



Clinical presentation of Ulcerative Colitis

UC is a chronic inflammatory condition of the colon, characterized by continuous mucosal inflammation that begins in the rectum and extends proximally in a contiguous fashion. Unlike CD, UC is confined to the colon and does not exhibit skip lesions or transmural inflammation. The clinical presentation of UC depends on both the extent and severity of inflammation, influencing gastrointestinal as well as extraintestinal manifestations.
Chronic inflammation in UC may lead to long-term complications, including iron deficiency anemia and an increased risk of colorectal cancer. These risks emphasize the importance of routine surveillance colonoscopy and proactive disease management.

Gastrointestinal Manifestations

Diarrhea and rectal bleeding
The hallmark symptom of UC is diarrhea, often accompanied by visible blood, mucus, or pus in the stool. The frequency of bowel movements varies, ranging from mild to debilitating. Rectal bleeding is a dominant feature, present in approximately 90–95% of patients. The severity of bleeding is proportional to the extent of mucosal involvement, and in some cases, may lead to iron deficiency anemia [9].

Abdominal pain and cramping
Lower abdominal pain, typically cramping in nature, is common and often coincides with bowel movements.

Urgency and tenesmus
Patients frequently report urgency and tenesmus (the persistent sensation of needing to defecate despite an empty rectum) and sometimes incontinence.

Systemic manifestations

Fever and fatigue
During active disease flares, systemic inflammation may result in low-grade fever and persistent fatigue, significantly impacting quality of life.

Anemia and Weight Loss
Anemia is one of the most common EIMs of IBD. The cause of anemia in IBD is multifactorial, with the two most frequent aetiologies being iron deficiency anemia [IDA] and anemia of chronic disease [ACD], frequently occurring in conjunction. Ongoing diarrhea, anorexia, and the metabolic burden of inflammation contribute to weight loss and, in some cases, malnutrition particularly in patients with extensive disease or frequent relapses [10].

Extraintestinal manifestations

Discussed in detailes in (Chapter 5).

Table 1 and 2 summarize the key clinical and histological difference between Crohn's disease and Ulcerative Colitis.

Table 1. Summary of the clinical difference between Crohn's disease and Ulcerative Colitis.

Feature	Crohn's Disease	Ulcerative Colitis
Location	Any part of the GI tract	Colon and rectum only
Distribution	Patchy, skip lesions	Continuous from rectum proximally
Depth of inflammation	Transmural	Mucosal and submucosal only
Rectal involvement	Often spared	Almost always involved
Ileal involvement	Common	Occasional 15% (backwash ileitis) not more than 10 cm.
Perianal Disease	Common (fistula, abscess)	Rare
Fistulas and abscesses	Common	Rare
Strictures	Common	Rare
Bleeding	Less common, mild	Common, may be severe
Diarrhea	Often non-bloody	Typically, bloody
Abdominal Pain	Common	Cramps with urgency
Weight Loss/ Malnutrition	Common	Less common
Surgery Recurrence	High recurrence post-resection	Low after ileal pouch-anal anastomosis

Table 2. Histological differences between Crohn's disease and Ulcerative Colitis.

Feature	Crohn's Disease	Ulcerative Colitis
Discrete mucosal ulcers	Common	Absent (except in fulminant colitis)
Mucosal edema	Common	Usually, absent
Fissures	Present	Rare
Granulomas	Often seen (non-caseating)	Absent, except in crypt rupturing
Abnormal crypt architecture	Minimal	Frequent
Architectural distortion	Focal	Diffuse
Lymphoid aggregates	Frequent	Rare
Paneth cell metaplasia	Absent	Occasionally present

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Chapter 4: Incidental Terminal Ileitis

Nahla Azzam

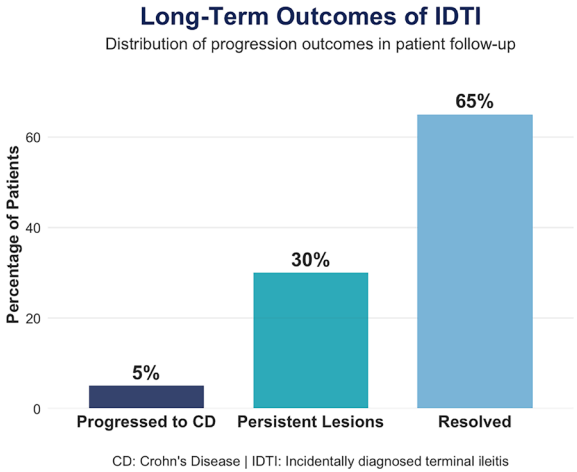
Introduction

With the increasing use of colonoscopy for colorectal cancer (CRC) screening and surveillance, incidentally diagnosed terminal ileitis (IDTI) is being identified more frequently in otherwise asymptomatic individuals. However, its true prevalence, clinical significance, and long-term outcomes remain unclear. While IDTI can result from various causes, including NSAID use or early Crohn's disease (CD), there is no clear consensus on how to manage these cases.

Prevalence and Long-Term Outcomes

Prevalence ranges from 0.04% to 6.77%, with significant variation in diagnostic criteria [1]. A pooled prevalence analysis estimated IDTI in about 0.7% of non-diagnostic colonoscopies. The diagnostic work-up for CD was based on varying combinations of clinical, biomarkers, endoscopic, and radiological findings, The long-term follow-up of IDTI patients (median 13–84 months) suggests that most cases do not progress to overt CD. However, in some cases, particularly when associated with additional symptoms or persistent inflammation, progression to CD has been observed [2,3].

The clinical significance of IDTI remains to be determined. Although IDTI can occur in the context of other etiologies such as non-steroidal anti-inflammatory drugs (NSAIDs) use and rheumatological diseases [4,5].



The following is recommended:

• A minority of patients (ranging from none to a few in each study) progressed to CD.

• Some patients had lesions that persisted but did not worsen, while most had complete resolution.

• No specific predictive factors for disease progression were consistently identified.

• Abdominal pain at the time of colonoscopy was associated with a higher risk of progression in studies including both diagnostic and screening colonoscopies.

Current Understanding and Management

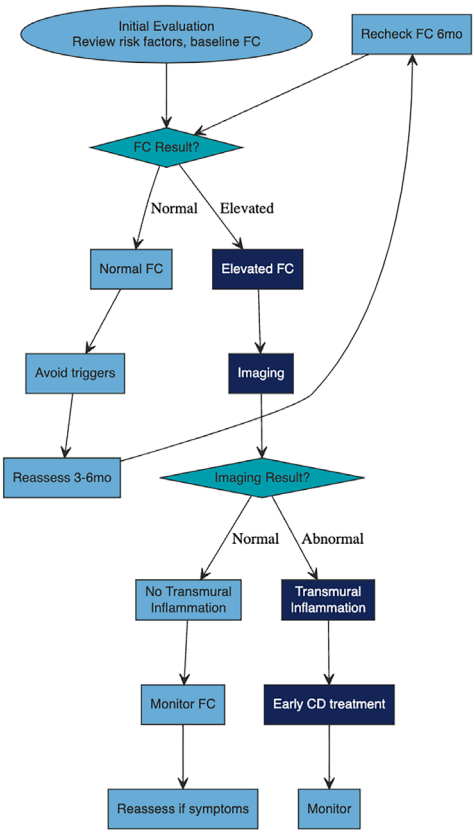
The lack of clear predictors of progression complicates decision-making. Some cases of IDTI may represent early, pre-clinical CD, while others are due to transient, non-specific inflammation. NSAID use has been implicated in IDTI

but was only reported in a minority of patients in the studies reviewed. Given this uncertainty, a cautious, stepwise approach is recommended.
The proposed clinical pathway for IDTI management lies in steps as the following

Step 1: Initial evaluation
• Review potential risk factors: NSAID use, smoking, recent infection.
• Obtain baseline fecal calprotectin (FC) to assess intestinal inflammation.

Step 2: Follow-up based on FC levels
A. If FC is normal:
• Likely transient ileitis.
• Avoid potential triggers (NSAIDs, infections) and reassess in 3–6 months.
• No further intervention needed unless symptoms develop.
B. If FC is elevated:
• Consider cross-sectional imaging (e.g., MRI enterography or CT enterography) to assess for transmural inflammation.
• Recheck FC in 6 months.

Step 3: Imaging findings & ongoing management
A. No evidence of transmural inflammation:
• Likely reversible etiology.
• Monitor FC periodically and reassess if symptoms arise.
B. Evidence of transmural inflammation or persistently elevated FC:
• Consider early treatment for CD, even in the absence of symptoms.
• Longitudinal monitoring with FC, clinical assessment, and imaging may be necessary.



While most cases of IDTI do not progress to CD, careful follow-up is needed to identify those at risk. A systematic approach including FC monitoring, imaging, and evaluation of risk factors can help differentiate between transient ileitis and early CD, ensuring appropriate management while avoiding unnecessary interventions[1].

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Chapter 5: Extra-Intestinal Manifestations

Hamod Al Ghamdi

Introduction

Extra-intestinal manifestations (EIMs) represent a significant aspect of IBD, extending beyond the gastrointestinal tract and impacting various systems. EIMs have been defined as ***"an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either 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"*** [1].

These frequently affect the joints, skin, and eyes, but can also involve the liver, lungs, and pancreas [2]. Up to 50% of patients with IBD may develop at least one extra-intestinal condition [3]. EIMs can be categorized into those stemming from inflammatory pathologies at remote anatomical sites (classical, true EIMs), those resulting from systemic inflammation and associated treatments, and those with broader associations with the disease [1]. (Table 1).

The occurrence of EIMs can precede, coincide with, or follow the diagnosis of IBD, and their presence can substantially diminish the quality of life for affected individuals [4]. Often, these manifestations necessitate specific therapeutic interventions or at least require careful consideration when formulating treatment strategies for the underlying IBD [2]. The precise origins of EIMs in IBD are complex and not fully elucidated but are thought to arise from a combination of factors, including immune-mediated mechanisms, genetic predispositions, and environmental influences [2].

Table 1. Extraintestinal Manifestations in IBD (Adapted from [1])

Body Region	***Classical true EIMs***	***Complications of IBD and its treatment***	***Associated conditions***
Eyes	Uveitis, Episcleritis, Scleritis	Drug-induced cataracts and other drug-induced and nutritional eye disease	
Oral cavity	Oral CD, Orofacial granulomatosis, Metastatic CD		
Liver	Primary sclerosing cholangitis	Portal vein thrombosis, Hepatic amyloidosis, DILI, Autoimmune hepatitis, Autoimmune pancreatitis	Granulomatous hepatitis
Musculoskeletal	Spondyloarthritis	Metabolic bone disease/ Osteoporosis (drug or nutritionally induced)	Non-inflammatory arthralgia
Nervous system		Peripheral neuropathy (drug or nutritionally induced), Venous sinus thrombosis, Stroke	Central demyelination
Cardiovascular		Ischaemic heart disease, Cerebrovascular accident, Mesenteric ischemia	
Lungs		Drug-induced lung fibrosis	Inflammatory bronchial/parenchymal lung disease (e.g. asthma, bronchiectasis)
Skin	Erythema nodosum, Pyoderma gangrenosum, Sweet syndrome	Drug-induced skin disease (e.g. anti-TNF induced psoriasis), Drug-induced skin cancer, Drug hypersensitivity	Vitiligo, Psoriasis, Eczema, Epidermolysis bullosa acquisita, Cutaneous polyarteritis nodosa, Hidradenitis suppurativa

Musculoskeletal manifestations

Most prevalent impacting as many as 40% of patients [5]. They are classified within the spectrum of spondyloarthritis (SpA), which are a group of chronic, immune-mediated inflammatory joint diseases. These can be broadly categorized based on the predominant manifestations into axial SpA, primarily affecting the spine and sacroiliac joints, and peripheral SpA, involving the joints of the limbs.

The most common SpA conditions associated with IBD are peripheral arthritis (13%), followed by sacroiliitis (10%) and ankylosing spondylitis (3%) [6]. Peripheral SpA are classified as oligoarticular (< 5 joints) or polyarticular (>=5 joints) and is usually non-deforming [2]. (Table 2).

Axial SpA is characterized by inflammation of the sacroiliac joints (sacroiliitis) and spine (spondylitis) and further divided into ankylosing spondylitis (radiographic axial SpA) and non-radiographic axial SpA. Patients with axial SpA typically experience chronic lower back pain and stiffness that is worse in the morning or after periods of inactivity and improves with exercise [7]. Ankylosing spondylitis in patients with IBD occurs in 5% to 10% of patients and the strength of the HLA-B27 association in spondylitis complicating IBD is less (approximately 50%–70%) compared to idiopathic spondylitis (>90%).

The pooled prevalence of sacroiliitis on cross-sectional imaging in IBD patients is 21.0% (95% CI 17–26%) [8]. The prevalence of IBD among patients with spondyloarthritis ranges from 4% to 12%, and subclinical gut inflammation has been reported in approximately 40-50% of SpA patients [8].

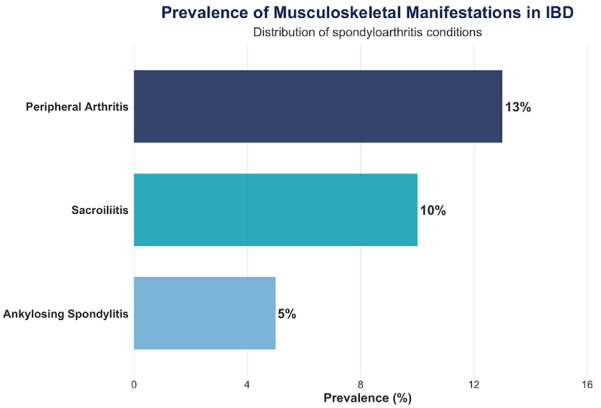


Table 2. Comparison of Type 1 and Type 2 peripheral spondyloarthritis (SpA) in IBD

Feature	Type 1 Pauciarticular	Type 2 Polyarticular
Prevalence	More common in CD than UC	
Number of joints	Less than 5 joints	Five or more joints
Joint type	Mainly large joints	Mainly small joints
Joint distribution	Knee > ankle > wrist > elbow > MCP > hip > shoulder	MCP > knees > PIP > wrist > ankle > elbow > shoulder
Symmetry	Asymmetric involvement	Symmetric or asymmetric, may be erosive
Relation to IBD activity	Parallels intestinal disease activity	Clinical course independent of IBD activity
Duration	Self-limited episodes that last < 10 weeks	Persistent inflammation for months or even years

Management of peripheral and axial spondyloarthropathy (Table 3)

Management of bowel inflammation is an important therapeutic target as this can also induce remission or reduction of activity for musculoskeletal manifestations. Use of non-steroidal anti-inflammatory drugs (NSAIDs) in IBD is still controversial due to concerns of increasing bowel inflammation. While there is no convincing evidence that NSAIDs exacerbate UC flare, there is potential association with CD flare [9].

Selective cyclooxygenase-2 (COX-2) inhibitors have fewer gastrointestinal side effects than traditional nonsteroidal anti-inflammatory drugs and can be considered for short-term use. For peripheral SpA, treatment options include nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, corticosteroids, sulfasalazine, methotrexate and anti-TNF agents. Ustekinumab might be useful for managing peripheral arthritis while existing evidence for vedolizumab is conflicting. Both medications are not recommended for axial SpA. For axial SpA, treatment options include physical therapy, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, anti-TNF agents, and JAK inhibitors [2].

Table 3. Management of Peripheral and Axial Spondyloarthropathy in IBD (Adapted from [10 and 11]).

Treatment Options for Spondyloarthropathy in IBD

Therapeutic recommendations based on manifestation type

	Axial	Peripheral
TNF-antagonists	Can be used	Can be used
Sulfasalazine	Should not be used	May be used
S1P-R modulators	Should not be used	Should not be used
Methotrexate	Should not be used	Can be used
JAK inhibitors	Can be used	Can be used
Anti-IL-23 p19	Should not be used	May be used
Anti-IL-12/23	Should not be used	May be used

Skin manifestations

Skin manifestations of IBD are common and occur in up to 15% of patients, often reflecting underlying disease activity and posing diagnostic and therapeutic challenges. Cutaneous EIMs can be categorized into four groups based on their pathophysiological mechanisms and association with underlying intestinal disease. (Table 4 & Table 5)

Table 4. Cutaneous EIMs categorization (Adapted from [12])

Category	Characteristics	Examples
Reactive	Share common pathogenic links, but not histopathological features of IBD.	Erythema nodosum, pyoderma gangrenosum, Sweet syndrome, oral lesions.
Specific	Same histopathological features of IBD but occurs outside GI tract.	Metastatic CD
Associated	Do not share histological or pathogenic links but observed frequently with IBD.	Hidradenitis suppurativa, psoriasis, atopic dermatitis, rosacea, vitiligo, alopecia areata, leukocytoclastic vasculitis, systemic lupus erythematosus, polyarthritis nodosa.
Complications	Consequences of IBD or adverse events to IBD treatment	Anti TNF adverse events like paradoxical psoriasis, Eczema-like/psoriasiform eczema, Paradoxical hidradenitis Suppurativa.

Table 5. Most common cutaneous manifestations in IBD. (Adapted from [11])

Manifestation	Features	Management
Erythema nodosum	-In 2–15% of IBD population -CD > UC -F > M -Symmetrical, raised, tender, erythematous, or violaceous subcutaneous nodules [1–5 cm] -Extensor surface of lower limbs > head, neck, trunk and arms	Treat underlying IBD -Supportive: bed rest, elevation, analgesia, compression hosiery -Skin directed: topical corticosteroids -Systemic: corticosteroids [if severe], potassium iodide, dapsone, TNFα antagonists, hydroxychloroquine
Pyoderma gangrenosum	-In 0.4–5% of IBD population -IBD in 30–50% of PG -UC > CD -F > M -Single or multiple erythematous papules/pustules -Rapid necrosis with irregular violaceous margins and purulent discharge -Often occurs after trauma [pathergy] -Secondary infection may occur -Shins and peristomal areas most common -High recurrence rate [>25%] -Can be severe and debilitating	-Supportive: wound care, analgesia, avoidance of trauma -Topical corticosteroids, topical tacrolimus -Systemic corticosteroids, TNFα antagonists, dapsone, tetracyclines, metronidazole -Severe: IV cyclosporin, TNFα antagonists, Ustekinumab, JAKi

Manifestation	Features	Management
Sweet syndrome [acute febrile neutrophilic dermatosis]	Rare -CD > UC -F > M -Acute onset of tender erythematous papules and nodules on limbs, trunk, head, and neck, varying sizes, associated with fever and neutrophilia	Treatment of underlying IBD -Topical corticosteroids -Systemic corticosteroids
Oral lesions	-In 5–50% of IBD population -CD > UC -Aphthous ulcers: painful avoid or round ulcers, labial or buccal mucosa, and pseudomembranous base and erythematous margin -Periodontitis: swelling, redness, bleeding of gingiva, loose teeth associated with perianal disease and smoking -Peristomal vegetans: pustules, hemorrhagic erosions, ulcers -Orofacial granulomatosis: Recurrent and persistent buccal swelling and oral ulcers, facial palsy, cervical lymphadenopathy	- Aphthous ulcers: topical corticosteroids and or lidocaine for pain - Periodontitis: treat underlying IBD and oral care. - Peristomal vegetans: treat underlying IBD, and Dapson and Doxycycline. - Orofacial granulomatosis: treat underlying IBD

Manifestation	Features	Management
Metastatic CD	-Rare, CD only -Extraintestinal sites: legs, intertriginous areas > facial, genital -Abscesses, fistulae, ulcers, nodules.	Treat underlying IBD
Hidradenitis Suppurativa	-0.4–15% in CD -0.1–6.1% in UC -F > M -IBD in 3.3% of HS -Obesity and smoking are risk factors -Recurrent, painful inflamed skin lesions, developing abscesses and interconnected sinus tracts in flexural sites [axillae, inguinal, perianal]	Smoking cessation Antibiotics: Clindamycin and Rifampicin, or tetracycline Steroid use Biological therapy including Anti-TNFs Surgical interventions
Anti TNF adverse events	-Paradoxical psoriasis: body, scalp, face; flexures > extensors [in contrast to typical psoriasis] -Palmoplantar pustulosis -Paradoxical hidradenitis suppurativa	Change the medication

Hepatobiliary manifestations

Hepatobiliary manifestations of IBD are common, affecting up to 50% of patients. They encompass a range of conditions affecting the liver, gallbladder, and biliary ducts, with primary sclerosing cholangitis (PSC) being the most well-recognized and extensively studied association [11]. Although, other hepatobiliary disorders, such as fatty liver disease, granulomatous hepatitis, autoimmune liver and pancreas disease, gallstone formation, can also occur in association with IBD [2].

Primary sclerosing cholangitis

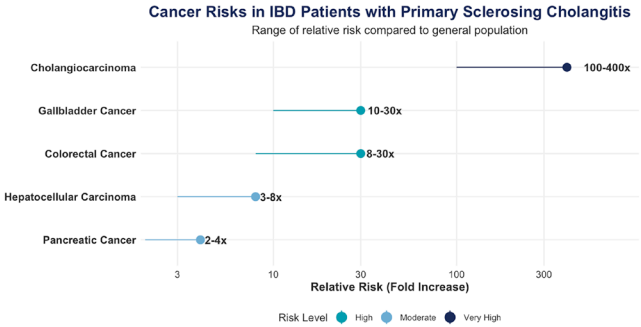
Is a chronic, progressive cholestatic liver disease characterized by inflammation and fibrosis affecting both the intrahepatic and extrahepatic bile ducts with a substantial risk of developing end-stage liver disease, malignancies, and increased mortality [2]. PSC has a well-established association with IBD, particularly UC, with approximately 60%–80% of PSC patients also having underlying IBD [2]. Approximately 4% of UC patients and 0.6% of CD patients have PSC [13].

PSC may precede the development of IBD, but in some instances, patients are diagnosed with PSC several years after undergoing proctocolectomy for UC. Male sex, extensive ulcerative colitis, non-smoking status, and a history of appendectomy were found to be significantly associated with primary sclerosing cholangitis [13].

The diagnosis involves a combination of clinical, biochemical, and imaging findings. Elevated liver enzymes, particularly alkaline phosphatase, are often the first indication of PSC. Magnetic resonance cholangiopancreatography (MRCP) is the imaging modality of choice and characteristic features

include multifocal strictures, beading, and dilation of the bile ducts.

IBD patients with asymptomatic PSC have a worse prognosis compared to IBD patients without PSC [14]. PSC greatly increases the risk of hepatobiliary (cholangiocarcinoma and gallbladder malignancy) and colorectal cancer, and surveillance using ultrasound and/or MRCP for hepatobiliary cancer and annual colonoscopy starting at the time of diagnosis for colorectal cancer is recommended [15].



Several drugs have been evaluated for the treatment of PSC, none have shown a benefit in slowing progression, or preventing complications. Liver transplantation (LT) remains the only proven life-extending intervention. Ursodeoxycholic acid [UDCA] [15–20 mg/kg/day] improves liver biochemistry but does not improve fatigue, pruritus, risk of cholangiocarcinoma, or mortality [11]. The role of UDCA on the risk of CRC development remains controversial and cannot be recommended solely for reducing colorectal cancer risk in IBD due to conflicting evidence [11].

Ocular manifestations

Ocular EIMs manifest in 2%–7% of IBD patients and include anterior uveitis, episcleritis, and scleritis (Table 6). There are several other less common ocular manifestations that have been reported in the literature including conjunctivitis, keratitis, retinal vasculitis, optic neuritis, central retinal vein occlusion and orbital myositis [16].

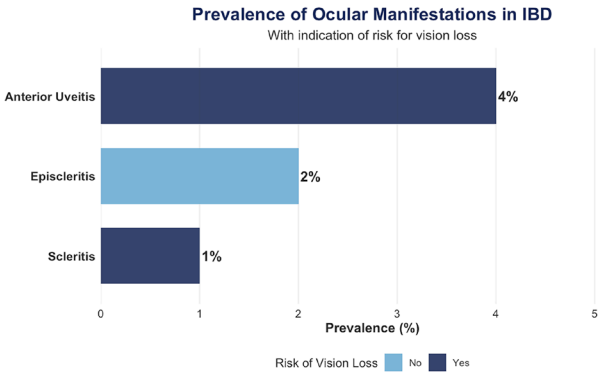


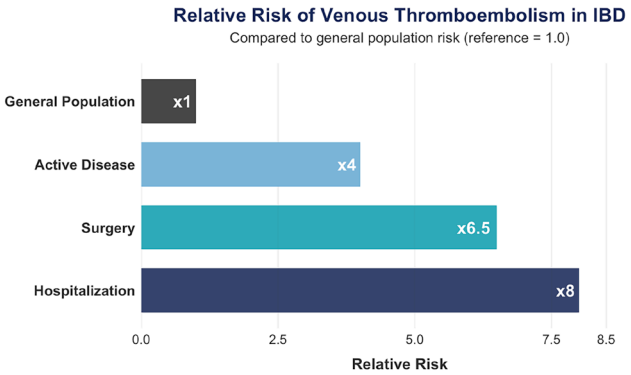
Table 6. Ocular Manifestations of IBD

	Clinical features	Association with IBD activity	Risk of Vision Loss	Management
Anterior Uveitis (iritis)	Discomfort or pain, may be bilateral, red eye, blurred vision, headache, photophobia.	May or may not be associated	Yes	Urgent ophthalmology referral if suspected -First line: topical steroids -Second line: systemic steroids, steroid-sparing agents, or biologic therapy [TNFα antagonists]
Scleritis	Severe pain that wakes patients from sleep, unilateral or bilateral, with or without red eye.	Yes	Yes	Urgent ophthalmology referral if suspected -First line: oral NSAIDs or oral steroids -Second line: steroid-sparing immunomodulators, biologics [TNFα antagonists]
Episcleritis	Painless or mild discomfort, unilateral or bilateral, hyperemia.	Yes	No	Treatment of underlying disease, topical lubricants, and cool compresses Topical NSAIDs

Venous thromboembolism

Is a prevalent and potentially life-threatening complication for patients with IBD. CD and UC are independent risk factors for the development of venous thromboembolism (VTE) with an estimated risk to be approximately two-fold or higher compared to the general population. This heightened risk is particularly pronounced during periods of active disease, hospitalization, and surgical interventions. The thrombotic risk appears similar between men and women, and between patients with UC and CD.

All individuals with IBD who require hospitalization, regardless of the underlying cause, including disease exacerbation or surgical intervention, should receive pharmacological prophylaxis against VTE [11]. Prophylactic low-molecular-weight heparin is recommended over unfractionated heparin to prevent VTE in acutely and critically ill patients with IBD [17].



Extended thromboprophylaxis (3-6 weeks) following discharge from the hospital is recommended for patients with IBD who have undergone major surgery [11]. Extended pharmacological thromboprophylaxis after discharge in non-surgical hospitalized patients and outpatients with active IBD is currently not recommended. However, outpatients with severe IBD flares and a high risk of VTE, whether related to the disease or not, may benefit from pharmacological thromboprophylaxis until the flare resolves [11].

Direct oral anticoagulants (DOACs) at therapeutic doses are recommended as first line in patients with IBD presenting with an acute VTE [11]. Risk factors for VTEs should be investigated to guide duration of anticoagulation.

IBD flare, recent surgical procedure, and hospitalization are considered risk factors for VTE and VTE is considered provoked, and 3 months of anticoagulation is recommended, while unprovoked VTE should be treated indefinitely [11].

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Maan Alkhattabi & Mahmoud Mosli

Introduction

Diagnosing IBD can be challenging due to the complexity and wide variation of its clinical features, chronically over months and sometimes years, it is seldom that the presentation is subacute over weeks [1-3]. Therefore, it is essential to rule out infections that mimic IBD by performing proper stool and/or tissue testing (Table 1) [4]. Patients with UC are frequently diagnosed with recurrent dysentery (amoeba) and are unnecessarily given repetitive courses of antibiotics. Another challenge is to differentiate between IBD, mainly CD, and irritable bowel syndrome (IBS), as a large proportion of patients with CD are initially misdiagnosed with IBS or have overlapping features for an extended period, which leads to delays in diagnosis and treatment. These warrants paying careful attention to "red flags" during history taking.

Table 1. Pathologic features of infections that can mimic inflammatory bowel disease.

Pathogen	Key IBD like features	Ancillary studies
Salmonella enterica typhi & paratyphi serovars Shigella spp.	Lymphoid hyperplasia, ulcers, crypt architectural distortion Continuous distribution proximally from the rectum, chronic active colitis with marked architectural distortion	Stool culture and PCR
Entamoeba histolytica	Cryptitis, ulcers, pyloric metaplasia, Paneth cell hyperplasia, architectural distortion	Trophozoites are positive with trichrome and PAS stains

Sexually transmitted proctitis (Treponema pallidum, Chlamydia trachomatis)	Dense lymphohistiocytic infiltrate with prominent plasma cells, lymphoid aggregates, mild actively cryptitis, poorly formed granulomas	Treponema pallidum: Immunohistochemistry, serologic studies Chlamydia trachomatis: Nucleic acid amplification test or PCR on rectal swab specimens
Mycobacterium tuberculosis	Hyperplastic Peyer patches, fissures, architectural distortion, transmural lymphoid aggregates, mural fibrosis, inflamed submucosal blood vessels, granulomata	Acid-fast stains, RT-PCR on paraffin-embedded tissue or stool, serologic gold test QuantiFERON

Pathogen	Key IBD like features	Ancillary studies
Yersinia spp.	Architectural distortion, mural lymphoid hyperplasia and fibrosis, transmural lymphoid aggregates, and epithelioid granulomata	Stool culture and RT-PCR on paraffin-embedded tissue
Actinomyces spp.	Mucosal lymphoid hyperplasia, transmural lymphoid aggregates and epithelioid granulomata, perianal fibrosing, and can cause perianal fistulas	Organisms are gram positive and stain with GMS

Basidiobolus ranarum	Increased lamina propria inflammation including plasma cells, neutrophils, eosinophils, ulcers, granulomata, thickening of pericolic fat	GMS, PAS-D

The red flag score

The red flag score is a partially validated tool that can be used to detect patients with a high probability of CD (Table 2) [5,6]. Delays in diagnosing IBD can lead to the development of disease complications and treatment resistance [7]. In certain parts of the world where intestinal tuberculosis (ITB) is endemic, patients with CD can be misdiagnosed with ITB and treated with anti-tuberculous medications for periods that extend to 2 years before the diagnosis is challenged. Predictive models incorporating clinical, biochemical, and endoscopic findings have been introduced to help distinguish both conditions and mitigate this obstacle [8].

Table 2. The Red Flag Index (RFI)

Item	Score
Non-healing or complex perianal fistula or abscess or perianal lesions (apart from hemorrhoids)	5
First-degree relative with confirmed inflammatory bowel disease	4
Weight loss (5% of usual body weight) in the last 3 months	3
Chronic abdominal pain (>3 months)	3
Nocturnal diarrhea	3

Mild fever in the last 3 months	2
No abdominal pain 30-45 min after meals, predominantly after vegetables	2
No rectal urgency	2

A minimum Red Flags index value of 8 highly predicted CD diagnoses with sensitivity and specificity bootstrap estimates of 0.94 (95% confidence interval 0.88-0.99) and 0.94 (0.90-0.97), respectively. Positive and negative likelihood ratios were 15.1 (9.3-33.6) and 0.066 (0.013-0.125). The association between CD diagnosis and a Red Flags index value of ≥8 corresponds to an OR of 290 ($p < 0.01$).

Patients with IBD can have both local and systemic manifestations with very high variability. This symptom heterogeneity can be attributed mainly to disease location, extent, severity, and phenotype. The most common gastrointestinal symptoms are diarrhea, abdominal pain, tenesmus, and malnutrition. Presenting with dominant systemic symptoms such as fever, weakness, fatigue, and extra intestinal manifestations of IBD is not uncommon, especially in younger patients, or in those with complications related to the disease.

Symptoms of UC include bloody diarrhea, rectal bleeding, urgency, tenesmus, and abdominal cramps. In a small percentage of patients, the first presentation of UC can be severe and require urgent hospitalization due to the higher risk of perforation or exsanguination, which is labeled acute severe ulcerative colitis (ASUC). These patients typically present with very severe symptoms and systemic toxicity. Acute infections should be carefully excluded in patients before initiating rescue therapies, such as intravenous corticosteroids, infliximab, or cyclosporin as concomitant Clostridium Difficile and Cytomegalovirus (CMV) is not uncommon.

It is prudent to be able to distinguish between the two major types of IBD, UC and CD, as this has significant implications for the patient's future disease course. This is, however, quite difficult sometimes, which is why around 10% percent of patients with IBD are initially labeled as IBD unclassified (IBDU) [9].

Patients' CD typically presents with abdominal pain, diarrhea, vomiting, weight loss, and fever. About a quarter of patients with CD present with perianal manifestations such anal fissures, perianal fistulae and abscesses, and skin tags, which can be very implicative of the diagnosis [10]. Upper GI involvement of CD is commonly seen in young patients and less so in adults [2,3]. It is worth noting that symptoms are often dependent on the location and severity of involvement of the gastrointestinal tract.

How to investigate a patient who might have IBD?

Laboratory investigations

Baseline laboratory testing of patients presenting with symptoms suspicious of IBD includes essential blood and stool testing.

Complete blood count (CBC) is beneficial in detecting anemia, which could be caused by chronic inflammation, malabsorption, or bleeding; leukocytosis, which could reflect active inflammation of superimposed infection; and thrombocytosis, which reflects ongoing inflammation.

Additional blood tests include liver profile (Especially Alkaline Phosphatase for Primary Sclerosing Cholangitis), electrolytes, renal profile, thyroid function test, and c-reactive

protein (CRP). CRP is a non-specific inflammatory marker that supports the diagnosis of IBD when elevated but with limited sensitivity, as 15-20% of patients do not produce CRP.

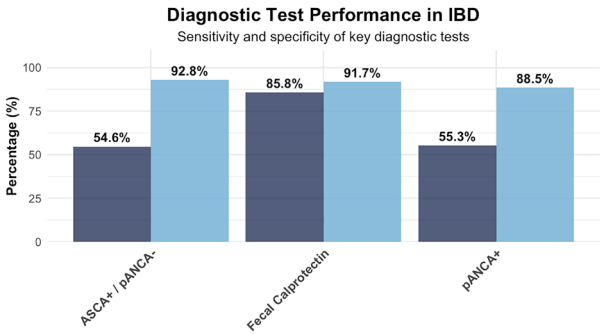
Stool tests

These include stool analysis, stool culture, polymerase chain reaction (PCR) assay for clostridium difficile toxin, and fecal calprotectin (FC). FC is a protein released from neutrophils during inflammation and detected in the stool. The level of FC correlates with the degree of intestinal inflammation and disease location. FC is more likely to be elevated in the presence of colonic involvement and less likely if the disease is limited to the small bowel. Nevertheless, a normal FC decreases the likelihood of IBD, and an elevated FC should prompt further investigations such as ileocolonoscopy, cross-sectional imaging, or video capsule endoscopy (VCE) to confirm or rule out IBD. FC is widely used to screen for IBD with a sensitivity of 85.8% (95% CI: 78.3–91) and a specificity of 91.7% (95% CI: 84.5–95.7) to distinguish between IBD and IBS. Issues that require careful attention when interpreting FC levels include sample acquisition, sample processing, cut-off points, and the pre-test probability of IBD [11].

Antibody tests

Several antibodies to microbial antigens that can be associated with the diagnosis of IBD have been identified and studied. Anti-saccharomyces antibodies (ASCA) and anti-neutrophil cytoplasmic antibodies (ANCA) are seldom used to help differentiate between CD and UC, respectively. For example, positive ASCA and negative pANCA tests can predict CD with a sensitivity of 54.6% and a specificity of 92.8% (receiver operating characteristic (ROC) curve (AUC)= 0.85, likelihood ratio positive (LR+) = 6.5, likelihood ratio negative (LR-) = 0.5). On the other hand, the sensitivity and specificity of a

positive pANCA test alone for UC were 55.3% and 88.5%, respectively (AUC = 0.82; LR+ = 4.5, LR- = 0.5). Other markers, namely anti-outer-membrane protein C (anti-OmpC), anti-pseudomonas fluorescence-associated sequence I2 (anti-I2), and anti-bacterial flagellin (anti-CBir1), can be used to predict the risk of complications and surgery in CD patients but with limited accuracy [12, 13].



Radiological investigations

Intestinal Ultrasound

Intestinal ultrasound (IUS) is a non-invasive, radiation-free imaging modality that has become increasingly useful in diagnosing IBD. It detects bowel wall thickness and intramural vascularization and can help detect strictures, abscesses, or fistulae. IUS has the advantage of being point-of-care but is limited by being highly operator-dependent and less accurate in obese patients and for rectal involvement [14, 15].

Computed Tomography Enterography (CTE)

Contrast (oral and IV contrasts) enhanced computed tomog-

raphy (CT) scans focused on the bowel are frequently used to assess the small bowel for areas of inflammation, e.g., wall thickness, mesenteric engorgement, and stenosis or fistulization due to complicated CD [16]. Although they require a short duration to perform and provide comprehensive details of the bowel and surrounding organs, their main disadvantage is radiation exposure.

Magnetic Resonance Enterography (MRE)

MRE is a radiation-free, cross-sectional modality that provides a high-quality, detailed description of the bowel and the surrounding tissue. MRE's primary role is to detect inflamed or damaged bowel areas. For this purpose, oral and IV contrasts are needed. MRE is more accurate than CTE in differentiating between active inflammation and fibrosis in areas with luminal narrowing. Susceptibility to motion artifacts and prolonged examination duration are among its main disadvantages [17].

Table 3: Imaging modalities used to investigate for inflammatory bowel disease.

	CT Enterography	*MR Enterography*	*Intestinal Ultrasound*
Feature	CTE	MRE	IUS
Radiation Exposure	Radiation	No radiation	No radiation
Resolution	High (excellent for bowel wall assessment)	High (excellent for soft tissue and bowel layers)	Moderate (depends on operator and patient factors)
Detectable Complications	Fistulas, abscesses, perforation, strictures	Fistulas, abscesses, strictures, perianal disease	Abscesses, fistulas, thickening, strictures
Procedure Duration	Fast (5-15 minutes)	Longer (30-45 minutes)	Fast (10-20 minutes)
Cost	Moderate to high	High	Low
Availability	Widely available	Limited availability in some centers	Available (operator dependent)

Endoscopy

Ileocolonoscopy

Documenting mucosal inflammation through endoscopy is considered the cornerstone of diagnosing IBD. During the index evaluation, documentation of the site and the extent, pattern, and severity of inflammation is essential. Furthermore, identifying potential disease complications is an integral part of risk stratification [18].

Esophagogastroduodenoscopy (EGD)

In adults, examination of the upper GI tract is usually reserved for patients suspected of having upper GI CD, such as those with symptoms of dyspepsia, nausea, vomiting, dysphagia, or

epigastric pain. In contrast, EGD is routinely done at baseline in children being worked up for CD due to the higher prevalence of upper GI CD in this patient population [19].

Video capsule endoscopy (VCE)

VCE is typically used when there is a high suspicion of isolated small bowel CD, especially in the presence of a normal ileocolonoscopy and a high index of suspicion. It is more accurate than cross-sectional modalities (CTE or MRE) for detecting proximal small bowel aphthous ulcers. However, due to the risk of capsule retention, it must be done after ruling out small bowel strictures using cross-sectional imaging or after using a patency capsule [20].

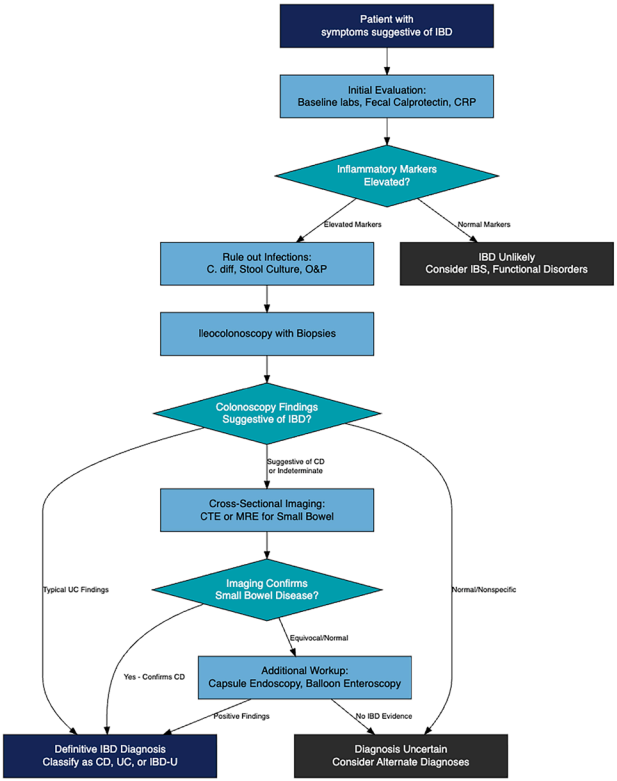
Device-assisted enteroscopy (DAE)

DAE, such as push enteroscopy, anterograde, or retrograde balloon enteroscopy, is used to reach small bowel lesions suspected of CD. This is typically undertaken when tissue biopsy is needed following the detection of inflamed areas by cross-sectional imaging or VCE or for endoscopic dilatation [21].

Histopathology

Histopathology plays an essential role in confirming the diagnosis of IBD. Features of chronicity and activity must be present to confirm the diagnosis. Features of chronic inflammation include crypt architecture distortion and inflammatory expansion of the lamina propria with basal lymphoplasmacytosis and paneth cell metaplasia or hyperplasia. In CD, other features include pyloric gland metaplasia of the small bowel and right colon, and non-caseating granulomas, which are pathognomonic for CD. Still, they are only seen in up to 25% of cases. Features of activity include neutrophil infiltration in lamina propria, cryptitis, crypt abscesses, and ulcerations [22,23].

Figure 1: Suggested diagnostic Algorithm for Crohn's disease.



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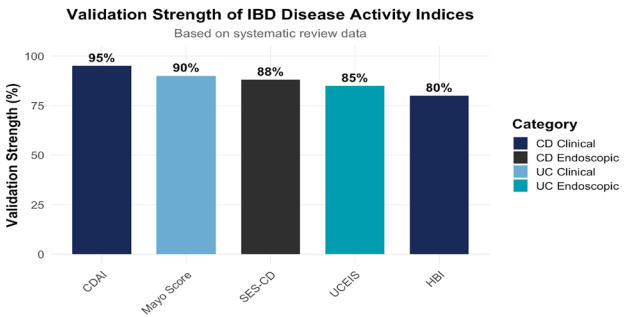
Sameer Al Awadhi

Introduction

Inflammatory Bowel Diseases (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic relapsing-remitting conditions requiring precise disease activity assessment to guide treatment escalation and monitor therapeutic response. In IBD, disease activity and disease severity are related but distinct concepts and confusing them can lead to inappropriate treatment decisions. Disease activity refers to the current, reversible inflammatory burden at a given point in time, while disease severity reflects the overall impact and complexity of the disease over time, including cumulative damage and prognosis. The STRIDE-II guidelines emphasize composite endpoints incorporating clinical, endoscopic, and patient-reported outcomes [1].

The validation strength of IBD disease activity indices varies widely, and this has important implications for clinical trials, treat-to-target strategies, and daily practice. A well-validated disease activity index should demonstrate a reliability – reproducible between observers and over time), construct validity that reflects true inflammatory activity, criterion validity – correlates with a gold standard (endoscopy/histology), responsiveness changes with treatment and prognostic value – predicts outcomes (hospitalization, surgery).



Crohn's Disease Activity Assessment

Clinical Indices

The Crohn's Disease Activity Index (CDAI) remains the gold standard for clinical trials, integrating eight weighted variables including stool frequency, abdominal pain, and laboratory parameters [2]. A CDAI <150 defines clinical remission, while >450 indicates severe disease.

Table 1: Crohn's Disease Activity Index (CDAI) Scoring System

Variable	Description	Weight
Daily stool frequency (×7)	Number of liquid/soft stools	**×2**
Abdominal pain (×7)	Rated 0–3 (0=none, 3=severe)	**×5**
General well-being (×7)	Rated 0–4 (0=very well, 4=terrible)	**×7**
Extra-intestinal symptoms	Arthritis, iritis, etc.	**+20**
Use of antidiarrheal drugs	Yes = 1, No = 0	**+30**
Abdominal mass	0 (none) to 3 (definite and tender)	**×10**
Hematocrit deviation	From standard (47% men, 42% women)	**×6**
Body weight deviation	% below standard weight	**×1**

Score Interpretation: CDAI Interpretation: <150 = Remission; 150–220 = Mild activity; 221–450 = Moderate activity; >450 = Severe activity

The Harvey-Bradshaw Index (HBI) provides a simplified alternative for clinical practice, with scores <5 indicating remission and >16 representing severe disease [3].

Table 2: Harvey-Bradshaw Index (HBI)

Component	Points	Score Range
General well-being	0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	**0-4**
Abdominal pain	0 = none, 1 = mild, 2 = moderate, 3 = severe	**0-3**
Number of liquid stools/day	Count of liquid stools	**0-∞**
Abdominal mass	0 = none, 1 = dubious, 2 = definite, 3 = definite and tender	**0-3**
Complications	1 point each: Arthralgia, iritis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissure, new fistula, abscess	**0-∞**

Score Interpretation: HBI Interpretation: <5 = Remission; 5–7 = Mild disease; 8–16 = Moderate disease; >16 = Severe disease

Endoscopic Assessment

Endoscopic evaluation is critical for assessing mucosal healing. The Simple Endoscopic Score for Crohn's Disease (SES-CD) has replaced the complex Crohn's Disease Endoscopic

Index of Severity (CDEIS) as the preferred tool, with scores <3 defining endoscopic remission [4,5].

Table 3: Crohn's Disease Endoscopic Index of Severity (CDEIS)

Endoscopic Variable	Scoring	Assessment Segments
Deep ulcers	Present = 12, Absent = 0	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum
Superficial ulcers	Present = 6, Absent = 0	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum
Non-ulcerated stenosis	Present = 3, Absent = 0	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum
Ulcerated stenosis	Present = 3, Absent = 0	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum
Proportion of ulcerated surface	0-10% = 0, 11-30% = 1, 31-60% = 2, >60% = 3	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum
Proportion of surface affected by disease	0-10% = 0, 11-30% = 1, 31-60% = 2, >60% = 3	Rectum, sigmoid colon, left colon, transverse colon, right colon, ileum

Notes: Total CDEIS score range: 0-44; Higher scores indicate more severe disease. Assessed in 5 ileocolonic segments.

Table 4: Simple Endoscopic Score for Crohn's Disease (SES-CD)

Variable	Score 0	Score 1	Score 2	Score 3
Ulcer size	None	Aphthous ulcers (0.1-0.5 cm)	Large ulcers (0.5-2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	<5%	5-50%	>50%	-
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Score Interpretation: SES-CD Interpretation: 0-2 = Remission; 3-6 = Mild activity; 7-15 = Moderate activity; ≥16 = Severe activity. Assessed in 5 ileocolonic segments.

Ulcerative Colitis Activity Assessment

Clinical and Endoscopic Indices

The Mayo Score integrates clinical symptoms and endoscopic findings, with scores 0-2 indicating remission and 11-12 representing severe disease [6]. The Mayo Endoscopic Subscore (MES) specifically evaluates mucosal inflammation, while the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) provides more granular assessment [7].

Table 5: Mayo Score for Ulcerative Colitis

Component	Score 0	Score 1	Score 2	Score 3
Stool Frequency	Normal	1–2 more than normal	3–4 more than normal	>4 more than normal
Rectal Bleeding	None	Streaks of blood	Obvious blood	Mostly blood
Endoscopic Findings	Normal or inactive disease	Mild disease: erythema, decreased vascular pattern	Moderate disease: marked erythema, friability, erosions	Severe disease: spontaneous bleeding, ulceration
Physician Global Assessment	Normal	Mild	Moderate	Severe

Score Interpretation: Total Mayo Score Interpretation: 0-2 = Remission; 3-5 = Mild activity; 6-10 = Moderate activity; 11-12 = Severe activity

Table 6: Mayo Endoscopic Score (MES)

Score	Endoscopic Description	Clinical Correlation
0	Normal or inactive disease: Normal vascular pattern, no erythema, no friability	Complete mucosal healing
1	Mild disease: Erythema, decreased vascular pattern, mild friability	Mild inflammation, usually responsive to 5-ASA
2	Moderate disease: Marked erythema, absent vascular pattern, friability, erosions	Moderate inflammation, may require steroids/biologics
3	Severe disease: Spontaneous bleeding, ulceration	Severe inflammation, often requires hospitalization

Note: MES is specifically used to evaluate endoscopic appearance independent of clinical symptoms

Table 7: Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

Descriptor	Score 0	Score 1	Score 2	Score 3
Vascular pattern	Normal	Patchy obliteration	Obliterated	-
Bleeding	None	Mucosal bleeding (visible)	Luminal bleeding (post-wash)	Spontaneous bleeding
Erosions and Ulcers	None	Erosions (≤5mm)	Superficial ulcers (>5mm)	Deep ulcers

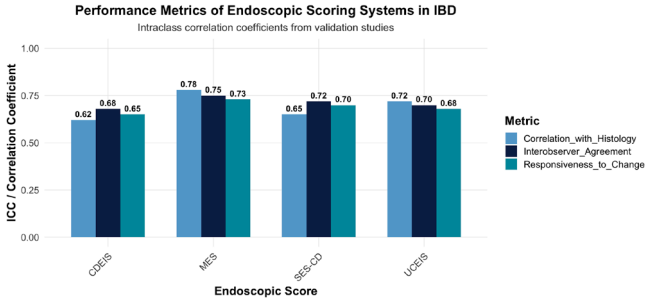
Score Interpretation: UCEIS Interpretation: 0-1 = Endoscopic remission; 2-4 = Mild to moderate activity; 5-8 = Severe disease

The Truelove and Witts Severity Index classifies UC severity based on clinical and laboratory parameters, defining acute severe UC (ASUC) as ≥6 bloody stools daily with systemic toxicity markers [8].

Table 8: Truelove and Witts Severity Index for Ulcerative Colitis

Parameter	Mild UC	Moderate UC	Severe UC
Stool frequency per day	<4	4–6	>6
Blood in stool	Small	Moderate	Visible
Temperature (°C)	Normal	37.1–37.8	>37.8
Pulse (bpm)	<90	90–100	>100
Hemoglobin (g/dL)	>11.5	10.5–11.5	<10.5
ESR (mm/hr)	<20	20–30	>30

Clinical Note: Severe UC definition: ≥6 bloody stools/day plus at least one systemic marker (fever, tachycardia, anemia, or elevated ESR)



Biomarker Correlates

C-reactive protein (CRP) and fecal calprotectin serve as non-invasive biomarkers correlating with endoscopic activity, with calprotectin <150 µg/g predicting mucosal healing [9].

Table 9: Laboratory Biomarkers in Inflammatory Bowel Disease

Marker	Clinical Relevance	Normal Range	Clinical Significance
C-reactive protein (CRP)	Acute phase reactant; correlates with inflammation (better in CD than UC)	<5 mg/L	High
Erythrocyte Sedimentation Rate (ESR)	Elevated in moderate to severe flares; slower to respond than CRP	Men: 0-15 mm/hr; Women: 0-20 mm/hr	Moderate
Fecal calprotectin	Sensitive marker for mucosal inflammation; correlates with endoscopic activity	<50 µg/g	High
Hemoglobin	Reduced in chronic disease, active bleeding, or iron deficiency	Men: 13.5-17.5 g/dL; Women: 12.0-15.5 g/dL	Moderate
Albumin	Low in malnutrition, protein-losing enteropathy, or severe inflammation	3.5-5.0 g/dL	Moderate
Fecal lactoferrin	Marker of neutrophil activity in intestinal lumen	<7.25 µg/g	Moderate
Fecal hemoglobin	Specific marker for gastrointestinal bleeding	Negative	Low

Note: Biomarkers should be interpreted in clinical context and are complementary to endoscopic and imaging assessments

Imaging and Histologic Assessment

In addition to endoscopic evaluation, imaging techniques are often required to assess disease severity, particularly in CD. Magnetic Resonance Enterography (MRE) and Computed Tomography Enterography (CTE) are useful imaging modalities for detecting strictures, fistulas, transmural inflammation

and complications. Recently, Intestinal ultrasound (IUS) has become a key, non-invasive tool in the assessment and monitoring of IBD, particularly Crohn's disease, and increasingly ulcerative colitis.

Histological analysis provides another dimension to disease assessment, particularly in UC where inflammation is generally limited to the mucosa. Biopsies may reveal architectural distortion, basal plasmacytosis, crypt abscesses, and neutrophilic infiltration. Histologic remission is now recognized as a desirable endpoint and has been incorporated into emerging clinical trial designs [10].

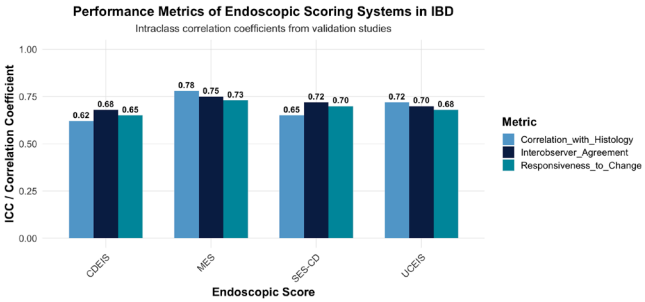


Table 10: Imaging Modalities for IBD Assessment

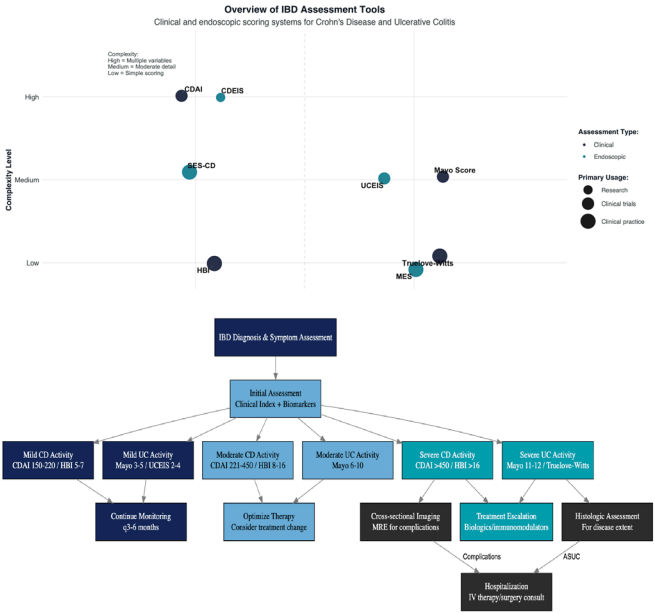
Imaging Modality	Primary Indications	Advantages	Limitations	Radiation Exposure
Magnetic Resonance Enterography (MRE)	Transmural inflammation assessment, fistulas, abscesses, strictures	No radiation, excellent soft tissue contrast, dynamic imaging	Longer scan time, contraindicated with certain implants	None
Computed Tomography Enterography (CTE)	Acute complications, obstruction, perforation, abscess	Fast acquisition, excellent spatial resolution, widely available	Ionizing radiation, contrast allergy risk, limited soft tissue contrast	Moderate-High
Intestinal Ultrasound	Non-invasive monitoring, wall thickness assessment, disease activity	No radiation, bedside availability, low cost, serial monitoring	Operator-dependent, limited depth penetration, bowel gas interference	None
Capsule Endoscopy	Small bowel mucosal visualization, early CD diagnosis	Complete small bowel visualization, mucosal detail	Contraindicated in strictures, retention risk, no biopsy capability	None
Small Bowell Follow-Through	Stricture identification, mucosal pattern assessment	Traditional method, functional assessment of transit	Radiation exposure, limited sensitivity for early inflammation	Low-Moderate

Clinical Decision: Choice of imaging modality depends on clinical question, patient factors, and local availability

Table 11: Evidence-Based Characteristics of IBD Disease Activity Assessments Tools

Evidence-Based Characteristics of IBD Disease Activity Assessment Tools

Assessment Tool	Disease	Components	Remission Definition	Validation Reference	Primary Utility
CDAI	CD	8 weighted variables	<150	Gastroenterology 1976	Clinical trials
Harvey-Bradshaw	CD	5 clinical items	<5	Lancet 1980	Clinical practice
SES-CD	CD	4 endoscopic variables	<3	Gastrointest Endosc 2004	Endoscopic trials
Mayo Score	UC	4 domains	0-2	NEJM 1987	Clinical trials/practice
UCEIS	UC	3 endoscopic descriptors	0-1	Gut 2012	Endoscopic trials
Truelove-Witts	UC	6 clinical/lab criteria	Mild criteria	BMJ 1955	Severe UC definition



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Badr Albawardy & Mashary Attamimi

Introduction

This chapter will summarize the principles of the treat-to-target approach in IBD and provide an overview of available medical therapies, including insights into treatment efficacy based on specific disease phenotypes and severity. Drug dosing, route of administration, key therapy considerations, side effects, and monitoring protocols are explained in latter chapter.

Key principles of treat-to-target in moderate-to-sever IBD

- Focusing solely on symptom resolution fails to alter the disease course [1].
- Achieving targets beyond symptom control, such as biomarker normalization (C- reactive protein (CRP) and fecal calprotectin (FCP)) and endoscopic healing, improves patient long-term outcomes and can modify the disease course [2].
- The STRIDE 2 consensus provided a timeline-based treatment target approach focusing on symptoms, biomarkers, and endoscopic outcomes (Figure 1) [3].

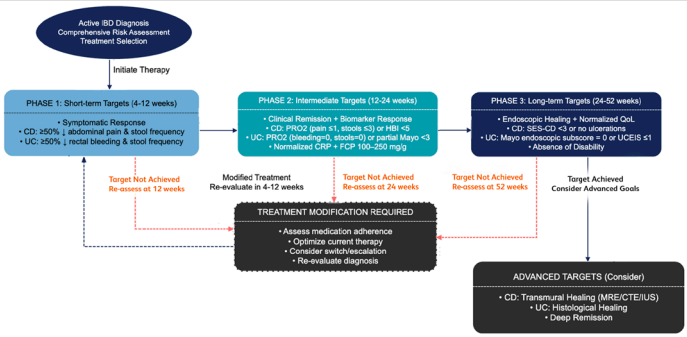


Figure 1. Selecting therapeutic targets in IBD consensus (STRIDE-II) [3].
Treatment targets in IBD. IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; PRO: patient-reported outcome; CRP: C-reactive protein; FCP : Fecal calprotectin; QoL: quality of life; SES-CD: Simple Endoscopic Score for Crohn's disease; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; MRE: magnetic resonance enterography; CTE: computed tomography enterography; IUS: Intestinal ultrasoun

- Therapy should be adjusted or modified if treatment targets are not met, with close monitoring being a critical component throughout the course of management [3].
- The time required to achieve each target varies depending on the disease (UC or CD) and the selected therapy [3].
- Transmural healing in CD and histologic remission in UC improve outcomes (e.g., fewer hospitalizations, lower relapse rates) but are not yet formal targets [3-4].
- Less stringent, individualized targets may be appropriate for frail patients, those with comorbidities, or refractory disease after multiple therapy failures [5].

Therapeutic Options for Crohn's Disease
- The medical therapy of CD is tailored based on disease phenotype, severity, and the burden of inflammation [6].
- Early treatment with effective therapy (top-down approach) in patient at risk of complications has demonstrated greater efficacy and improved outcomes compared to the step-up approach (Figure 2) [7].

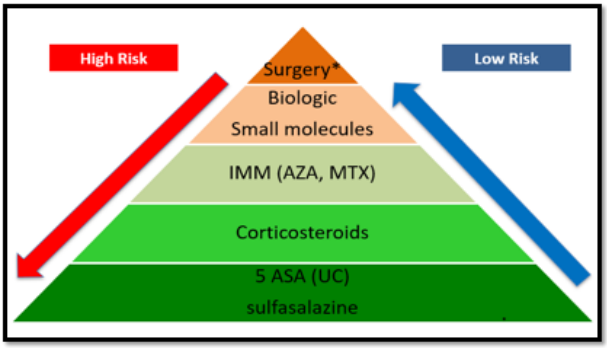


Figure 2. Top-down vs. step-up approach in CD . The top-down approach demonstrates greater efficacy and fewer disease complications compared to the step-up approach in Crohn's disease. *Surgery can be considered at any time in the treatment algorithm. 5-ASA: 5-aminosalicylic acid; AZA: Azathioprine; MTX: Methotrexate.

- A proposed treatment positioning and sequencing for Crohn's disease is outlined in Table 2. Approved therapies for IBD patients, including their efficacy in different scenarios, are detailed in Table 4.
- Management of stricturing and penetrating Crohn's disease, beyond medical therapy, is covered in latter chapter.

5-Aminosalicylates (5-ASA)

- 5-ASA have no role in the management of CD, either for induction or maintenance therapy [8].
- Sulfasalazine may be considered for patients with mild colonic CD [8].

Corticosteroids

-Enteric-release budesonide is effective for inducing clinical

remission in mild to moderate CD limited to the ileum and/or ascending colon. [9]
-Systemic corticosteroids (intravenous or oral) can be used to induce remission in Crohn's disease, but it is essential to ensure the patient has no abscess or pelvic sepsis [10].
-Steroids, in any form, should not be used for maintenance therapy or to induce remission in perianal disease [11].

Immunomodulators
- Thiopurines monotherapy are not used for induction but may be effective for maintaining remission in CD. Their use should balance the risk of side effects with the availability of safer therapies [11].
- Thiopurines are best used in combination with anti-TNF agents in CD to enhance efficacy and reduce immunogenicity of anti-TNF therapy [12].
- Unlike thiopurines, methotrexate can be used for both induction and maintenance therapy in CD when administered via the parenteral route [11].
- Given the safety of newer therapies, methotrexate monotherapy is rarely used and is best combined with anti-TNF agents [11].
- Immunomodulators, when used in combination with anti-TNF therapy, can be safely withdrawn after achieving long-term remission, with caution for patients with prior anti-TNF immunogenicity [11].

TNFα antagonists
- Infliximab, adalimumab, and certolizumab pegol can be used for both induction and maintenance therapy in moderate to severe CD [9].
- Infliximab has shown greater efficacy and durability in CD when combined with immunomodulators [13].
- Anti-TNF agents, specifically infliximab, have shown efficacy in patients with penetrating or perianal CD and should be

considered first-line therapy for these cases. Certolizumab not recommended as first line therapy for perianal disease. [11,14]
- Anti-TNF agents have shown effectiveness in treating most extraintestinal manifestations, such as peripheral and axial arthropathy and pyoderma gangrenosum [15].
- Secondary loss of response to anti-TNF therapy is common, often due to antibody formation, with only one-third maintaining remission after three years. Key risk factors are low drug levels at the end of induction and lack of immunomodulator use [16].
- Infliximab is effective as maintenance therapy in intravenous (IV) and subcutaneous (SC) forms. Switching from IV to SC is safe, with SC dosing based on prior IV dose and subsequent drug level after transition (Table 1) [17].
- Patients in clinical remission and with fecal calprotectin levels <250 at the time of switching have a low risk of relapse after transitioning to SC from [17].

IFX maintenance dose	Switching to 120 mg eow	Switching to 240 mg eow	IFX levels do not increase after 8 weeks
5mg/kg/8weeks	✓		Escalate to 240 mg eow
10mg/kg/8weeks	✓		
10mg/kg/6weeks	✓		
10mg/kg/4weeks		✓	

Table 1. Guidance for switching from IV maintenance Infliximab to SC form based on the Remiswitch study. 17 eow: every other week; IFX: Infliximab.

IL-12/IL-23 inhibitor (Anti IL12/23)
- Ustekinumab, an anti-p40 subunit agent, inhibits IL-12 and IL-23 and is effective for both induction and maintenance therapy in moderate to severe CD [11].
- In head-to-head trial (SEAVUE), both ustekinumab and adalimumab have been shown to be equally effective in bio-

logic-naive moderate-to-sever CD patients [18].
- Adding immunomodulators to ustekinumab does not provide additional benefit and can compromise the favorable safety profile of the drug [19].

IL23 inhibitors (Anti IL23)
- Risankizumab, guselkumab and mirikizumab, anti-p19 agents that selectively inhibit IL-23, are approved for moderate to severe CD [20-22].
- In a head-to-head trial (SEQUENCE), risankizumab was noninferior to ustekinumab for clinical remission and superior for endoscopic remission in moderate-to-sever CD patients with prior anti-TNF exposure [20].
- In the GALAXI trial, guselkumab outperformed ustekinumab in clinical and endoscopic remission in bio-naïve and bio-exposed moderate-to-severe CD [21].
- In the VIVID trial, mirikizumab was non-inferior to ustekinumab for clinical remission but did not show superiority in endoscopic response in moderate-to-severe CD [22].

Anti-integrin therapy
- Vedolizumab, an anti-integrin agent that inhibits α4β7 integrin, is effective for both induction and maintenance of remission in CD [11].
- Vedolizumab is available in IV form for induction and in both IV and SC forms for maintenance therapy [11].

Janus kinase (JAK) inhibitors
- Upadacitinib, a JAK-1 selective oral inhibitor, is the only JAK inhibitor recommended for induction and maintenance in CD [11].
- It functions with relatively higher selectivity for JAK-1 inhibition [11].
- JAK inhibitors should be used with caution in patients with a history of or at risk for venous thromboembolism (VTE), ma-

jor adverse cardiovascular events (MACE), and malignancy. Additionally, inactivated herpes zoster vaccine (Shingrix®) should be administered prior to starting therapy [23].

Therapeutic positioning and sequencing in moderate to severe Crohn's disease

Early initiation of highly effective therapy is crucial in moderate to severe Crohn's disease. The choice of therapy depends on factors such as disease phenotype, the presence or absence of extraintestinal manifestations (EIMs), prior treatment exposure, and comorbidities. The following figure showing a proposed potential therapeutic positioning and sequencing of medications.

	Anti TNF*	Anti IL12/23	Anti IL23	Anti-integrin	Jak Inhibitor
Bio-naïve and inflammatory phenotype					
Fistulizing or perianal disease	**				
Anti-TNF failure					***
Anti-IL12/23 failure					
Safety concerns****					

Preferred as first line Preferred second line No efficacy or insufficient data

Table 2. A proposed approach for the positioning and sequencing of therapy in Crohn's disease. Note: This is primarily based on the authors' opinions, supported by available evidence and clinical experience, and treatment decisions should be made on a case-by-case basis

* Anti-TNF therapy is most effective when combined with immunomodulators.

** Infliximab combination therapy with an IMM is the preferred choice.

preferred with fistulizing disease. * Patients over 65, frail, or with severe comorbidities.

Therapeutic Options for Ulcerative Colitis

- Management of UC depends on disease severity, extent of

colonic involvement, and the presence of complications [24].
- Acute severe ulcerative colitis (ASUC) is considered an emergency and should be managed promptly in an inpatient setting in collaboration with colorectal surgery. Management of ASUC is detailed in in latter chapter.
- Management of pouchitis is discussed latter chapter .
- A proposed treatment positioning and sequencing for UC is outlined in (Table 3). Approved therapies for IBD patients, including their efficacy in different scenarios, are detailed in (Table 4).

5-Aminosalicylates (5-ASA)

-For mild to moderate UC, 5-ASA (in oral or topical form) is effective for both induction and maintenance therapy [24].
- A starting dose of at least 2 g/day is recommended for mild disease, while up to 4.8 g/day may be used for moderate disease, with no efficacy difference between divided and once-daily 5-ASA dosing. Better adherence is achieved with once daily dosing and is recommended [24].
-Topical 5-ASA alone is effective for induction and maintenance in mild to moderate distal UC. For proctosigmoiditis and beyond, combined oral and topical 5-ASA is preferred over monotherapy for induction [25].
-5-ASA can may be stopped when treatment escalation to advanced therapy is needed, offering no added benefit [26].
- 5-ASA is very safe, but creatinine should be checked biannually to monitor for potential interstitial nephritis [27].

Corticosteroids

- Topical steroids can be used for induction of remission in patients with active distal UC, although some studies suggest the superiority of topical 5-ASA [28].
- Colonic-release corticosteroid (Budesonide MMX®) is effective for inducing remission in mild to moderate UC [24].
- Systemic steroids (oral for outpatient and IV for inpatient)

are used to induce remission in patients with moderate to severe UC [24].
-Steroids, in any form, should not be used for maintenance therapy [11].

Immunomodulators
-Thiopurine monotherapy is not used for induction but may be effective for maintaining remission in UC. Its use should balance the risk of side effects with the availability of safer therapies [24].
-Thiopurines are best used in combination with anti-TNF agents (specifically infliximab) in UC [29].
- Unlike in CD, methotrexate is ineffective for induction or maintenance in UC. Its use is limited to combination with anti-TNF agents to reduce immunogenicity or as concomitant therapy for coexisting immune-mediated diseases [24].
- Immunomodulators, when used in combination with anti-TNF therapy, can be withdrawn after achieving long-term remission, with caution for patients with prior anti-TNF immunogenicity [11].

TNFα antagonists
- Infliximab, adalimumab, and golimumab are effective for both induction and maintenance of remission in moderate to severe UC [24].
- Infliximab is approved for use as rescue therapy in acute severe ulcerative colitis (ASUC), as is cyclosporine [30].
- Anti-TNF agents have shown effectiveness in treating most extraintestinal manifestations, such as peripheral and axial arthropathy and pyoderma gangrenosum [15].
- Secondary loss of response to anti-TNF therapy is common in UC. Patients with low drug levels after induction, high inflammatory burden, low albumin levels, and lack of immunomodulator use are at higher risk of immunogenicity [31].
- Both IV and SC forms of infliximab are effective for main-

tenance therapy following IV induction in UC. Transitioning from IV to SC during maintenance is also safe (see 'Anti-TNF in Treatment of Crohn's Disease' and Figure 3) [17].

IL-12/IL-23 inhibitor (Anti IL12/23)

- Ustekinumab, an anti-p40 subunit agent, inhibits IL-12 and IL-23 and is effective for both induction and maintenance therapy in moderate to severe UC [24].
- Adding immunomodulators to ustekinumab does not provide significant additional benefit [19].

IL23 inhibitors (Anti IL23)

Risankizumab, mirikizumab, and guselkumab, anti-p19 agents that selectively inhibit IL-23, are approved for moderate to severe UC [32-34].

Anti-integrin therapy

- Vedolizumab, an anti-integrin agent targeting α4β7 integrin, is effective for both induction and maintenance of remission in UC, available in both IV and SC forms.35
- Vedolizumab demonstrated superiority over adalimumab in a head-to-head trial and is preferred for use over adalimumab (VARSITY) [36].

Janus kinase (JAK) inhibitors

- Tofacitinib (non-selective JAKi), upadacitinib (high selectivity for JAK1 inhibition), and filgotinib are approved for moderate to severe UC [37-39].
- JAK inhibitors should be used with caution in patients with a history of or at risk for venous thromboembolism (VTE), major adverse cardiovascular events (MACE), and malignancy. Additionally, inactivated herpes zoster vaccine (Shingrix®) should be administered prior to starting therapy [23].
- Multiple studies have shown that tofacitinib and upadacitinib are effective in patients with ASUC, particularly in cases

of prior infliximab exposure, although they are not formally approved for this indication [40,41].

Sphingosine-1-phosphate (S1P) receptor modulators

- S1P receptor modulators, ozanimod and etrasimod, are approved for moderate-to-severe UC [26].
- Ozanimod selectively binds to S1P receptors 1 and 5, whereas etrasimod targets S1P receptors 1, 4, and 5 [26].
- Proper evaluation is required before initiating S1P receptor modulators in patients with heart block, arrhythmia, or macular edema; baseline electrocardiogram (ECG) and ophthalmologic assessments are recommended [42].

Therapeutic positioning and sequencing in UC

Choosing therapy for ulcerative colitis depends on disease severity, extent of colonic involvement, presence of EIMs, prior treatment exposure, and comorbidities. The following figure outlines a proposed therapeutic positioning and sequencing of available therapies.

	5-ASA*	Anti TNF**	Anti IL12/23	Anti IL23	Anti-integrin	Jak Inhibitor	S1PR Modulator
Mild to moderate disease							
Moderate to severe disease							
ASUC		***				****	
Anti-TNF failure							
Anti-IL12/23 failure							
Safety concerns*****							

Preferred as first line | Preferred second line | No efficacy or insufficient data

Table 3. A proposed approach for the positioning and sequencing of therapy in ulcerative colitis. Note: This is primarily based on the authors' opinions, supported by available evidence and clinical experience, and treatment decisions should be made on a case-by-case basis

* Oral and topical forms. ** Adalimumab has low efficacy in UC and is not preferred.

*** Infliximab is the only anti-TNF agent used in ASUC . **** Can be used if prior exposure to infliximab
***** Patients over 65, frail, or with severe comorbidities.

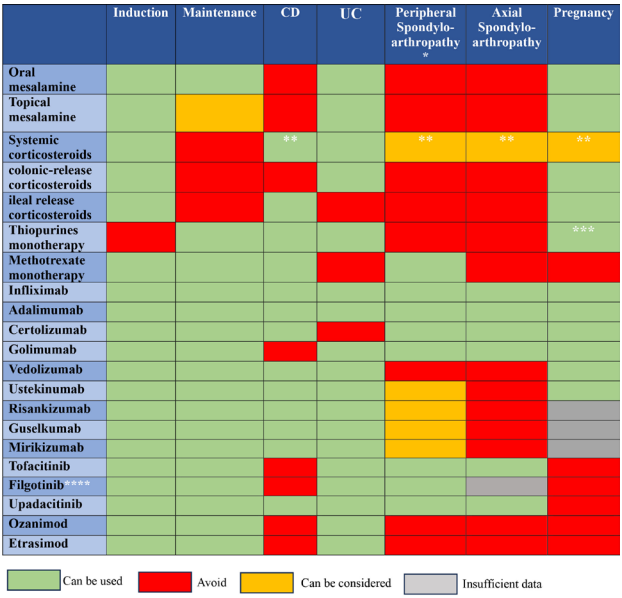
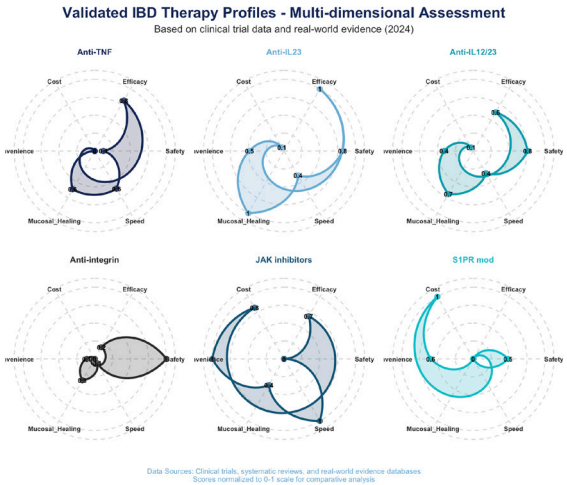


Table 4. Medical therapy in the management of IBD . This figure serves as guidance and does not replace clinical decision-making.
* Peripheral arthropathy may respond to any medication that effectively controls luminal disease.
**Systemic corticosteroids should be used only when no alternatives are available or as a bridge to starting effective maintenance therapy.
***Thiopurines can be continued in pregnancy but not started

as monotherapy or for induction.
**** Approved by the EMA but not by the FDA.



Interpretation Guide:

- Efficacy: Clinical effectiveness in maintaining remission
- Safety: Favorable side effect profile
- Speed: Rapidity of onset of action
- Convenience: Administration route and frequency
- Cost: Relative treatment expense (lower = more expensive)

Each therapy class is rated on a normalized scale from 0 to 1 across these five dimensions, with higher values indicating better performance in each category.

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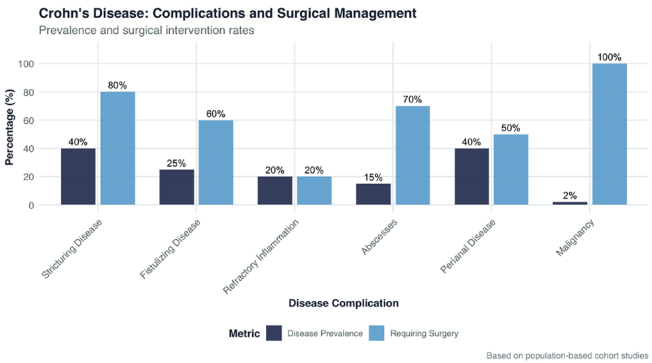
Ahmed Al Zubaidi

Introduction

Surgery remains a cornerstone in the management of inflammatory bowel disease (IBD), with distinct roles in ulcerative colitis (UC) and Crohn's disease (CD). Approximately 30% of UC patients and 70% of CD patients require surgery during their lifetime [1,2]. Surgery should not be seen as a last resort but as an integral part of IBD management. The interplay between medical and surgical therapies highlights the need for a coordinated approach, where biologics and surgical interventions complement each other. Modern surgical advancements, including minimally invasive techniques and perioperative biologic optimization, have improved outcomes and reduced complications [3,4].

Crohn's Disease: Surgical Indications

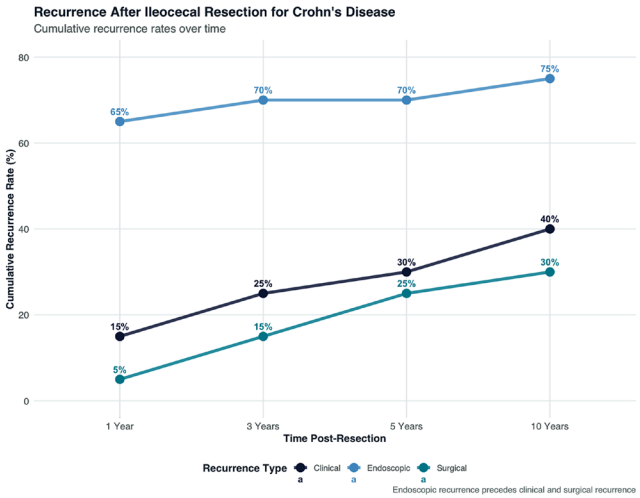
Surgery for CD is not curative and focuses on managing complications, symptom relief, and bowel preservation.
Despite advancements in medical therapy, approximately two-thirds of CD patients still require surgery during their disease course [5,6].



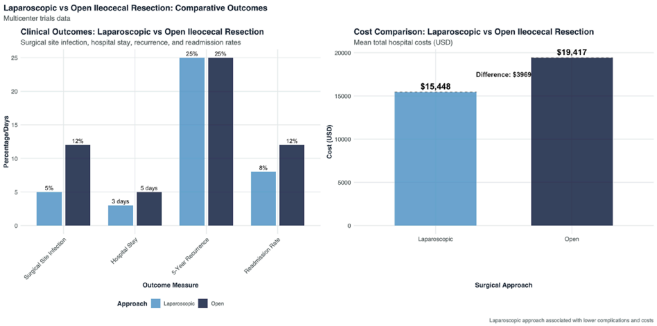
Surgical Procedures for Crohn's Disease

i. Laparoscopic/Open Ileocecal Resection:
It is the most common surgery for CD; it is indicated for localized terminal ileal disease that is not medically responsive. It must be limited to patients with localized disease who have had relatively few previous resections to prevent the development of short bowel syndrome from combined bowel loss.

Ileocecal Resection: Recurrence Patterns



Laparoscopic vs Open Ileocecal Resection



ii. Segmental Colonic Resection:

Indicated in localized colonic disease that fails to respond to medical management [7].

iii. Strictureplasty [8].

Stricturoplasty Techniques and Outcomes

Strictureplasty Techniques in Crohn's Disease: Comparative Outcomes

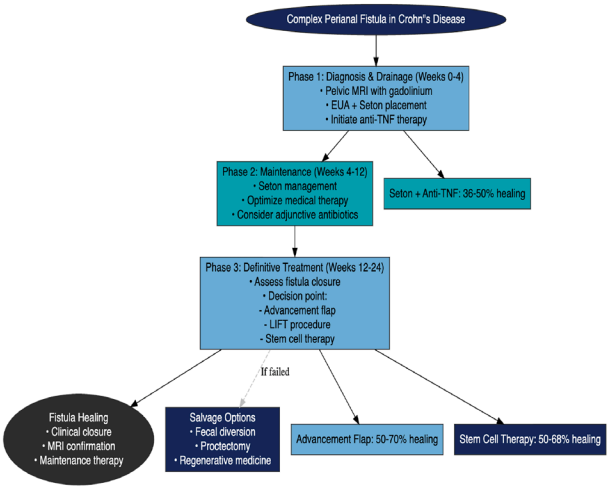
Technique	Stricture Length	Configuration	Success Rate	Leak Rate	5-Year Reoperation Rate
Heineke-Mikulicz	<10cm	Longitudinal closure	92%	2%	25%
Finney	10-20cm	Side-to-side	90%	3%	28%
Michelassi II	>20cm	Isoperistaltic loop	88%	4%	30%

Note:

Data from multicenter series of strictureplasty outcomes

Perianal Crohn's Disease Management [9-12].

Multimodal Treatment Algorithm



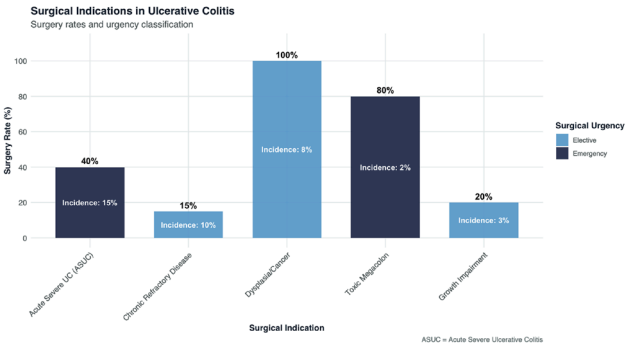
Regenerative Medicine for Perianal Fistulas [13-15].

Parameter	Advancement Flap*	Darvadstrocel (Alofisel®)**	MFAT***
Healing Rate	58%	50%	68%
Continence Issues	22%	3%	5%
Cost (USD)	$12,000	$75,000	$28,000
Durability (3 years)	45%	75%	62%

*A segment of normal rectal mucosa or full-thickness flap is mobilized to cover the internal opening of the fistula.
**Darvadstrocel (Alofisel®): An allogeneic mesenchymal stem cell (MSC) treatment
***MFAT: Micro-Fragmented Adipose Tissue

Ulcerative Colitis: Surgical Indications

Unlike CD, UC is cured by colectomy, making surgery a definitive therapeutic option rather than a failure of medical care. Approximately 20–30% of UC patients will require surgery during their lifetime despite advances in biologics and small-molecule therapies [16,17].



Surgical Procedures for Ulcerative Colitis

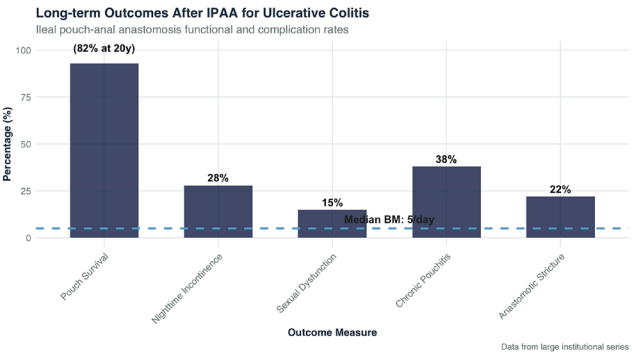
i. Subtotal Colectomy with Ileostomy:
indicated mostly in patients with Acute severe UC (ASUC) or toxic megacolon who are not responding to 72 hours maximal medical therapy, or uncontrolled hemorrhage. The procedure is potentially life-saving in the setting of an emergency with a mortality rate of less than 5% in high-volume centers. Pa-

tients can eventually ideally undergo completion proctectomy with an ileal pouch-anal anastomosis (IPAA) for curative treatment [18,19].

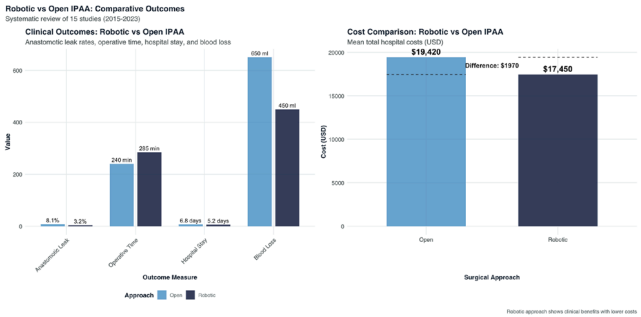
ii. Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis (IPAA)

it is considered as the elective procedure of choice for medically managed UC - typically younger patients desiring to avoid a permanent stoma and maintain fecal continence who has with colorectal adenocarcinoma or high-grade dysplasia, chronic refractory UC (failed ≥3 drug classes), steroid dependence (>10mg prednisone for >6 months) or growth retardation in pediatric UC [20-23].

Ileal Pouch-Anal Anastomosis (IPAA) Outcomes

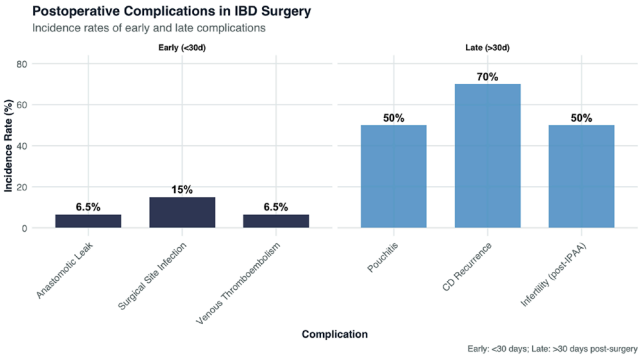


Robotic vs Open/Laparoscopic IPAA: Comparative Outcomes

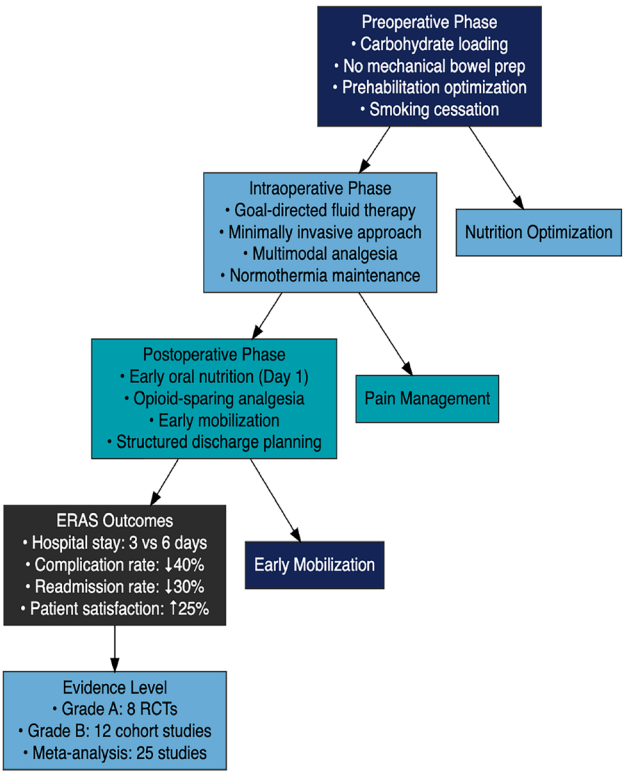


Surgical Complications

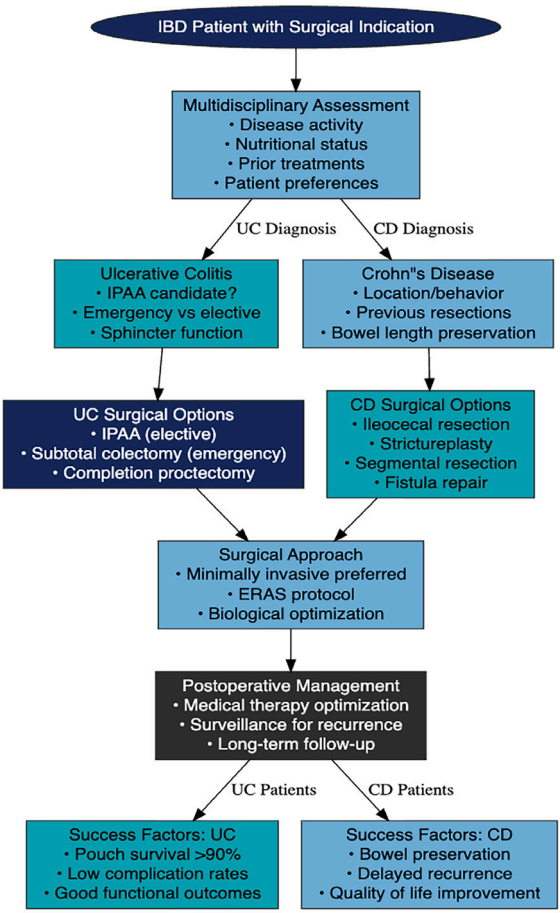
Early and Late Postoperative Complications



Enhanced Recovery After Surgery (ERAS) Protocol



Decision Support Framework
Surgical Decision Algorithm for IBD



Summary and Key Recommendations

Core Principles of IBD Surgery

1. **Multidisciplinary Approach:** Involve gastroenterologists, surgeons, nutritionists, and stoma therapists from diagnosis through postoperative care
2. **Timing Optimization:** Elective surgery preferred over emergency intervention when possible
3. **Organ Preservation:** Minimize bowel resection in CD; consider strictureplasty for multiple strictures
4. **Minimally Invasive Techniques:** Laparoscopic/robotic approaches reduce complications and enhance recovery
5. **Enhanced Recovery Protocols:** Implement ERAS pathways to improve outcomes and reduce length of stay
6. Biological Optimization: Coordinate biologic therapy timing with surgical planning if feasible, but should not delay necessary surgery
7. **Patient-Centered Decisions:** Consider patient preferences, lifestyle, and quality of life goals
8. **Long-term Surveillance:** Regular follow-up for recurrence monitoring and complication management
9. **Regenerative Options:** Consider stem cell therapies for complex perianal fistulas
10. **Quality Metrics Tracking:** Monitor outcomes including complications, recurrence, and patient satisfaction

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Mansour Altuwaijri

Introduction

Crohn's disease (CD) leads to significant morbidity, work loss, and health-care expenditure[1, 2]. Around 10-15% of individuals with ulcerative colitis (UC) undergo colectomy because of medically refractory disease or neoplasia [3]. Despite advances in biologic therapy, nearly half of CD patients still undergo intestinal resection within 10 years [4]. Although surgery induces remission, relapse is common in CD, necessitating proactive postoperative strategies, in majority of high risk patients, to balance benefit against drug toxicity and cost and reduce recurrence [5,6].

Crohn's Disease

Patterns and Frequency of Recurrence

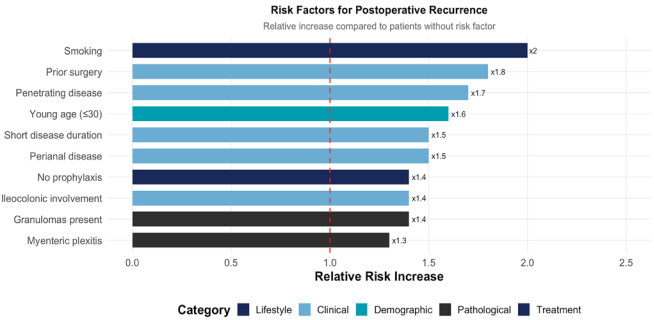
Recurrence follows a histologic, endoscopic, clinical sequence. Microscopic inflammation can be detected within 8 days of resection [7]. By 6-12 months, 70-90 % manifest endoscopic lesions [8, 9]; clinical relapse occurs in 20-37 % at 1 year and up to 86 % by 3 years [10]. A meta-analysis reported re-resection rates of 24 % at 5 years and 35 % at 10 years [11]. Late relapse (> 1 year) remains a concern even after initial endoscopic remission [12].

Risk Factors for Postoperative Recurrence

Several factors are associated with increased risk of postoperative recurrence of CD, including:

- **Smoking** - doubles both clinical and surgical relapse risk [13]
- **Short pre-operative disease duration,** proximal or diffuse ileocolonic involvement [14]
- **Penetrating behavior** [14]

- **Prior intestinal surgery** [6]
- **Absence of prophylactic treatment** [6]
- **Perianal location** [6]
- **Granulomas in resection specimen** [6]
- **Myenteric plexitis** [6]
- **Age ≤ 30 years** [15]
- **Surgical technique:** Side-to-side stapled anastomosis is associated with less recurrences compared to end-to-end sutured anastomosis [16]; ileorectal anastomosis has higher relapse than end ileostomy [17].



Monitoring

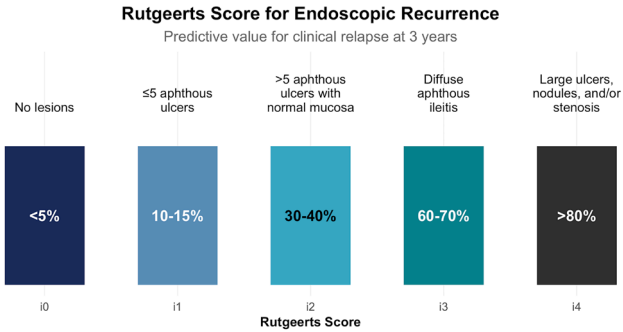
Guidelines recommend colonoscopy at 6-12 months for all patients [12]. Original Rutgeert's scoring predicts outcome; i0-i1 lesions translate into < 5 % clinical relapse over 3 years, whereas i3-i4 lesions predict rapid progression [9]. Based on Modified Rutgeerts Score and Endoscopic, table 1, where i2 score is divided into i2a and i2b. i2a: Lesion confined to the ileocolonic anastomosis, including anastomotic stenosis, and i2b: >5 aphthous lesions in the neoterminal ileum with normal mucosa between the lesions, or skip areas of larger lesions. Initiation of treatment is recommended when there

is evidence of inflammation on colonoscopy (Rutgeert's i2b or above) [18].

The POCER trial demonstrated that therapy escalation for score ≥ i2 reduced 18-month endoscopic relapse (49 % vs 67 %) [19]. Biomarkers (fecal calprotectin, CRP) checked every 4-6 months help prioritize colonoscopy. Fecal calprotectin level >100 µg/g correlate with endoscopic recurrence (sensitivity of 89%) [20].

Table 1: Modified Rutgeert's Score [18]

Modified Rutgeert's score	Endoscopic findings
i0	No lesions
i1	≤5 aphthous lesions in the neoterminal ileum
i2a	Lesion confined to the ileocolonic anastomosis, including anastomotic stenosis
i2b	>5 aphthous lesions in the neoterminal ileum with normal mucosa between the lesions, or skip areas of larger lesions
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation of the neoterminal ileum with larger ulcers, nodules, and/or narrowing



Medical Prophylaxis

• **Lower-risk patients:** Older age at the time of surgery (greater than 50 years), milder disease course, first intestinal resection involving a short segment of fibrostenotic disease (approximately 10-20 cm), long-standing disease duration (more than 10 years), nonsmoker, nonpenetrating disease, may be observed and monitored closely including clinical, radiological, and biochemical evaluation regularly; and colonoscopy at 6-12 months [18].

• **Higher-risk patients** (with one risk factor for recurrence) including, active tobacco smoking after surgery (particularly among women and heavy smokers, which is consistently linked with higher recurrence rates), penetrating disease pattern, characterized by fistulas, abscesses, or intestinal perforation, indicating more aggressive disease behavior, history of two or more previous intestinal surgeries, suggesting chronic or refractory disease, need for surgery despite prior use of immunomodulators or biologic therapy, reflecting a resistant or severe disease phenotype, should begin prophylactic treatment such as anti-TNF therapy ± thiopurine post-op-

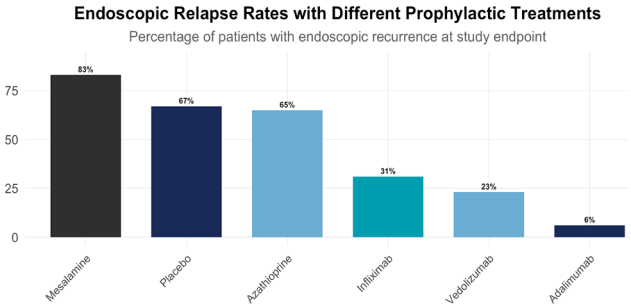
eratively [6, 18].
• A 3-month metronidazole [20 mg/kg/day] course reduces early recurrence but is limited by neuropathy [21].

Anti-Tumor Necrosis Factor (TNF) Agents

A pooled analysis of six trials showed anti-TNF prophylaxis reduces clinical and endoscopic relapses to one-quarter of controls [22]. The PREVENT trial cut endoscopic recurrence to 31 % vs 60 % with infliximab [22]. Adalimumab achieved 6 % endoscopic relapse at 2 years vs 65 % for azathioprine and 83 % for mesalamine [23].

Other Biologics and Immunomodulators

Vedolizumab reduced severe endoscopic relapse to 23 % vs 62 % at 26 weeks in the REPREVIO study[24]. Azathioprine monotherapy, although not widely used, modestly reduces clinical relapse (RR 0.79) but is less effective than biologic therapy [25].



Postoperative Care

Smoking cessation, vaccination, bone-density screening, and dietetic support are integral to long-term outcomes [13, 26].

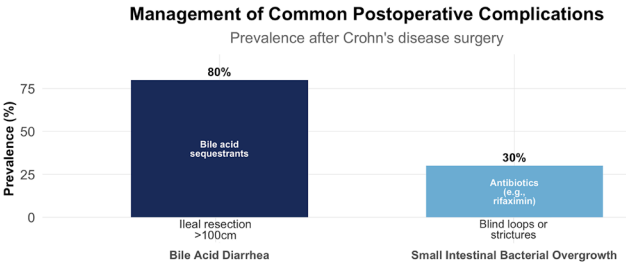
Management of non-inflammatory surgery-related symptoms

Bile acid diarrhea

Bile acid diarrhea is considered a possible cause of diarrhea in patients with CD after surgery without luminal inflammation, that can reach up to 80%. Risk is increased postoperatively with ileal resections of more than 100 cm [27]. Bile acid sequestrant therapy is recommended to treat this condition [20].

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth can occur in up to 30% of patients. It can present with variable symptoms including diarrhea, bloating, nausea, or vomiting. It presents commonly with blind loops or strictures. Empirical antibiotic treatment is recommended using oral antibiotics e.g. rifaximin [20].



Ulcerative Colitis

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is currently regarded as the standard surgical approach for patients with ulcerative colitis who exhibit refractory disease despite optimal medical therapy [28]. Pouch

disorders can be categorized into inflammatory, functional, neoplastic, and structural, as demonstrated in (Table 2) [3].

Table 2: Pouch Disorders [3]

Pouch Disorders Categories	Type
	• Acute pouchitis • Chronic antibiotic-dependent pouchitis • Chronic antibiotic-refractory pouchitis
Inflammatory	• Crohn's-like disease of the pouch • Cuffitis
Functional	• Pelvic dyssynergia • Fecal incontinence • Irritable pouch syndrome
Structural	• Pouch prolapse • Anastomotic leakage • Pouch-related fistula • Pouch volvulus • Pouch strictures • Afferent limb syndrome • Long rectal cuff syndrome
Neoplasia	• Afferent limb neoplasia • Pouch body neoplasia • Cuff neoplasia

Pouchoscopy with biopsy is recommended to help diagnose and distinguish the different causes of pouch inflammation in symptomatic patients. The endoscopic report should describe key anatomic landmarks, including the prepouch ileum, pouch inlet, pouch body, anastomosis, and anal cuff.

Biopsies should be obtained from these specific areas to evaluate for possible pouchitis, Crohn's-like inflammation of the pouch, cuffitis, ischemic injury, or CMV infection. The Pouchitis Disease Activity Index (PDAI) can be used to assess disease activity and monitoring.

Table 3: Pouch Surveillance Recommendations [28].

Risk Group	Recommended Interval
High-Risk - prior colitis-associated neoplasia before colectomy.	Every 1 year
Moderate-Risk - patients with PSC, chronic pouchitis, Crohn's-like disease of the pouch, chronic cuffitis, or a family history of colorectal cancer.	Every 1–3 years
Average-Risk – average risk for dysplasia.	Every 3 years

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Chapter 11: Management of Inpatient IBD

Fahad Alsohaibani

Introduction

Inpatient management of Inflammatory Bowel Disease (IBD) represents a critical phase of care for patients admitted with acute severe disease, complications, or failure of outpatient therapy. It requires prompt assessment of disease activity and severity, exclusion of infectious triggers, initiation or escalation of anti-inflammatory and immunosuppressive treatment, vigilant monitoring for complications, and coordinated multidisciplinary decision-making to optimize outcomes and prevent surgery and readmission. In large cohort studies about 23% of IBD patients are hospitalized at some point during their disease course. Despite declining hospitalization rates due to advances in outpatient biologic and small-molecule therapies, inpatient IBD care remains challenging, with substantial variation in practice, delayed surgical intervention, and high readmission rates [1].

Indications for Hospitalization

Hospitalization is recommended for expedited multidisciplinary evaluation and initiation of treatment for the following IBD patients with [2]:

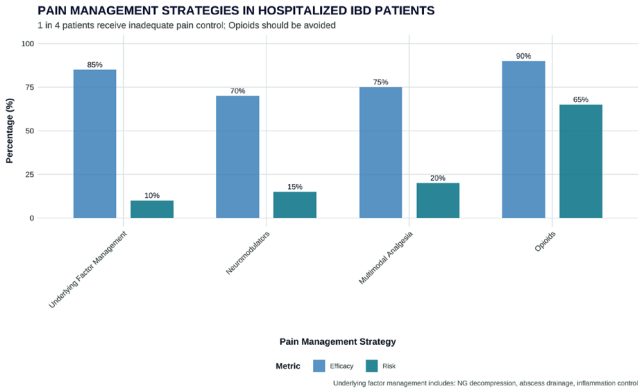
- Severe disease refractory to outpatient therapy.
- Suspected IBD-related complications (e.g. bowel obstruction, perforation, or intra-abdominal abscess).
- Acute severe ulcerative colitis (ASUC).
- Dehydration or electrolyte imbalance.
- Severe malnutrition.
- Anemia requiring transfusions,
- Significant nutritional compromise.

Initial Inpatient Evaluation and Supportive Care

All hospitalized patients with IBD should undergo a structured initial evaluation including an IBD-focused history, physical examination, laboratory testing (CBC, CRP, albumin, electrolytes), fasting lipid profile before cyclosporine or JAK inhibitors, and investigations for anticipated immunosuppressive therapy, such as screening for latent tuberculosis and hepatitis B. Supportive care is a cornerstone of management and includes intravenous hydration, electrolyte repletion, treatment of anemia, and early nutritional assessment using validated screening tools.

All hospitalized patients with IBD should be screened for malnutrition using validated screening tools (e.g. Subjective Global Assessment or Malnutrition Universal Screening Tool) and refer to a dietitian for a complete evaluation. Patients should also be screened for vitamin deficiencies, in particular vitamin B12 and vitamin D, and iron deficiencies. Intravenous iron is preferred over oral iron in patients with active inflammation, moderate to severe anemia, or intolerance to oral therapy [3,4]. (***Nutrition and Anemia are discussed in detail in Chapter 18,19***)

Pain management should focus on treating underlying cause s (nasogastric decompression in case of bowel obstruction, drainage of abscess, and effective treatment of underlying inflammation). Neuromodulators, including tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, and tetracyclic antidepressant such as mirtazapine have all demonstrated tolerability and efficacy in treating chronic gastrointestinal pain, in contrast to opioids that carry a potential risk of adverse effects, including narcotic bowel syndrome and addiction. NSAIDs should be used cautiously because of their potential to exacerbate intestinal inflammation [5-8].



Evaluation for Infections and Complications

Infectious etiologies frequently contribute to symptom exacerbation in hospitalized patients with IBD. All patients presenting with diarrhea should undergo stool testing for Clostridium difficile. Cytomegalovirus (CMV) infection should be considered in patients with steroid-refractory disease, particularly in UC [1,9].

Cross-sectional imaging is guided by clinical presentation 9abdominal radiography or CT) is indicated for suspected toxic megacolon, while CT or MR Enterography is recommended for suspected obstruction or intra-abdominal abscess in Crohn's disease. Intestinal ultrasound is increasingly recognized as a useful diagnostic and monitoring modality in selected centers [10].

Assessment of Disease Activity

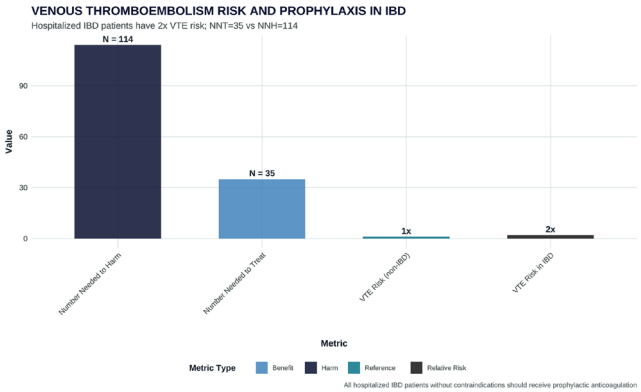
Objective assessment of disease activity is essential and should include inflammatory biomarkers such as fecal cal-

protectin, CRP, leukocyte count, platelet count, and serum albumin. CRP is particularly valuable due to its short half-life and predictive value for colectomy in ASUC. The CRP-to-albumin ratio has also been shown to correlate with disease severity [11].

Early endoscopic evaluation, preferably flexible sigmoidoscopy within 48 hours in hospitalized UC patients, is recommended to assess disease severity, obtain biopsies, and exclude CMV infection. Complete colonoscopy may be indicated in select cases, such as for patients with isolated Crohn's ileitis or when suspicion for right-sided pathology is high. Early endoscopy has been associated with reduced length of stay and lower hospital costs [1,12,13].

Venous Thromboembolism Prophylaxis

Hospitalized patients with IBD have an approximately twofold increased risk of venous thromboembolism (VTE) compared with non-IBD patients. Inflammation and corticosteroid exposure contribute to a hypercoagulable state. Pharmacologic thromboprophylaxis with low-molecular-weight heparin or fondaparinux is recommended for all hospitalized patients without contraindications. Evidence suggests a favorable benefit–risk ratio despite a small increase in bleeding risk [1,14-16]. The decision of whether to continue prophylactic anticoagulation after hospital discharge should be considered on an individual basis for patients who are at high risk of developing VTE, such as recent surgery (within 3 months), active malignancy, immobilization, or thrombophilia, although there is insufficient evidence to support this practice.

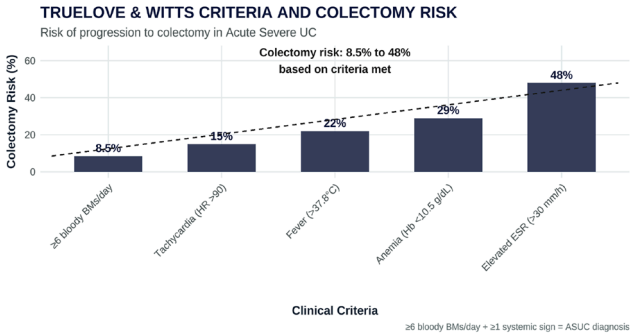


Management of Acute Severe Ulcerative Colitis (ASUC)

ASUC has classically been defined using the Truelove and Witts criteria, which predict colectomy risk. However, C-reactive protein (CRP) has emerged as a more responsive biomarker and is now widely used to guide admission and early treatment decisions. The first-line therapy for hospitalized patients with severe UC is intravenous steroids. The optimal dosing of intravenous corticosteroids is methylprednisolone 40–60 mg daily in 2-3 divided doses (40 mg daily can be considered in patients at high risk of steroid-related adverse events). Initiation of corticosteroids should not be delayed while awaiting the results of pathogen testing (e.g. C difficile or CMV) and should not be discontinued if these pathogens are detected and treatment for the pathogens initiated concurrently [1,17,18].

In ASUC, corticosteroid treatment response can be assessed by means of evaluating changes in stool frequency and CRP on day 3 of corticosteroid treatment to predict future colectomy as 85% of patients with UC receiving 3 days of corticos-

teroids who continue to have either 8 or more bowel movements daily or 3–8 bowel movements daily with a CRP >4.5 mg/ dL will require colectomy (Oxford criteria), therefore, continuing intravenous steroid beyond 7 days in the setting of nonresponse provides no benefit and increase the risk of complications and mortality [1,19].



The choice of rescue and salvage therapy (infliximab using standard, intensified or accelerated regimen, cyclosporine, and JAK inhibitors) depend on prior treatment responses, inflammatory burden, evidence of protein-losing colopathy (when small molecules like cyclosporine or JAK inhibitor may be preferred), availability of drugs and experience of the treating physician.

Approximately 10% of hospitalized patients with UC ultimately require colectomy, therefore, early surgical consultation is recommended for patients with ASUC, steroid-refractory disease, or complications such as toxic megacolon. Multidisciplinary management and care at high-volume centers improve outcomes and patient satisfaction. Enhanced recovery after surgery (ERAS) protocols are encouraged to reduce postoperative complications [20]. (ASUC is covered in more detail in Chapter 13).

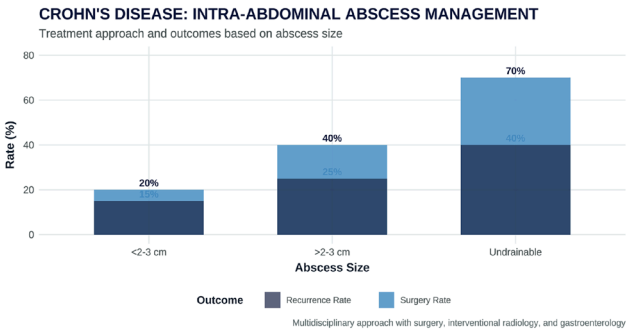
Crohn's Disease–Specific Complications

Intestinal Obstruction

Patients with Crohn's disease and suspected intestinal obstruction should initially be managed with bowel rest, nasogastric decompression, and intravenous fluids. Intravenous corticosteroids may be considered when active inflammation is present, although evidence for short-term benefit is mixed. Fibrotic strictures, perforation, or refractory obstruction generally require surgical intervention [21-23].

Intra-abdominal Abscess

The initial medical treatment requires broad-spectrum intravenous antibiotics with gastrointestinal flora coverage. Patients who present with peritonitis or uncontrolled sepsis require urgent surgical management. If an intra-abdominal abscess is >2–3 cm, percutaneous drainage should be pursued along with antibiotic treatment and nutritional optimization. After adequate infection control, initiation or resumption of steroid-sparing immune therapy is acceptable to control underlying inflammation [24,25].

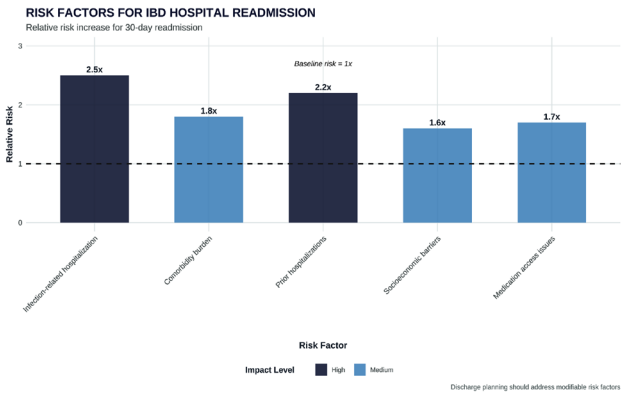


Perianal Disease

Active perianal Crohn's disease requires a combined medical–surgical approach, including antibiotics, anti-TNF therapy, examination under anesthesia with incision and drainage of abscesses followed by seton placement are important immediate steps. Contrast-enhanced cross-sectional CT/MRI may further delineate complex fistula tracts or perianal abscesses. This strategy provides the highest likelihood of fistula control and symptom improvement [1,26]. (This topic is covered in more detail in Chapter 12).

Discharge Planning and Transitions of Care

Discharge should occur only after stabilization of symptoms and establishment of a clear outpatient transition plan. This includes corticosteroid tapering instructions, coordination of biologic or infusion therapy, patient education, and early identification of social or logistical barriers to care. Hospital discharge does not necessarily require normalization of inflammatory biomarkers or imaging findings. Effective discharge planning is critical to reduce readmission rates and improving long-term outcomes [1].



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Chapter 12: Management of Relapsing, Stricturing and Penetrating Crohn's Disease

Mohammad Malik

Introduction

Crohn's disease (CD) is characterized by recurrent inflammatory flares after remission, risking progressive bowel damage. The STRIDE-II guidelines emphasize corticosteroid-free clinical remission (Crohn's Disease Activity Index [CDAI] <150), endoscopic healing (Simple Endoscopic Score for CD [SES-CD] <3), and normalized quality of life as treatment goals. Early intervention may prevent complications like strictures or fistulae, requiring personalized therapy based on disease severity, location, and prior treatment response [1,2].

Management of Relapsing Crohn's Disease

Anti-TNF Therapies

Tumor necrosis factor (TNF) inhibitors remain the first-line for moderate-to-severe relapsing CD. The ACCENT I trial demonstrated that patients with CD who respond to an initial dose of infliximab and received maintenance doses (5-10 mg/kg every 8 weeks) achieved 39-45% remission (CDAI <150) at week 30 compared to 21% with placebo [3]. The CHARM trial reported maintenance subcutaneous adalimumab (40 mg every other week) and (40 mg every week) achieved remission in 36% and 41% respectively at week 56 compared to 12% with placebo [4]. Immunogenicity is common with TNF antagonists, but may is be mitigated with combination therapy. The SONIC trial found infliximab plus azathioprine achieved 56.8% steroid-free remission at week 26 versus 44.4% with infliximab alone [5].

IL-12/23 and IL-23

Ustekinumab, an interleukin (IL)-12/23 inhibitor, is effective for bio-naïve and anti-TNF failures. The UNITI trials showed

maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53% and 49%, respectively, were in remission at week 44, as compared with 36% of those receiving placebo (P=0.005 and P=0.04, respectively) [6].

Risankizumab, a selective IL-23 p19 inhibitor, is at least as effective as Ustekinumab for inducing clinical remission in anti-TNF-experienced CD patients. Clinical Remission at week 24 was achieved in 59% Risankizumab group versus 40% in Ustekinumab and endoscopic remission at week 48 was seen in 32% in Risankizumab group versus 16% in Ustekinumab [7]. Guselkumab is another selective IL-23 p19 inhibitor that significantly achieved clinical remission compared to placebo in moderately to severely active CD (60% in 100 mg SC every 8 weeks, 66% in 200 mg SC every 4 weeks and placebo17%; P < .001) and endoscopic response (44%, 51%,6.8% respectively, P < .001) [8].

Integrin Inhibitors

Vedolizumab, an α4β7 integrin inhibitor, targets gut-specific leukocyte trafficking. Among patients who had a response to induction therapy, 39% and 36% of those assigned to vedolizumab every 8 weeks and every 4 weeks, respectively, were in clinical remission at week 52, as compared with 22% assigned to placebo (P<0.001) [9]. Vedolizumab 108 mg SC is also an effective and safe maintenance therapy in patients with CD who responded to two infusions of vedolizumab intravenous induction therapy [10].

Small Molecule Therapies

Upadacitinib, a JAK1-selective inhibitor, was approved in for moderate-to-severe CD. The U-EXCEL trial demonstrated 50% remission at week 12 (45 mg daily) versus 29% with placebo, with 46% endoscopic response versus 13%. Its oral administration enhances compliance, but safety concerns

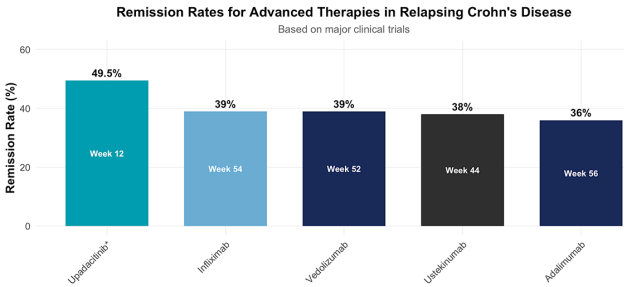
(e.g., herpes zoster risk, 2.11 per 100 patient-years) necessitate careful patient selection, avoiding for those ≥65 years or with cardiovascular risks [11].

Treat-to-Target and Monitoring

The CALM trial established that tight control, adjusting therapy based on biomarkers (C-reactive protein (CRP), fecal calprotectin), reduced major adverse outcomes (e.g., hospitalization, surgery) by 40% compared to symptom-driven care [12].

Adjunctive and emerging strategies

Thiopurines (azathioprine, 6-mercaptopurine) maintain remission in mild-to-moderate disease and reduce biologic immunogenicity [13]. Fecal microbiota transplantation is under investigation but lacks robust evidence for relapsing CD [14].



Management of Stricturing Crohn's Disease

Pathophysiology and Diagnostic Challenges

Stricturing CD, affecting up to 50% of patients within 10 years, results from chronic inflammation driving fibrosis, causing bowel narrowing and obstruction. Differentiating

inflammatory versus fibrotic strictures is critical, as fibrotic lesions resist medical therapy. Most strictures include both inflammatory and fibrosis-related components. Magnetic Resonance Enterography (MRE) is the gold standard for radiographic identification of strictures, with delayed gadolinium enhancement indicating probable fibrosis, while ultrasound elastography is emerging for non-invasive assessment. The Lémann Index is a comprehensive scoring system for CD that quantifies cumulative bowel damage by assessing strictures, penetrating lesions, and surgical history across the digestive tract using imaging and patient history, aiming to track disease progression and treatment effectiveness over time, with scores ranging from 0 to 140 [15].

Medical Therapy for Inflammatory Strictures

Starting anti-TNF therapy early in symptomatic stricturing CD (within18 months after the diagnosis) was effective in 87% and 73% of patients after 6 and 12 months, respectively, and continued to be effective in 26% after a median follow-up of 40 months. Importantly, a high proportion of patients were able to avoid surgery with this therapy in the long term. Younger age, lower albumin levels, strictures located in the descending colon, concomitant aminosalicylates use or presence of lymphadenopathy were associated with lower effectiveness [16]. A systematic review showed anti-TNF therapy appeared effective in stricturing CD, with 50% of patients avoiding surgery after 4 years of follow up [17].

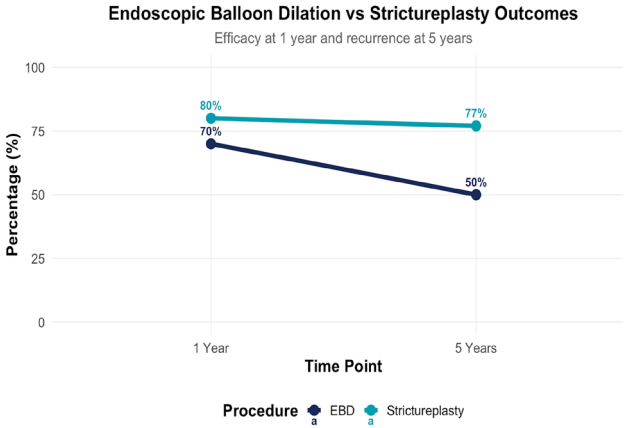
Ustekinumab and vedolizumab can help control inflammation, which may indirectly benefit strictures, especially when there is an inflammatory component, however, there is no large randomized controlled trial showing ustekinumab or vedolizumab resolve strictures in CD [18]. Upadacitinib's role is under investigation, with preliminary U-EXCEL data

suggesting endoscopic improvement in inflammatory strictures, but no specific fibrosis data exist [11].

Endoscopic Interventions

Endoscopic balloon dilation (EBD) is preferred for short (<5 cm), non-angulated, or anastomotic strictures with 90% technical success and 70% clinical efficacy at 1 year, though 50% required repeat dilation within 2 years. The use of biologics and endoscopic disease remission at the time of EBD were protective factors against the need for surgery, however, if no previous surgery or use of steroids at the time of EBD was associated with the need for surgery during follow-up. Perforation risk is seen in 3-5% [19-20].

Endoscopic stenting using self-expanding metal stents (partial and fully covered) or biodegradable stents in CD-related strictures is a safe technique that can be performed with clinical success and technical success was 61% and 93% respectively. Spontaneous stent migration was reported in 44% and pooled incidence of overall adverse events, proximal stent migration, perforation, and abdominal pain were 15.7%, 6.4%, 2.7%, and 17.9%, respectively [21].



Surgical Intervention

Intestinal stricture caused by CD can be managed by different surgical approaches. Such as Heineke-Mikulicz or Finney technique. Strictureplasty preserves bowel length, ideal for short, non-penetrating jejunal or ileal strictures with 23% recurrence rate at 5 years and 6% major complications (e.g., anastomotic leak). Resection is reserved for long, refractory, or fistulizing strictures, with laparoscopic approaches reducing complications by 30% versus open surgery. The decision between strictureplasty and resection depends on disease extent, prior resections, and short bowel syndrome risk [22,23].

Emerging Anti-fibrotic Therapies

No approved anti-fibrotic therapies exist, but Pirfenidone, a novel anti-fibrotic agent, is approved for the treatment of idiopathic pulmonary fibrosis. It has important therapeutic potential to be used as an anti-inflammatory and anti-fibrotic agent in CD. However, further studies are needed to evaluate its effects not only on mesenchymal stromal cells, such as fibroblasts and myofibroblasts but also on immune and epithelial cells [24-25].

Monitoring and Prevention

Regular imaging such as MRE, CTE, and IUS tracks stricture progression and together with fecal calprotectin and CRP to guide therapy escalation. Smoking, delayed biologics, and NSAID use, increase stricture risk, necessitating lifestyle modification and early aggressive therapy. The treat-to-target approach, applies to minimize inflammatory burden and development of stricturing disease [12,15].

Management of Fistulizing Crohn's Disease

Clinical Burden and Classification

Approximately, 25-30% of CD patients will develop fistulae at some point in their disease course either (perianal fistulas in15-25%) or internal fistulas (entero-enteric, entero-vesical, entero-cutaneous in 5-10%) causing significant morbidity and impaired quality of life. Effective management requires a multidisciplinary approach, integrating medical, surgical, and emerging therapies, guided by pelvic MRI or rectal endoscopic ultrasound for accurate fistula mapping [26].

Anti-TNF Therapies

Infliximab remains the cornerstone for perianal fistulae, with the ACCENT II trial showing absence of draining fistulas in 36% at week 54 versus 19% with placebo (P=0.009) [27]. Adalimumab can induce perianal fistula closure within 12 weeks of treatment, with rates that were sustained for more than 5 years [28]. In real-world study reporting Adalimumab achieved 41% closure at 1 year [29]. Combination of Anti-TNF with azathioprine enhances efficacy and reducing relapse by as per SONIC trial [5]. Therapeutic drug monitoring may be used to optimize outcomes, with infliximab trough levels >5 µg/mL correlating with fistula healing.

IL-12/23 and IL-23 Inhibitors

Ustekinumab is effective for perianal fistulizing CD. Fistula response and even remission were seen in some patients with fistulizing CD, especially perianal fistulas, although the evidence is mixed and mostly from real-world and retrospective data rather than large RCTs. In systematic review and real-world data — found that about 50% of patients with active perianal fistulas had a clinical fistula response at 12 months after starting ustekinumab [30]. Guselkumab and Risankizumab are biologics that targets interleukin-23, both

being actively studied for fistulizing CD, show promise and real-world data is emerging, but as of now not yet approved as standard therapy for this specific indication.

JAK Inhibitors

Upadacitinib shows promise for fistulizing disease. In a post-hoc analysis of the U-EXCEED and U-EXCEL trials reported 48% complete fistula resolution at week 12 versus 9.1% with placebo [11]. Filgotinib achieved significant fistula response at week 24 in perianal CD (47% in the Filgotinib 200 mg group, 29% in the Filgotinib 100 mg group, and 25% in the placebo group) [31]. Safety concerns, including herpes zoster (relative risk 4.8) require careful monitoring, especially in patients ≥65 years or with comorbidities. JAK inhibitors' oral administration and rapid onset are advantageous, but data on long-term fistula closure are pending [32].

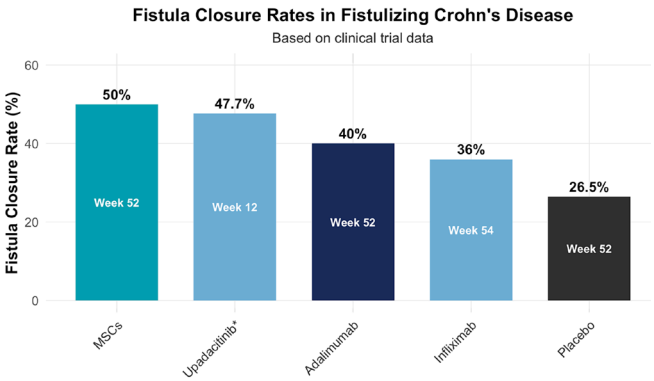
Surgical interventions (Details in Chapter 9)

All fistulas are potential sources of pelvic sepsis, ensuring adequate drainage is fundamental. Seton drains maintain patency of the fistula tracts and hence limit recurrent abscess formation in complex fistulae, with 80% maintaining drainage at 1 year [33]. The optimal timing for seton removal is not well established. In the ACCENT 2 study, all setons were removed by week 2 and the overall new abscess rate was 15%. Several studies reported maintaining seton in situ for longer period. It is recommended to keep the seton in place until at least the induction of the anti-TNF treatment period has been completed [32].

Fistulotomy is reserved for simple fistulae due to sphincter damage risk. The ligation of the intersphincteric fistula tract (LIFT) procedure achieves 60% healing at 1 year in CD, offering a sphincter-sparing option [33]. Surgical decisions are guided by fistula complexity and response to medical therapy, with MRI assessing track resolution.

Mesenchymal Stem Cells (MSCs)

Darvadstrocel is the **first allogeneic stem cell therapy approved** for fistulizing CD in the European Union for who have had an **inadequate response to conventional or biologic therapies**. The approval was based primarily on results from the **ADMIRE-CD phase 3 randomized, double-blind, placebo-controlled trial**. Clinical remission at week 104, was reported in (56%) patients in the Darvadstrocel group and (40%) patients in the control group.

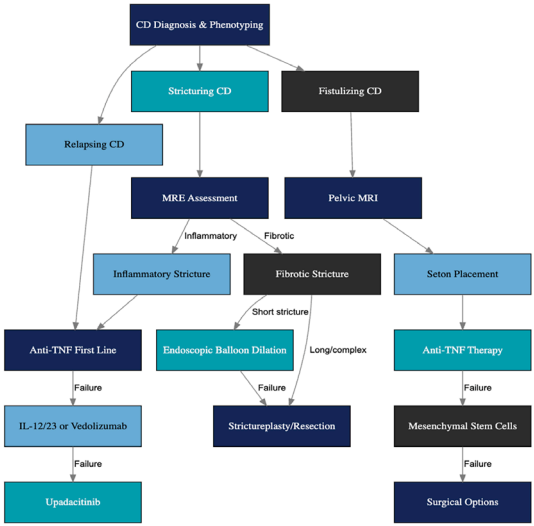


Treatment Comparison Table

Comparative Efficacy of Advanced Therapies Across Crohn's Disease Phenotypes

Therapy Class	Drug	Relapsing CD Remission	Stricturing CD Efficacy	Fistulizing CD Closure	Key Trial
Anti-TNF	Infliximab	39% (Week 54)	Early use reduces strictures	36% closure	ACCENT I
Anti-TNF	Adalimumab	36% (Week 56)	Limited data	40% closure	CHARM
IL-12/23 Inhibitor	Ustekinumab	38% (Week 44)	25% remission	24% response	UNITI
Integrin Inhibitor	Vedolizumab	39% (Week 52)	20% remission	Limited data	GEMINI 2
JAK Inhibitor	Upadacitinib	49.5% (Week 12)	Under investigation	47.7% closure	U-EXCEL
Stem Cell	Darvadstrocel (MSCs)	N/A	N/A	50% closure	ADMIRE-CD

Management Algorithm



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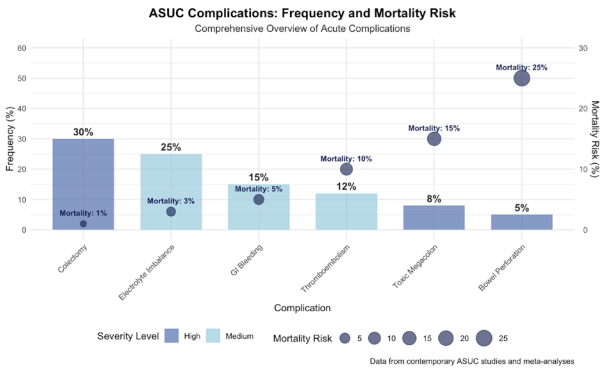
Raed Alsulaiman

Introduction

Acute Severe Ulcerative Colitis (ASUC) is a medical emergency affecting up to 25% of patients with UC with 1% mortality rate [1]. Diagnosis is based on the modified Truelove and Witts criteria [2] which includes:

• ≥6 bloody stools per day plus at least one of the following features of systemic toxicity:
    • Temperature ≥ 37.8°C
    • Heart rate > 90 bpm
    • Hemoglobin < 10.5 g/dL
    • ESR > 30 mm/hr
• Complications include: Toxic megacolon, bowel perforation, gastrointestinal bleeding, thromboembolism, electrolyte imbalance, and colectomy.
• Red Flags: Watch for toxic megacolon, severe anemia, systemic toxicity, or signs of perforation.
• Always evaluate for triggering factors like NSAID use or enteric infections (especially concomitant C. difficile or Cytomegalovirus infection).

Complications and Risk Factors



Initial Management (Day 0–3)

• ***Admission:***
o Admit urgently with gastroenterology and colorectal surgical consultation.

• ***Initial Investigations:***
o Blood tests: CBC, CRP, ESR, albumin, renal function.
o Rule out infections: Stool studies including cultures.
o C. difficile: PCR for toxin A and B.
o Abdominal X-ray to assess for colonic dilation (>6 cm suggests toxic megacolon).
o Abdominal CT if signs of peritonitis or suspected perforation. Immunosuppressive treatment and old age can mask the signs of toxicities so keep a high index of suspicion.
o Screen for biological therapy eligibility: viral serologies, latent TB, lipid and magnesium levels (should no delay treatment).

• ***Endoscopy:***
o Perform an unprepared flexible sigmoidoscopy to confirm diagnosis and exclude CMV.
o CMV: Look for inclusion bodies on biopsy (immunohistochemistry) and quantify viral load on tissue. CMV-related ASUC is associated with higher colectomy rates (up to 50% vs 15% without CMV reactivation) [3].
o Use the UC Endoscopic Index of Severity (UCEIS)—deep ulcers are linked to higher colectomy risk.

• ***Avoid:***
o Opioids and anticholinergics, as they increase risk of perforation and toxic megacolon.

• ***First-Line Therapy:***
o Supportive care: IV fluids, electrolyte correction.

o IV corticosteroids at least 0.8-1 mg/kg for a maximum duration of 7 days (e.g., Methylprednisolone 60 mg/day or Hydrocortisone 100 mg every 8 hours) [4].
o There is some limited evidence that JAK inhibition with tofacitinib or upadacitinib may be considered as an alternative for induction in patient who experience ASUC with prior TNF antagonist failure (based on emerging evidence) [5].
o DVT prophylaxis: Enoxaparin 40 mg SC daily (all patients should be strongly considered for pharmacologic prophylaxis even with disease-related rectal bleeding).
o Assess need for Pneumocystis jirovecii pneumonia (PJP) prophylaxis in high -risk ASUC patients
o Nutrition: Encourage regular diet if tolerated.
o Use parenteral nutrition only if severe symptoms prevent oral intake.
o Stop enteral feeds if toxic megacolon is suspected.
o Exclusive Enteral Nutrition (EEN) has shown potential benefits: improved response to steroids, shorter hospital stays, and better inflammatory marker profiles [6].
o Blood Transfusion if:
Hb <9 g/dL with hemodynamic instability or cardiac disease, or Hb <7 g/dL in stable patients without cardiac disease.
o No evidence supporting the systematic use of antibiotics in ASUC unless specific context as high grade fever or suspected complications.

• ***Monitoring:***
o Track stool frequency, CRP, albumin, vitals, hydration status.
o Monitor respond to IV steroid on day 3 by applying one of the following validated score:
1-The Oxford criteria [7] help assess the need for escalation:
• More than 8 stools/day, or
• 3–8 stools/day with CRP > 45 mg/L
• Associated with an 85% risk of colectomy.

2-The Lindgren score [7], calculated as:
• (CRP [mg/L] × 0.14) + number of bowel movements
• A score >8 also predicts a high risk of colectomy.
o Steroid responsive patient start combination therapy with infliximab and azathioprine with quick steroid weaning 60 mg po od for 2 weeks then decrease by 5-10 mg per week till dose of 20 mg then 2.5 mg per weak till discontinuation [8].
o Steroid-refractory: 30% of ASUC do not respond to initial intravenous corticosteroid therapy [9].

Rescue Therapy (Day 3–5)

If there is no response to IV corticosteroids after 3 days based on the above criteria, initiate rescue therapy [10].

Options include:
1. ***Infliximab:*** 5 mg/kg IV at weeks 0, 2, and 6 [11].
o Three recent meta-analyses did not show that an intensive dosing regimen was superior to standard dosing infliximab with primary endpoints being short and long-term colectomy rates in ASUC [12]. The American Gastroenterology Association (AGA) review in 2020 stated that 'in hospitalized patients with ASUC being treated with infliximab, the benefit of routine administration of accelerated dosing regimens over standard dosing regimens is uncertain [11].
2. ***Cyclosporine:*** Rapid onset of action with median time to clinical response of 4 days if no response after 7 days discontinuation is recommended.[12]
3. Dose: (2 mg/kg/day IV) monitor levels (targeting trough levels between 150 and 250 ng/mL), BP, renal function.
o Switch to oral formula after 7 days if respond (decrease stool frequency by 50% and no hematochezia) dose 4 mg/kg BID divided dose and withdrawn after 3 months.
o Continue after cyclosporine with maintenance therapy (ustekinumab, vedolizumab).

o Colectomy-free survival ~68% at 1 year, clinical remission ~79% at 1 year [13].
o Common side effects: 30-50% hypokalemia, hypocalcemia, tremor, paresthesia, hirsutism.
o Major side effects: up to 17% hypertension, nephrotoxicity, opportunistic infection, neurotoxicity.

• ***Cyclosporine VS Infliximab;***
* Short term outcomes are comparable between infliximab and cyclosporin as salvage therapies (CONSTRUCT trial) [14]. * Efficacy: ~70% short-term colectomy-free survival for both [14].
* Long-term efficacy and safety results remain similar for both treatments.
* Cyclosporin-treated patients had a higher relapse rate than those treated with infliximab.
* In case of previous failure to anti-TNF and especially to infliximab, cyclosporin is an alternative to surgery and a bridge to another biological maintenance therapy.
* The selection of second-line therapies can be influenced by clinicians' habits, patients' features, safety, or efficacy concerns.
* Infliximab is generally preferred due to ease of administration and familiarity.
* Cyclosporine may be considered in patients previously exposed to anti-TNF agents.

• ***Contraindications to rescue therapy:***
o Sepsis, active infections, or signs of perforation.

Surgical Management

Despite the use of salvage therapy like calcineurin inhibitors or infliximab, colectomy rates remain close to 30% for patients presenting with ASUC.

• ***Indications:***
o Perforation, toxic megacolon, unresponsive to salvage therapy.
• ***Procedure:***
o Subtotal colectomy with end ileostomy and rectal stump.
o Consider IPAA or IRA in appropriate patients.
• Avoid delaying surgery beyond day 7 in non-responders to medical therapy,prolonged delays to surgery increase the risk of mortality.

Discharge Planning

• ***Criteria for discharge:***
o Resolution of symptoms.
o Normalizing inflammatory markers.
o Stable oral intake and bowel function.

• ***Before discharge:***
o Initiate maintenance therapy.
o Ensure appropriate follow-up within 2 weeks.
o Provide steroid tapering schedule and DVT prophylaxis if needed.
o Educate the patient about signs of relapse and when to seek help.

Maintenance Therapy

After induction of remission, long-term maintenance therapy is critical to prevent relapse [13].
• ***Options include:***
o Thiopurines (azathioprine or 6-mercaptopurine).
o Biologics (infliximab, vedolizumab, ustekinumab).
o Small molecules (tofacitinib, Upadacitinib, ozanimod, etrasimod).
• Therapy should be tailored based on patient response, prior medications, and risk factors.
• Steroids should not be used for maintenance due to long-term side effects.

Special Considerations

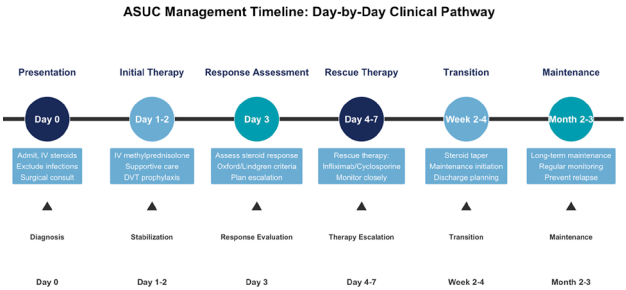
• Pregnancy:
o Most medications used in ASUC, including biologics and thiopurines, are safe in pregnancy.
o Avoid methotrexate and consider risks vs. benefits of tofacitinib. (risk of teratogenicity).

• ***Infections:***
o Reactivation of latent infections is a risk with immunosuppressive therapy.
o Ensure screening for TB, hepatitis B and C (includine testing HBV cores), HIV, and varicella.
• ***Vaccination:***
o Patients should be up to date with vaccines, especially before initiating immunosuppressants.
• ***Nursing Priorities:***
o Monitor fluid balance, skin care, emotional support.
o Educate on mobilization and DVT prevention.

Resident/Fellow Tips:

• Use predictive scores, reassess daily, escalate early.
• ***Pitfalls:***
o Delayed colectomy, prolonged steroids, infection misdiagnosis.

Management Timeline



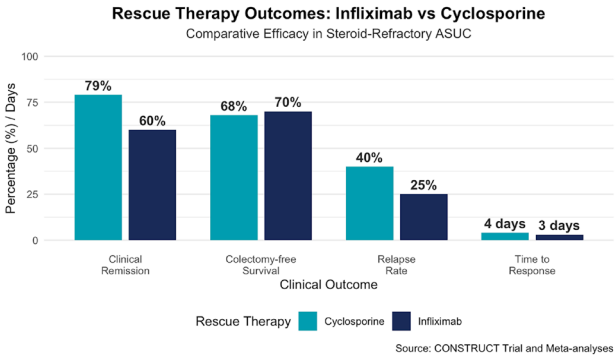
Non-Responders and Sequential Therapy

Consider switching salvage agent if first fails.
o After failure of infliximab as salvage therapy switching to cyclosporine as 3rd salvage therapy show mean colectomy-free rates of 42% [15].
o After failure of cyclosporine as salvage therapy switching to infliximab as 3rd salvage therapy show mean colectomy-free rates of 58% [15].
o ECCO guidelines discourage routine third-line therapy, recognizing that prolonged delays to surgery increase risk of mortality.
o Monitor closely for infections.

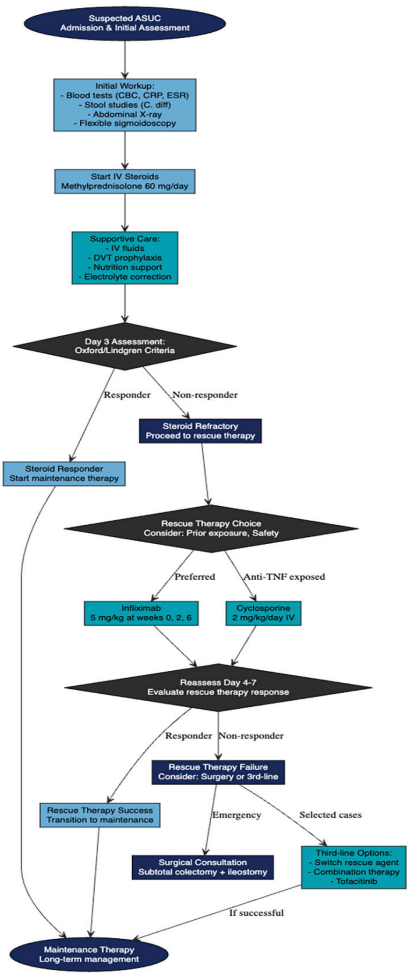
Tofacitinib: oral JAK inhibitor
o Advantage: Oral medication with rapid absorption and half-life of 3 hours.
o Clinical response in 3 days, no known immunogenicity and likely reduced risk of infection and wound healing.
o Best results with 10 mg three times daily (HR for colectomy: 0.11) [16].

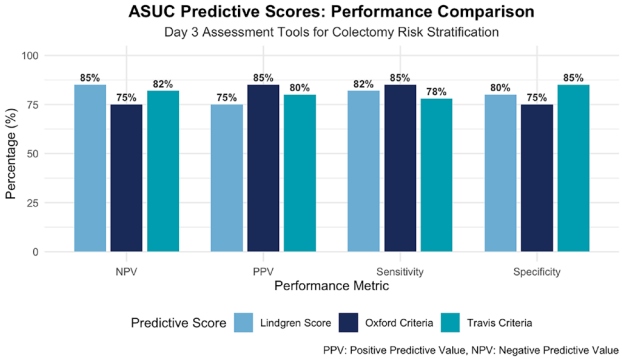
o Colectomy-free survival at 3 months: 78.9%.
o Avoid in older patients or those with cardiovascular risk.

Rescue Therapy Comparison



ASUC Management Algorithm





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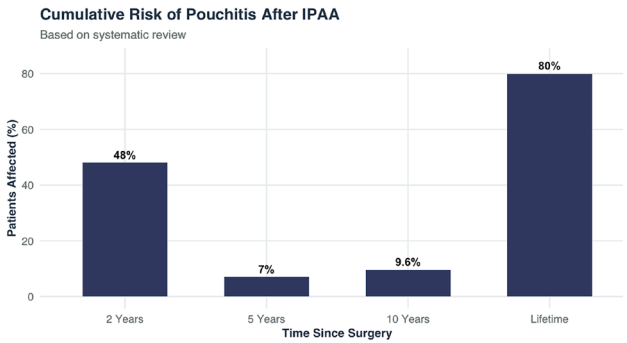
Hend Almuhaya

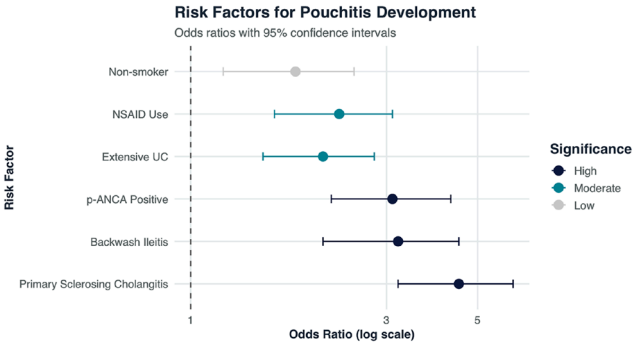
Introduction

Ileal pouch-anal anastomosis (IPAA) is the standard surgical treatment for ulcerative colitis, but pouchitis remains the most common complication after IPAA affecting 48% of patients within the first 2 years, and up to 80% at some point after surgery [1]. Pouchitis has a significant impact on patient quality of life and is associated with a high healthcare cost burden. Approximately, 15-20% of patients develop chronic pouchitis with a relapsing–remitting course and 10% of patients may go on to develop Crohn's-like disease of the pouch [1].

The surgery for a pouch almost always involves two or three steps. There are two techniques to perform the IPAA: hand-sewn IPAA with mucosectomy and stapled IPAA. On the other hand, cuffitis refers to inflammation of the remaining rectal cuff, following double-stapled IPAA without mucosectomy, results in inflammation of the residual cuff of rectal mucosa that may lead to pouch dysfunction. It often presents with symptoms that mimic pouchitis such as urgency and frequency. Rectal bleeding is more commonly associated with cuffitis than with pouchitis [2].



Risk Factors for pouchitis

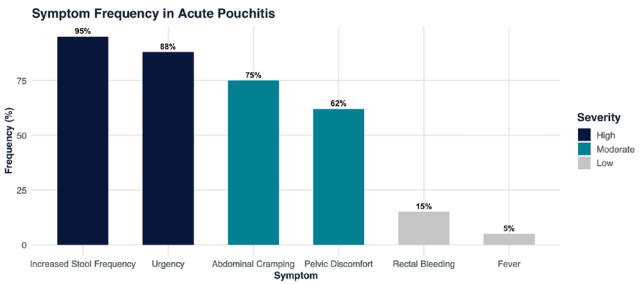


Type of Inflammatory Pouch Disorders

- Intermittent Pouchitis: Isolated and infrequent episodes of typical pouchitis symptoms that resolve with antibiotics or spontaneously, followed by extended periods of normal pouch function.
- Chronic Antibiotic-Dependent Pouchitis: Recurrent episodes of pouchitis that respond to antibiotic therapy but relapse shortly after stopping antibiotics and requires recurrent or continuous antibiotic therapy or other advanced therapies to achieve symptom control.
- Chronic Antibiotic-Refractory Pouchitis: Relapsing–remitting or continuous symptoms of pouchitis with inadequate response to typical antibiotic therapy, often needing escalation to other therapies.
- Crohn's-like Disease of the Pouch: Diagnostic criteria include presence of a perianal or other fistula that developed at least 12 months after the final stage of IPAA surgery, stricture of the pouch body or pre-pouch ileum, or presence of pre-pouch ileitis.

Clinical Presentation

The most frequent symptoms of pouchitis are increased number of liquid stools, urgency, abdominal cramping and pelvic discomfort. Fever and bleeding are rare. Clinical symptoms do not necessarily correlate with endoscopic or histologic findings [1].



Diagnosis of Pouchitis

The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities. Biomarkers such as fecal calprotectin and lactoferrin are not routinely used in clinical practice for pouch disorders. Pouchoscopy is recommended in patients with frequent recurrent pouchitis, inadequate response to antibiotics, atypical symptoms, or suspected Crohn's-like disease of the pouch. The Pouchitis Disease Activity Index (PDAI) has been developed to standardize diagnostic criteria and assess the severity of pouchitis.

Pouchitis Disease Activity Index (PDAI)

Table 1: Pouchitis Disease Activity Index (PDAI) Components

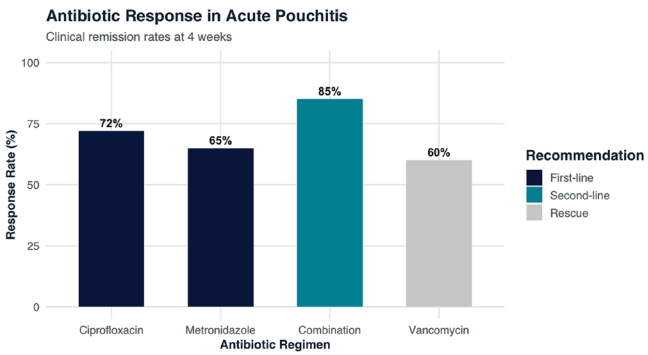
Domain	Item	Score	Cutoff
Clinical (0-6)			
Clinical Symptoms	Stool frequency	0-2	
	Rectal bleeding	0-2	
	Fecal urgency	0-2	
Endoscopic (0-4)			
Endoscopic Findings	Edema	0-1	
	Granularity	0-1	
	Friability	0-1	
	Loss of vascular pattern	0-1	
Histologic (0-6)			
Histologic Findings	Polymorph infiltration	0-3	
	Ulceration per low-power field	0-3	
	Total Score	0-18	≥7 confirms pouchitis

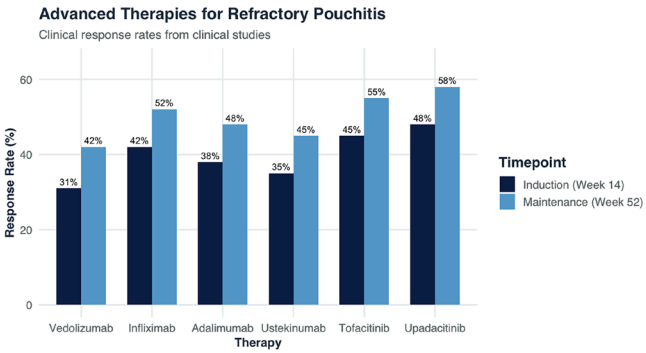
Treatment Algorithms

The primary treatment goal in pouchitis is resolution of symptoms. Endoscopic and/or histologic healing is not considered a critical treatment target due to limited supporting data. Therefore, asymptomatic patients with endoscopic evidence of pouchitis may not require treatment. In patients presenting with atypical symptoms of pouchitis, inadequate response to conventional treatment, or recurrent symptoms despite therapy, clinicians should consider alternative causes beyond classic inflammatory pouch disorders.

In patients with infrequent symptoms, using antibiotics for treatment of pouchitis such as ciprofloxacin and/or metronidazole for 2-4 week is preferred for treatment of pouchitis. In patients with recurrent episodes of pouchitis that respond to antibiotics, probiotics can be used for prevention of recurrent pouchitis.

In chronic antibiotic-dependent pouchitis, antibiotic therapy using lowest effective dose of antibiotics (e.g. ciprofloxacin 500 mg daily or 250 mg twice daily) with intermittent gap periods (such as one week per month), or cyclical antibiotics may be considered to decrease risk of antimicrobial resistance. In patients with antibiotic intolerance or when concerns about long-term antibiotic risks are present, immunosuppressive therapies including biologics and small molecules can be used before colectomy may be considered. In chronic antibiotic-refractory pouchitis and Crohn's-like disease of the pouch, immunosuppressive therapies approved for treatment of IBD can be used, however, Vedolizumab is the only biologic to have been evaluated in a randomized, double-blind, placebo-controlled trial in chronic pouchitis and received regulatory approval from the European Medicines Agency for this indication. In addition, short-term (< 12 weeks) use of ileal-release budesonide can be considered [3,4].





Clinical Management Pathways Treatment Algorithm Summary

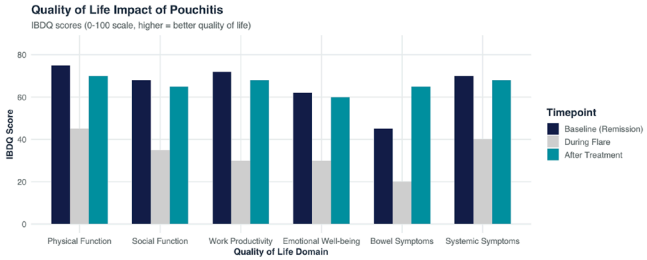
Table 2: Treatment Algorithm Based on AGA Guidelines

Clinical_Scenario	First_Line	Second_Line	Success_Rate
Acute Pouchitis (<4 weeks)	Ciprofloxacin 500mg BID × 2-4 weeks	Metronidazole 500mg TID or combination	72-85%
Recurrent Pouchitis (≥3 episodes/year)	Probiotic maintenance (VSL#3)	Continuous low-dose antibiotics	40-60%
Chronic Antibiotic-Dependent	Cyclic antibiotics (1 week/month)	Advanced therapy (consider prior effective agents)	65-75%
Chronic Antibiotic-Refractory	Advanced immunosuppressive therapy	Combination therapy or alternative agent	31-58%
Crohn's-like Disease of Pouch	Budesonide ≤8 weeks	Advanced therapy (anti-TNF, vedolizumab)	45-55%
Cuffitis	Topical 5-ASA/steroids	Oral/systemic UC therapies	70-80%

Prevention Strategies

In patients with UC who undergo IPAA, there are no recommendations in favor of, or against the use of probiotics for primary prevention of pouchitis. The use of antibiotics for the primary prevention of pouchitis is not recommended [1,5].

Quality of Life Impact



Key Clinical Takeaways

Table 3: Key Clinical Statistics

Metric	Value
Lifetime risk of pouchitis	Up to 80%
Acute pouchitis response to ciprofloxacin	72%
Chronic refractory response to vedolizumab	31% (induction)
Patients developing Crohn's-like disease	10%
Diagnostic PDAI cutoff	≥7 points
Average daily bowel movements post-IPAA	4-8

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Mishal Alshowair

Introduction

The use of biologic and small-molecule therapies has transformed the management of IBD. However, their safe and effective use requires a structured approach that begins before treatment initiation and continues throughout therapy. A comprehensive pre-biologic workup is essential to identify latent infections, vaccination gaps, and comorbid conditions that may influence drug selection or increase treatment-related risk. Understanding the pharmacologic profiles of available agents allows for individualized therapy. Equally important is recognition of potential adverse effects, ranging from mild reactions to serious infections, malignancy risk, and organ-specific toxicities. Ongoing therapeutic drug monitoring plays a pivotal role in optimizing efficacy, minimizing toxicity, and guiding timely treatment adjustments [1-6].

Table 1: Pre-Biologic and Small-molecule Therapies Workup Requirements

Test	Population	Comments	Category
Stool cultures (×3), ova & parasites, C. difficile	Patients with diarrhea	Rule out infectious causes prior to immunosuppression	Infection screening
QuantiFERON-TB Gold or TST	All patients	If positive → chest X-ray ± infectious disease consult	TB screening

Test	Population	Comments	Category
Hepatitis B panel (HBsAg, anti-HBs, anti-HBc)	All patients	HBsAg+ → hepatology consult; isolated anti-HBc → monitor/reactivation risk	Viral screening
Hepatitis C antibody	All patients	If HCV Ab+ → check HCV RNA; refer to hepatology if positive	Viral screening
HIV screening	All patients	Refer to infectious disease if positive	Viral screening
Chest X-ray	Suspected or latent TB	Required to exclude active TB	TB screening
Lipid profile	Pre-JAK inhibitor	Baseline and repeat at ~12 weeks after initiation	JAK-specific
Pregnancy test	Pre-JAK inhibitor	Confirm non-pregnant status prior to therapy	JAK-specific
Zoster vaccine (Shingrix)	Pre-JAK inhibitor	2 doses: at baseline and 2–6 months later	JAK-specific
ECG	Pre Ozanimod	To exclude heart block	Ozanimod-specific

Test	Population	Comments	Category
Eye exam	Pre-Ozanimod	For patient with history of diabetes, uveitis or eye symptoms to exclude macular edema	Ozanimod-specific

Table 2: Pharmacologic Profiles

Comprehensive IBD Medications (2025)
Chronological FDA Approval with Drug Class & Indication

	Drug Information		Clinical Use	
Medication	Class	Route	Indication	Year_Approved
Sulfasalazine	5-ASA	Oral	UC	1950
Hydrocortisone	Corticosteroid	Rectal/IV	Both	1952
Prednisone	Corticosteroid	Oral/IV	Both	1955
Prednisolone	Corticosteroid	Oral	Both	1955
Azathioprine	Thiopurine	Oral	Both	1968
Mesalamine	5-ASA	Oral/Rectal	UC	1987
Methotrexate	Antimetabolite	SC/Oral	CD	1988
Olsalazine	5-ASA	Oral	UC	1990
Mercaptopurine	Thiopurine	Oral	Both	1993
Cyclosporine	Calcineurin Inhibitor	IV	UC	1995
Tacrolimus	Calcineurin Inhibitor	IV/Oral	Both	1998
Infliximab	TNF Inhibitor	IV	Both	1998
Balsalazide	5-ASA	Oral	UC	2000
Budesonide	Corticosteroid	Oral/Rectal	Both	2001
Natalizumab	Integrin Inhibitor	IV	CD	2004
Adalimumab	TNF Inhibitor	SC	Both	2007
Certolizumab pegol	TNF Inhibitor	SC	CD	2008
Golimumab	TNF Inhibitor	SC	UC	2013
Vedolizumab	Integrin Inhibitor	IV	Both	2014
Ustekinumab	IL-12/23 Inhibitor	IV/SC	Both	2016
Beclomethasone	Corticosteroid	Oral	UC	2018
Tofacitinib	JAK Inhibitor	Oral	UC	2018
Upadacitinib	JAK Inhibitor	Oral	Both	2019
Filgotinib	JAK Inhibitor	Oral	UC	2020
Ozanimod	S1P Modulator	Oral	UC	2021
Risankizumab	IL-23 Inhibitor	IV/SC	Both	2022
Mirikizumab	IL-23 Inhibitor	IV/SC	Both	2023
Guselkumab	IL-23 Inhibitor	IV/SC	Both	2023
Etrasimod	S1P Modulator	Oral	UC	2023

Notes:
UC = Ulcerative Colitis | CD = Crohn's Disease | Both = approved for both
5-ASAs: First-line for mild-moderate UC | Corticosteroids: For acute flares only; not maintenance
Biologics & small molecules for moderate-severe IBD

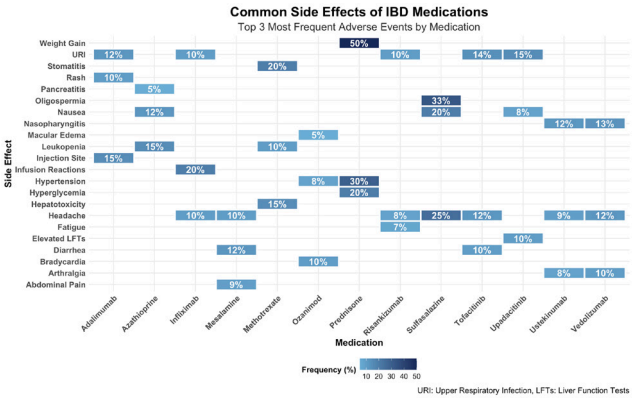
Table 3: Pharmacologic Profiles: Mechanism and Dosage

Medication	Mechanism of action	Dose
Sulfasalazine/ Mesalamine	5-ASA (5-aminosalicylic acid): Anti-inflammatory effect on colonic epithelium, blocks prostaglandin and leukotriene synthesis.	UC: Mesalamine: 2.4–4.8 g/day orally. Sulfasalazine: 2–4 g/day orally in divided doses.
Azathioprine	Purine analog → inhibits DNA/RNA synthesis → reduces T & B cell proliferation.	1.5–2.5 mg/kg/day orally
Mercaptopurine	Active metabolite of azathioprine; inhibits purine synthesis, suppresses lymphocyte proliferation.	1–1.5 mg/kg/day orally
Methotrexate	Folic acid antagonist → inhibits dihydrofolate reductase → reduces DNA synthesis, especially in activated T cells.	CD: 15–25 mg once weekly (IM or SC) UC: Not recommended

Medication	Mechanism of action	Dose
Infliximab	Anti-TNF-α monoclonal antibody → reduces inflammation via TNF blockade.	CD/UC: 5-10 mg/kg IV at weeks 0, 2, 6, then Q8 weeks CD: Same dosing, up to 10 mg/kg if loss of response or TDM directed. SC after IV induction therapy: 120 mg Q2 weeks starting at week 10 or next scheduled IV dose.
Adalimumab	Fully human anti-TNF-α monoclonal antibody	CD/UC: 160 mg SC at week 0, 80 mg at week 2, then 40 mg EOW
Vedolizumab	Anti-α4β7 integrin monoclonal antibody → gut-selective anti-inflammatory effect by inhibiting lymphocyte trafficking.	CD/UC: 300 mg IV at weeks 0, 2, 6, then Q8 weeks SC: 108 mg once Q2 weeks beginning after at least 2 IV infusions to be administered at next scheduled IV dose and then Q2 weeks thereafter.
Ustekinumab	IL-12/23 monoclonal antibody → blocks inflammatory cytokine signaling.	CD/UC ≤55 kg: IV: 260 mg as single dose >55 kg to 85 kg: IV: 390 mg as single dose >85 kg: IV: 520 mg as single dose Then 90 mg SC Q8 weeks

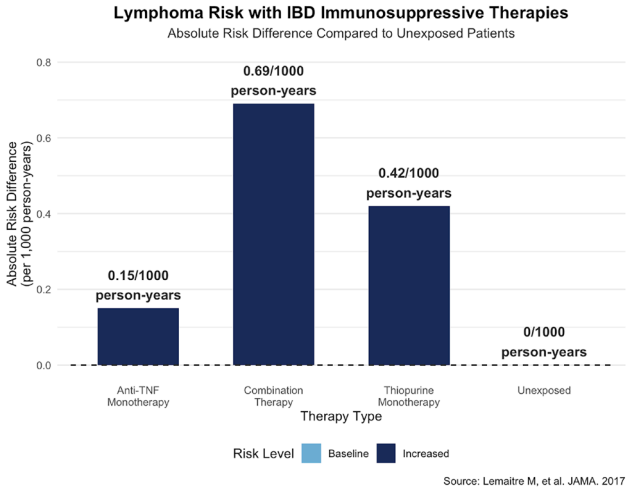
Medication	Mechanism of action	Dose
Risankizumab	IL-23 inhibitor → inhibits downstream inflammatory signaling.	CD: 600 mg IV at weeks 0, 4, 8 then maintenance 180-360 mg SC (OBI) at week 12 then Q8 weeks. UC: 1200 mg IV at weeks 0, 4, 8 then maintenance 180-360 mg SC (OBI) at week 12 then Q8 weeks.
Ozanimod	S1P receptor modulator → prevents lymphocyte egress from lymph nodes, reducing gut inflammation.	UC: Start 0.23 mg/day titrated to 0.92 mg/day
Upadacitinib	JAK1-selective inhibitor → inhibits pro-inflammatory cytokine signaling.	UC: 45 mg daily for 8 weeks, then 15–30 mg/day CD: 45 mg daily for 12 weeks; then 15–30 mg/day
Tofacitinib	Pan-JAK inhibitor (JAK1/3 > JAK2) → blocks cytokine-mediated inflammation.	UC: 10 mg BID for 8 weeks then 5–10 mg BID

Side Effects Frequency Comparison



Lymphoma Risk Comparison

While these therapies are associated with an increased relative risk of lymphoma, the absolute risk remains low. When making treatment decisions, patients and healthcare providers should carefully weigh these risks against the benefits, as the advantages of the medication often outweigh the risks, particularly the risk of lymphoma [7].



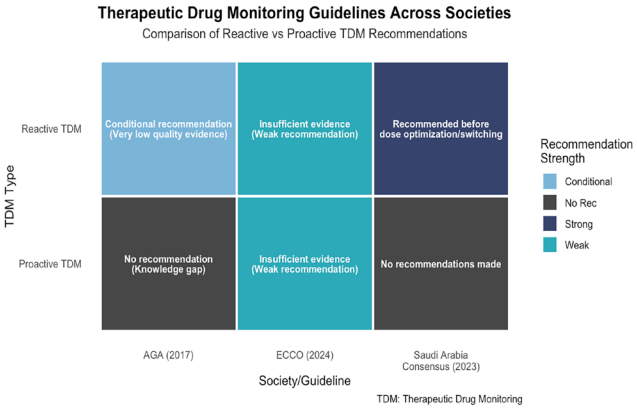
Source: Lemaitre M, et al. JAMA. 2017

Therapeutic Drug Monitoring Guidelines

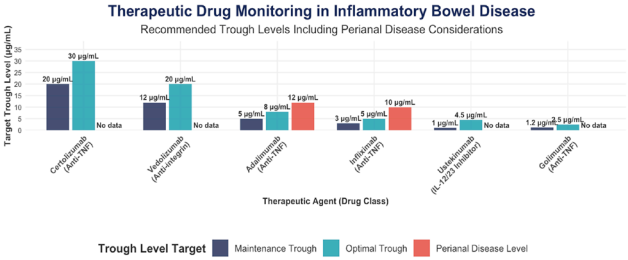
Definitions:

- Primary loss of response refers to the lack of an adequate clinical response to a biologic or other therapy during the initial induction phase of treatment.
- Secondary loss of response (sLOR): Patients who had initially responded after the induction phase, but then started to develop symptoms of disease activity, suggestive of treatment failure.
- Proactive TDM : is the measurement of drug levels and anti-drug antibodies ,regardless of clinical symptoms.
- Reactive TDM: Drug levels are checked only after a patient experiences worsening symptoms or loss of response.

Up to 30% of IBD patients fail to show an initial response after the induction period, and up to 50% showing sLOR during the maintenance phase, especially during the first year. TDM-guided therapy escalation has been shown to be up to 30% more cost-effective compared to empiric dose escalation in cases of secondary loss of response. Debate exists surrounding the use of TDM, in current practice, it is mainly used in the reactive setting and in severe complex IBD cases like fistulizing Crohn's disease. In general, two types of drug assays are available. Drug-intolerant assays detect anti-drug antibodies (ADAs) only when drug levels are low or absent. In contrast, drug-tolerant assays can detect ADAs even in the presence of therapeutic drug concentrations and appear to be more consistent [8,9].



TDM Target Levels



Evidence Citations:

- Anti-TNF agents: Papamichael K, et al. Gut 2019;68(6):964-975
- Vedolizumab: Williet N, et al. Aliment Pharmacol Ther 2017;46(9):873-882
- Ustekinumab: Adedokun OJ, et al. J Crohns Colitis 2018;12(5):556-564
- Perianal Disease: Yarur AJ, et al. Inflamm Bowel Dis 2016;22(5):1067-1071

Perianal Disease Notes:

- Anti-TNF agents require higher trough levels (≥10 µg/mL) for perianal Crohn's disease
- No specific data available for vedolizumab/ustekinumab in perianal disease
- Complex perianal fistulas may require combined medical-surgical approach

- Algorithm illustrating the approach to loss of response to biologic agents in IBD. Abbreviations: SIBO: Small Intestinal Bacterial Overgrowth; FCP: Fecal Calprotectin; ADA: Anti-Drug Antibodies; IMM: Immunomodulator
- Note : Optimal drug levels for infliximab and adalimumab are not defined and it depends on the assay used and clinical context.

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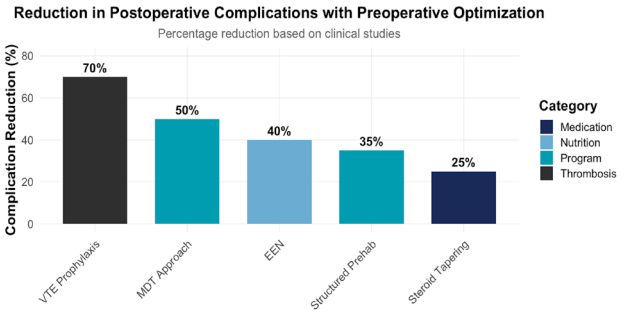
Heba Al Farhan

Introduction

Surgical intervention remains a critical component in the management of inflammatory bowel diseases, with approximately 20-30% of ulcerative colitis patients and up to 70-80% of Crohn's disease patients requiring surgery during their lifetime [1]. Preoperative optimization has demonstrated significant reductions in postoperative complications, highlighting the importance of structured multidisciplinary approaches.

Postoperative Complication Reduction with Optimization



Nutritional Assessment and Optimization

Malnutrition Screening

Malnutrition affects 50-60% of Crohn's disease patients and 20-40% of ulcerative colitis patients undergoing surgery [2]. The Malnutrition Universal Screening Tool (MUST) and serum albumin levels (<3.0 g/dL) provide validated assessment methods, with malnourished patients demonstrating 2.5-fold increased risk of postoperative infections [3].

Nutritional Interventions

Exclusive enteral nutrition (EEN) reduces postoperative infection rates by up to 40% and shortens hospital stays by 25% compared to standard oral nutrition. Parenteral nutrition reduces anastomotic leak incidence from 15% to 8% in malnourished individuals but was associated with an 8-12% increased risk of catheter-related infections [4]. Correcting deficiencies in iron, vitamin D and zinc is essential for recovery (Table 1).

Preoperative Nutritional Status in IBD Patients

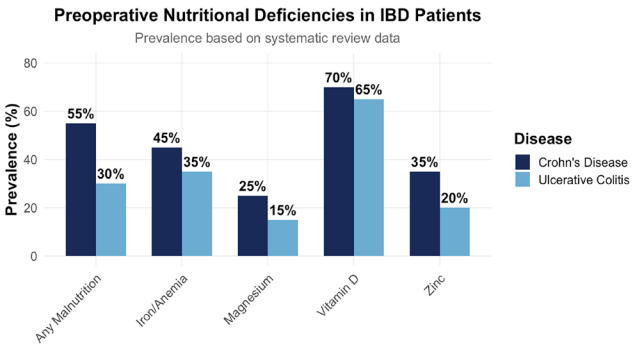


Table 1: Preoperative micronutrient supplementation

Deficiency Type	Prevalence	Cut-off Values	Impact	Treatment
Anemia	30-40% of IBD patients	- Men: Hb <13 g/dL . - Non pregnant women: Hb <12 g/dL. - Pregnant women: Hb <11 g/dL.	- Untreated anemia doubles the risk of postoperative complications, including infections and delayed wound healing. - Contributes to fatigue and poor quality of life.	- Iron Deficiency Anemia (IDA): Intravenous iron (e.g., ferric carboxymaltose) for active disease or severe deficiency. - ACD: Erythropoiesis-stimulating agents in severe cases. - Vitamin B12/Folate Deficiency: Parenteral vitamin B12 (1000 mcg IM monthly) and oral/IV folate.

Deficiency Type	Prevalence	Cut-off Values	Impact	Treatment
Vitamin D	Up to 70% of IBD patients	- Deficiency: 25(OH)D <20 ng/mL - Insufficiency: 20-30 ng	- Low bone density - Worsened inflammation - Potentially detrimental immunomodulatory effects.	- High-dose supplementation (50,000 IU weekly) until levels normalize >30 ng/mL. - Maintenance dose of 1,000-2,000 IU daily. - Regularly monitor levels.
Zinc	Common, especially in those with chronic diarrhea or	Serum zinc <70 mcg/dL	- Impaired wound healing - Increased risk of infections - Worsened diarrhea	- Mild Deficiency: Oral zinc sulfate (220 mg daily for 2-3 weeks). - Severe Deficiency: IV zinc for cases with severe malabsorption or prolonged PN.

Deficiency Type	Prevalence	Cut-off Values	Impact	Treatment
Magnesium	Seen in chronic diarrhea, ileostomies, or high-output fistulas	Varies (monitor levels closely)	Worsened diarrhea, muscle weakness, and potential cardiac arrhythmias.	- Use oral magnesium chloride or sulfate. - Severe cases may require IV magnesium sulfate.
Calcium	Common in patients on corticosteroids or with low bone density	Varies (typically assessed with serum calcium)	- Weak bones and increased risk of fractures in long term.	- 1,000-1,500 mg calcium daily along with vitamin D supplementation to improve absorption.
Selenium	Rare, seen in severe malnutrition or prolonged PN	Varies (often assessed indirectly)	- Poor antioxidant defense and immune function.	Selenium supplementation via oral or IV routes based on severity.

Pharmacological Management

1. Immunosuppressive Therapies

Balancing immunosuppression to maintain disease control while minimizing postoperative complications is a complex challenge. Studies indicate that the risk of postoperative infections in patients using biologics does not exceed 15% if the timing of the last dose aligns with the mid-treatment interval. It is recommended to administer the last dose at least four weeks before surgery to avoid adverse outcomes. Chronic steroid use (>20 mg/day of prednisone or equivalent) is strongly linked to complications, including a 20-30% increased risk of wound infections and a 15% higher chance of anastomotic leaks. Tapering corticosteroids to below 10 mg/day preoperatively has been shown to halve these risks (Table 2 and 4)[5-10].

Table 2: Management of immunosuppressive therapies in preoperative period.

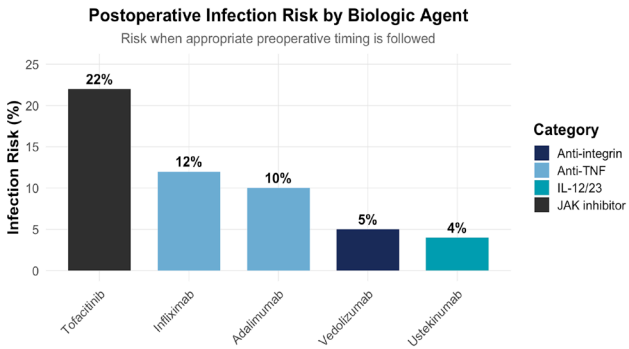
Medication	Timing of Last Dose/Preoperative Adjustments	Risk of Postoperative Complications	Recommendations for Continuation/Tapering	Special Considerations
Infliximab	4–8 weeks before surgery	Low if timed appropriately (≤15%)	Continue if last dose is within the treatment window	Plan surgery mid-dose interval; monitor closely in high-risk or malnourished patients.

Medication	Timing of Last Dose/Preoperative Adjustments	Risk of Postoperative Complications	Recommendations for Continuation/Tapering	Special Considerations
Adalimumab	2 weeks before surgery	Low if timed appropriately (≤10–15%)	Continue; adjust dose timing	Administer last dose 2 weeks pre-surgery to minimize infection risk while maintaining disease control.
Vedolizumab	4–6 weeks before surgery	Minimal (<5%)	Continue; no significant impact on wound healing	Focuses primarily on gut-specific immunity; generally safe for perioperative use.
Ustekinumab	8–12 weeks before surgery	Minimal if preoperative interval is respected (<5%)	Continue; administer last dose 8-12 weeks before	Adjust timing carefully due to long dosing interval; assess disease stability.

Medication	Timing of Last Dose/Preoperative Adjustments	Risk of Postoperative Complications	Recommendations for Continuation/Tapering	Special Considerations
IL-23 Inhibitors (Skyrizi, Tremfya)	8–12 weeks before surgery	Minimal if timed appropriately (<5%)	Continue; schedule surgery mid-dose interval	Long dosing intervals may require adjustment based on individual patient response. Monitor infection risk and ensure disease stability.
JAK Inhibitors (Tofacitinib, Upadacitinib)	7 days before surgery	Moderate to high (10–25% risk of infections, VTE risk higher with tofacitinib)	Temporarily discontinue 1 week before surgery	Increased infection risk, particularly with tofacitinib. Strong risk-benefit evaluation required; monitor for VTE in high-risk patients.

Medication	Timing of Last Dose/Preoperative Adjustments	Risk of Postoperative Complications	Recommendations for Continuation/Tapering	Special Considerations
Corticosteroids	Reduce to ≤10 mg/day prednisone equivalent; ideally discontinue before surgery	High (20–30% risk of wound infections, 15% chance of anastomotic leaks)	Taper to lowest effective dose; avoid abrupt discontinuation to prevent adrenal insufficiency	Chronic use increases infection risk; patients on prolonged corticosteroid therapy may require perioperative stress dosing.

Biologic Agent Timing and Infection Risk



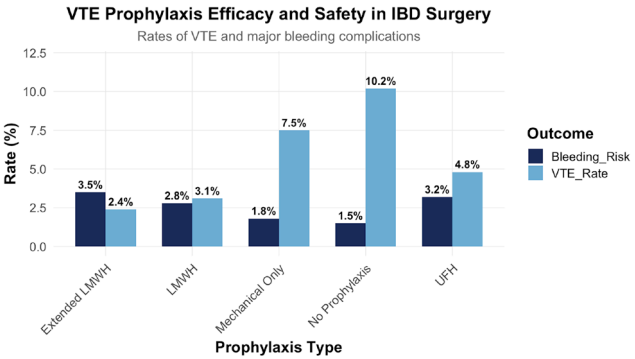
2. Venous Thromboembolism Prophylaxis
IBD patients exhibit threefold increased VTE risk compared to the general population. Extended low-molecular-weight heparin prophylaxis reduces VTE events from 10% to under 3%, establishing its essential role in perioperative protocols [11].

Table 3: Perioperative Thromboembolism Prophylaxis

Prophylaxis Type	Recommended Dose	Recommendations	Efficacy and Safety
Low Molecular Weight Heparin (LMWH)	- Enoxaparin: 40 mg SC once daily - Dalteparin: 5,000 IU SC once daily	- Recommended by ACG for all hospitalized IBD patients, including preoperative cases - Focus on high-risk or hospitalized individuals	- Significant reduction in VTE events (OR 0.27, NNT = 35) - Slight increase in major bleeding risk (OR 2.02, NNH = 114)
Extended Prophylaxis	LMWH continued up to 28 days post-surgery	- Suggested for patients undergoing major abdominal surgeries or those with additional risk factors such as immobilization or disease severity	- Effective in preventing post-discharge VTE - Requires patient-specific risk-benefit analysis due to bleeding concerns

Prophylaxis Type	Recommended Dose	Recommendations	Efficacy and Safety
Unfractionated Heparin (UFH)	Dosage dependent on patient-specific factors as per medical protocols	- Considered in patients where LMWH is contraindicated or unavailable	- Potentially less effective than LMWH - Associated with higher rates of heparin-induced thrombocytopenia compared to LMWH
Direct Oral Anticoagulants (DOACs)	Dose varies depending on the type (e.g., apixaban, rivaroxaban)	- Not universally recommended for routine use in preoperative IBD due to limited evidence specifically in this population	- Evidence around safety and efficacy in IBD remains limited - May be considered in selected cases under careful monitoring
Mechanical Prophylaxis	Use of compression stockings or pneumatic devices	- Often used as an adjunct, especially in patients at risk of bleeding or contraindications to pharmacologic prophylaxis	- No direct effect on reducing VTE mortality - Beneficial as part of a multifactorial approach to reducing clot formation during hospitalization

VTE Prophylaxis Efficacy in IBD Surgery



3. Antibiotics and Bowel Preparation

Preoperative bowel preparation and antibiotic prophylaxis can reduce surgical site infections by 20-30% in patients undergoing colorectal surgery. However, routine mechanical bowel preparation alone did not significantly improve outcomes [6].

Multidisciplinary Approach and Prehabilitation

Structured multidisciplinary care incorporating gastroenterologists, colorectal surgeons, dietitians, and psychologists reduces postoperative readmission rates by 50% and significantly decreases hospital stay duration. Prehabilitation programs combining physical, nutritional, and psychological optimization demonstrate 20% fewer complications and 15% shorter hospital stays [7,12,13].

Multidisciplinary Preoperative Optimization Pathway

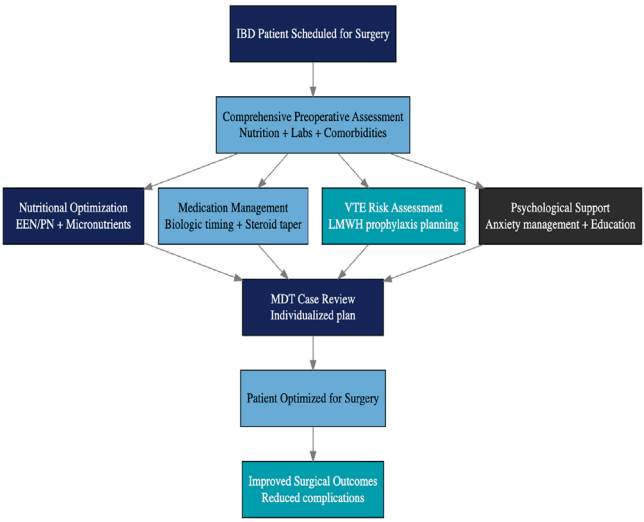


Table 4: Recommendations for resuming biologics and small molecules after IBD surgery

Biologic Agent	Timing	Key Findings	Notes
Anti-TNF Agents	Within 2 to 4 weeks post-surgery	- Strongly recommended for preventing postoperative recurrence. - Safe to use perioperatively; detectable drug levels are not associated with increased infections. - Earlier initiation is encouraged for high-risk patients.	- Timing remains debatable, especially in patients with complications.
Ustekinumab/ Vedolizumab	Within 2 to 4 weeks post-surgery	- Effective in reducing recurrence rates. - Recommended for high-risk patients.	- Limited data on long-term outcomes compared to anti-TNF agents.
JAK Inhibitors	As early as 3 to 5 days post-surgery (if no complications)	- Limited data available. - May provide rapid disease control without increasing complication rates.	- Lack of robust evidence makes their use controversial. - Not widely recommended in current guidelines.

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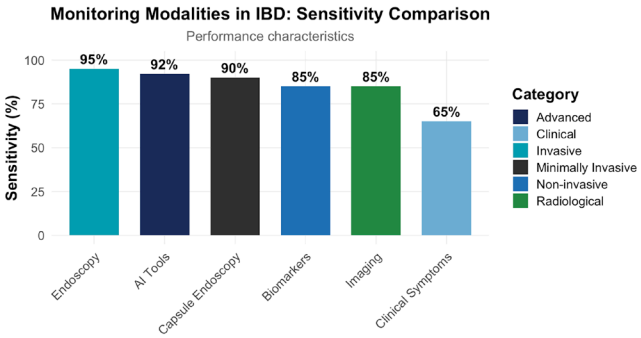
Chapter 17: Monitoring and Follow-Up of IBD Patients

Heba Al Farhan

Introduction

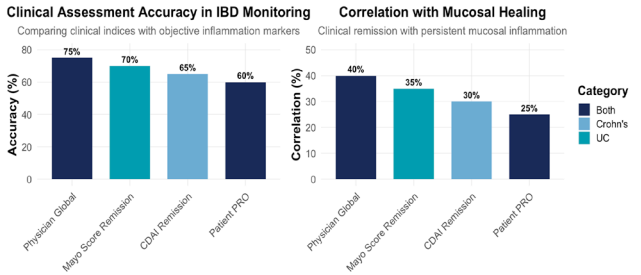
Effective management of Inflammatory Bowel Disease (IBD) hinges on timely therapeutic interventions and meticulous disease monitoring to tailor treatment adjustments, achieve sustained remission, and prevent progression. The development of the STRIDE II framework has revolutionized IBD care, emphasizing a treat-to-target approach that prioritizes long-term therapeutic goals. Under STRIDE II, clinical remission is defined as the absence of symptoms, achieved without corticosteroids, and confirmed through additional parameters such as biomarkers or imaging. Combining subjective and objective indicators ensures greater reliability in activity assessments [1].

Recommendations from different international organizations such as European Crohn's and Colitis Organization (ECCO) and the American College of Gastroenterology (ACG) provide complementary guidance, underscoring the necessity of personalized, evidence-based monitoring strategies that combine clinical assessments, biomarkers, imaging, and endoscopic evaluations. Individualized follow-up optimizes IBD management and monitoring modalities are selected based on patient age, disease phenotype, and comorbidities reduce unnecessary interventions while maintaining comprehensive care [2,3].



Monitoring Strategies in IBD

Clinical Symptom Assessment

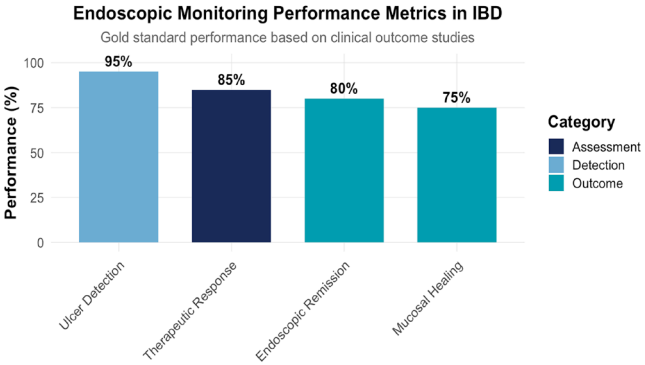


Symptom-based assessments rely on indices like the Crohn's Disease Activity Index (CDAI) for Crohn's disease and the Mayo Clinic Score (MCS) for ulcerative colitis. These tools focus on patient-reported outcomes such as stool frequency, rectal bleeding, abdominal pain, and overall health status to give preliminary disease activity estimates.

Strengths and Limitations: While commonly used, symptom-based measurements often lack correlation with objec-

tive inflammation markers. Studies reveal that over 30% of IBD patients classified as being in clinical remission through these indices still exhibit mucosal inflammation detectable via endoscopy. This highlights the need for additional monitoring modalities to verify disease activity accurately [3].

Endoscopic Monitoring



Endoscopy is considered the "***gold standard***" for visualizing mucosal healing and inflammation status. Achieving endoscopic remission has been linked to clinical remission rates of up to 80% and a significant reduction in disease-related surgeries over five years. Tools like the Mayo Endoscopic Score and the SES-CD aid in assessing disease severity and therapeutic response, ensuring precise stratification of patients for targeted interventions [4].

Limitations of Endoscopy: Despite its critical role, endoscopy is invasive, requiring sedation, and can cause significant discomfort for patients. There are also associated risks, such as bleeding and perforation, which may deter patients from undergoing frequent evaluations. Additionally, endoscopy is

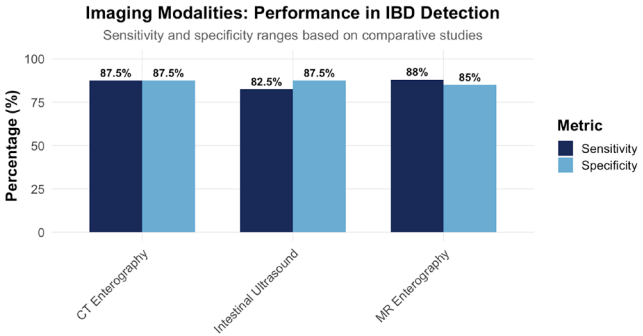
resource-intensive in terms of cost, accessibility, and healthcare infrastructure, making it less feasible for routine monitoring in some settings [4].

To address the limitations of endoscopy, non-invasive modalities such as capsule endoscopy biomarkers and imaging techniques are increasingly utilized. These alternatives enhance patient compliance, reduce procedural burdens, and support routine follow-ups in line with STRIDE II guidelines [1].

Capsule Endoscopy

Capsule endoscopy has emerged as a minimally invasive alternative that complements traditional endoscopic methods. Capsule endoscopy is useful for detecting small bowel involvement in Crohn's disease, visualizing mucosal abnormalities, and assessing mucosal healing. It is often indicated when other diagnostic methods fail to provide conclusive findings. Its ability to visualize the small bowel comprehensively makes it an essential tool for certain cases, however, capsule endoscopy has its drawbacks, including the inability to obtain biopsies, lacks therapeutic capabilities, and contraindicated in cases of strictures or obstructions. It is also reliant on battery life and which limits its versatility [5].

Imaging Modalities



CT Enterography (CTE): Sensitivity ranges from 85-90%, and specificity is 80-95% for detecting small bowel inflammation [6-8]. Provides detailed imaging of the bowel wall and surrounding structures but involves ionizing radiation exposure.

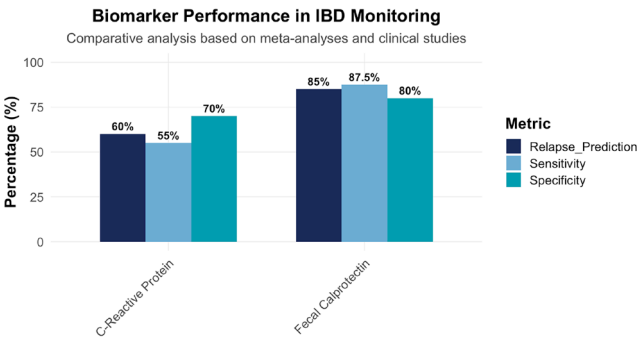
Magnetic Resonance Enterography (MRE): Both sensitivity and specificity exceed 85%, making it a precise tool for evaluating transmural inflammation without ionizing radiation [9-11].

Intestinal Ultrasound (IUS): Sensitivities range from 75-90%, and specificity is 80-95%, particularly for detecting bowel wall thickening and vascular changes. A cost-effective, portable, and radiation-free option [12].

Table 1: Comparative Insights for imaging modalities:

Imaging Modality	Sensitivity/ Specificity	Advantages	Limitations
CT Enterography (CTE)	Sensitivity 85–90%; Specificity 80–95%	Excellent for detecting small-bowel complications, fast imaging	Ionizing radiation exposure; not suitable for frequent monitoring
Magnetic Resonance Enterography (MRE)	Sensitivity/ Specificity >85%	No radiation, high soft-tissue contrast, precise transmural inflammation assessment	High cost, long procedural times; challenges for claustrophobic patients
Intestinal Ultrasound (IUS)	Sensitivity 75–90%; Specificity 80–95%	Portable, bedside-friendly, cost-efficient	Operator-dependent, limited visualization for deep structures or obese patients

Biomarkers



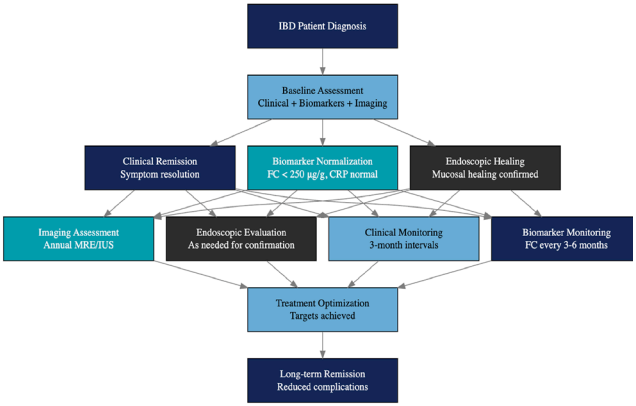
Fecal Calprotectin (FC): A highly sensitive marker that directly correlates with intestinal inflammation. Sensitivity ranges from 80-95%, and specificity from 70-90% when predicting active inflammation. Studies have shown that fecal calprotectin levels exceeding 250 µg/g are linked to a six-fold higher risk of clinical relapse [13,14].

C-Reactive Protein (CRP): An acute-phase reactant reflecting systemic inflammation. Sensitivity ranges from 40-70% and specificity from 60-80% in detecting IBD activity. Especially useful for monitoring treatment response due to its rapid serum half-life [15].

Table 2: Comparative Insights biomarkers use:

Biomarker	Sensitivity	Specificity	Applications in IBD	Limitations
Fecal Calprotectin	80–95%	70–90%	Detecting subclinical inflammation, predicting relapse risk	Affected by infections and medications interference
C-Reactive Protein (CRP)	40–70%	60–80%	Tracking systemic inflammation, monitoring treatment response	Limited use for isolated mucosal inflammation.

STRIDE II Integration Framework

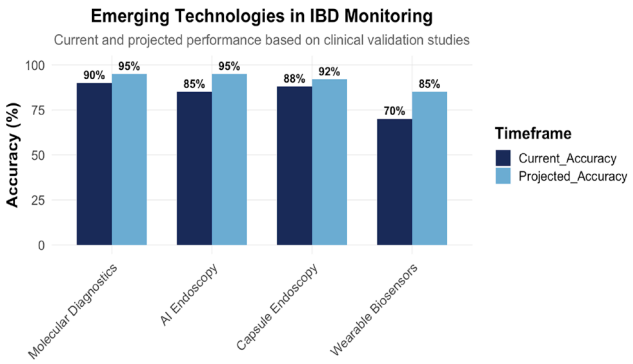


Future Advancements in IBD Monitoring

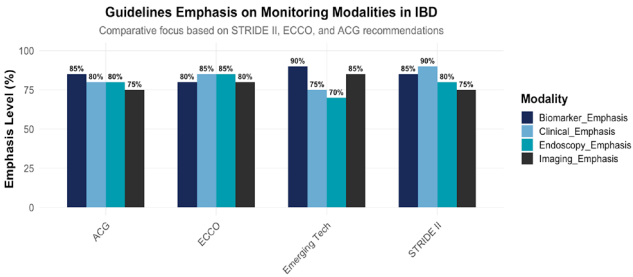
Artificial Intelligence (AI): AI-powered endoscopy and imaging algorithms improve lesion detection accuracy and efficiency in diagnosing and monitoring IBD by up to 35% and reduce interobserver variability [16].

Wearable Biosensors: Emerging non-invasive devices can continuously monitor systemic biomarkers like CRP, offering early indications of flare-ups and enhancing chronic disease management [17].

Advanced Molecular Diagnostics: Multiomics approaches, including transcriptomic and proteomic analyses, demonstrate an accuracy of over 90% in predicting therapeutic responses [18,19].



Personalized Follow-Up and Guidelines Integration



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Chapter 18: Nutrition in IBD

Eman Al Sulais & Reem Hawary

Introduction

Nutrition constitutes a cornerstone in the comprehensive management of Inflammatory Bowel Disease (IBD), exerting significant impact on disease activity, treatment outcomes, and patient prognosis. Malnutrition, micronutrient deficiencies, and sarcopenia are highly prevalent in this population, arising from chronic intestinal inflammation, malabsorption, increased metabolic demands, and inadequate oral intake. These nutritional derangements are associated with impaired immune response, delayed wound healing, increased postoperative complications, and diminished quality of life.

Pathophysiology of Malnutrition in IBD

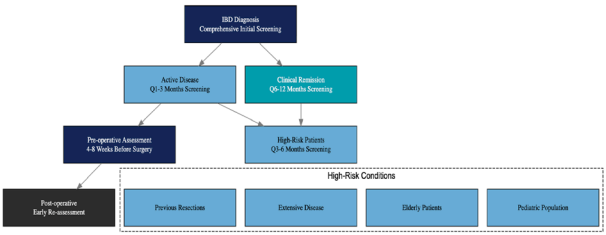
Mechanisms of Malnutrition in Inflammatory Bowel Disease

Pathophysiological Mechanism	Clinical Manifestation	Nutritional Consequences
Reduced Oral Intake	Anorexia, nausea, abdominal pain, dietary restrictions	Macronutrient deficiency
Malabsorption	Mucosal inflammation, surgical resection, bile acid deficiency	Fat-soluble vitamins, B12, minerals
Increased Losses	Protein-losing enteropathy, diarrhea, bleeding	Protein, iron, zinc, electrolytes
Increased Requirements	Chronic inflammation, fever, tissue repair	Energy, protein, micronutrients
Medication Effects	Corticosteroids, sulfasalazine, methotrexate	Folate, calcium, vitamin D

Nutritional Screening and Assessment

All patients should be screened for malnutrition at diagnosis and regularly thereafter. Malnutrition in IBD can exacerbate disease activity, increase postoperative complications, prolong hospital stays, and is associated with higher risks of ve-

nous thromboembolism, infections, and mortality. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Crohn's and Colitis Organization (ECCO) strongly recommend correction of malnutrition in patients with IBD before planned surgery. Reliance solely on serum albumin or BMI is discouraged due to lack of specificity and sensitivity for nutritional status. Instead, a multidisciplinary approach involving dietitian counseling is recommended to identify and manage nutrition-related disorders promptly [1,2].



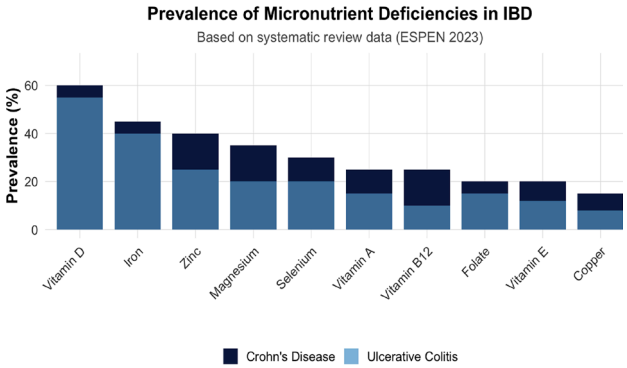
Comprehensive Nutritional Assessment Tools

Nutritional Screening and Assessment Tools for IBD Patients

Assessment Tool	Key Components	Recommended Population	Validated in IBD
MUST (Malnutrition Universal Screening Tool)	BMI, weight loss, acute disease effect	All patients	Yes
NRS-2002 (Nutritional Risk Screening)	Nutritional status, disease severity, age	Hospitalized patients	Yes
PG-SGA (Patient-Generated Subjective Global Assessment)	Weight history, symptoms, intake, functional capacity	Detailed outpatient assessment	Yes
GLIM (Global Leadership Initiative on Malnutrition)	Phenotypic + etiologic criteria	Standardized diagnosis	Emerging
Body Composition Analysis	DEXA, BIA, CT muscle	Research/specialized	Yes

Micronutrient Deficiencies in IBD

Patients with IBD are at risk for micronutrient deficiencies due to diarrhea, malabsorption, intestinal failure, inflammation and reduced dietary intake. Since most of the micronutrients are acute-phase reactants, screening should be performed at least annually and ideally during clinical remission. Screening tests should include vitamins A, E, K, D, B1, B2, B6 and B12 and trace elements, zinc, selenium, copper, and magnesium [1].



Comprehensive Micronutrient Screening Protocol

Comprehensive Micronutrient Screening Protocol in IBD

Clinical Scenario	Essential Laboratory Tests	Monitoring Frequency	Special Considerations
At Diagnosis	Fe, Ferritin, TSAT, B12, Folate, Vit D, Albumin	All patients	Baseline assessment
Active Disease	Fe studies, Vit D, Zn, Mg, B12, Albumin	Q1-3 months	Monitor response to therapy
Clinical Remission	Fe studies, Vit D, B12, Folate	Q6-12 months	Preventive assessment
Post-Resection	B12, Fat-soluble vitamins, Fe, Zn, Mg	Ileal resection >30 cm	Lifelong B12 if >20cm ileum resected
Annual Review	Comprehensive panel based on risk	Individualized based on history	Adjust based on medications, diet

Management of Specific Nutrient Deficiencies

Anemia in IBD

Anemia is a common extraintestinal manifestation of IBD, affecting 6–74% of IBD patients, and it is more common in Crohn's disease than ulcerative colitis. It often results from a combination of iron deficiency anemia (IDA) and chronic disease (ACD). For patients in remission or mild disease, screening should be obtained every 6-12 months, while patients with active disease such measurements should be obtained at least every 3 months [3]. Anemia in IBD is covered in more details in Chapter 18.

Comprehensive Management Strategies for Anemia in IBD

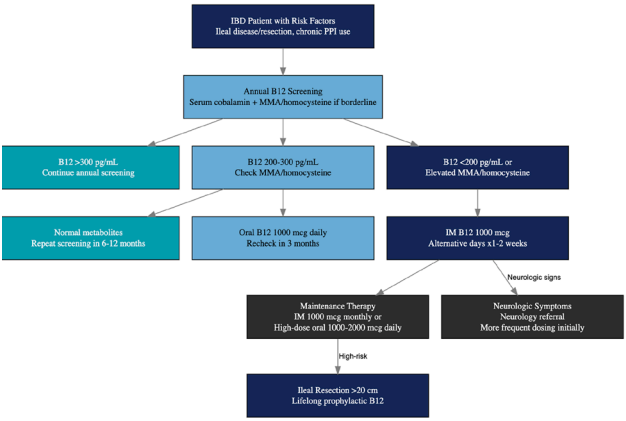
Parameter	Iron_Deficiency_Anemia	Anemia_of_Chronic_Disease	Combined_Deficiency
Diagnostic Criteria	Ferritin <30 (inactive) or <100 (active) µg/L TSAT <20%	|Ferritin >100 µg/L TSAT <20% Elevated CRP/ESR	|Ferritin 30-100 µg/L TSAT <20% Elevated inflammatory markers
First-line Treatment	Oral iron (ferrous sulfate 65mg elemental iron daily)	Treat underlying inflammation Consider EPO if Hb <100 g/L	|IV iron supplementation Treat underlying inflammation
Second-line/Alternatives	IV iron (ferric carboxymaltose/iron sucrose) Consider blood transfusion if Hb <70 g/L	|IV iron if functional iron deficiency Blood transfusion if symptomati	|EPO therapy Combined oral/IV approach
Monitoring	Hb reticulocytes at 2-4 weeks Ferritin/TSAT at 3 months	|CRP/ESR trend Hb response to anti-inflammatory therapy	|Comprehensive monitoring of iron and inflammation parameters
Special	IV iron preferred in active disease	|Address inflammation first EPO target	|Often requires combined approach

Vitamin B12 Deficiency

Vitamin B12 deficiency is prevalent in Crohn's disease, particularly after resection of >30 cm of the distal ileum. (18) Diagnosis involves low serum cobalamin levels and elevated biomarkers like homocysteine or methylmalonic acid. The diagnosis of clinical B12 deficiency further requires macrocytosis and/or neurological symptoms. Patients with clinical deficiency should receive 1000 mcg of vitamin B12 by intramuscular (IM) injection every other day for a week and then every month for life. Patients with > 20 cm of ileum resected,

should receive1000 mcg of vitamin B12 IM every month and then indefinitely [3].

Vitamin B12 Deficiency Management Algorithm



Vitamin D and calcium

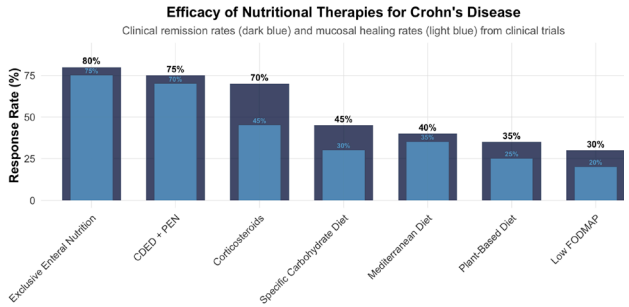
Adequate intake of calcium and supplementation with vitamin D is important for all patients with IBD, especially for those who are on high dose or long-term steroids, or if avoiding dairy products and levels should be monitored every 3–6 months, however, if disease in remission, monitoring can be extended to every 6–12 months. Supplementation helps prevent low bone mineral density, osteopenia, and osteoporosis. Osteopenia and osteoporosis should be managed according to current osteoporosis guidelines.

Evidence-Based Dietary Regimens for IBD

Evidence-Based Dietary Regimens for Inflammatory Bowel Disease

Diet	Induction_Evidence	Maintenance_Evidence	Key_Components	Contraindications	Practicality
Crohn's Disease Exclusion Diet (CDED)	Strong (RCT)	Moderate	Exclusion of emulsifiers, maltodextrin + PEN	None	Moderate (requires supervision)
Specific Carbohydrate Diet (SCD)	Moderate (Observational)	Moderate	No grains, lactose, sucrose	Strictures, undernutrition	Low (very restrictive)
Mediterranean Diet	Moderate (Observational)	Strong	High fruits, vegetables, olive oil, fish	Fiber intolerance during flares	High (sustainable)
Plant-Based Diet	Limited (Case series)	Emerging	Minimal animal products, high fiber	Strictures, need for high energy	Moderate-High

Efficacy of Nutritional Therapies for Remission Induction



Nutritional Interventions:

Oral Nutrition Supplements (ONS) is the first-line support when dietary intake is insufficient, but it is a supportive measure used in addition to normal food. Enteral Nutrition (tube feeding) is generally preferred over parenteral nutrition (PN) unless contraindicated (e.g., bowel obstruction, high-output fistula) and PN is reserved for patients who's oral and or tube

feeding are proved to be insufficient to meet their requirement, and for patients with severe gastrointestinal dysfunction or complications. Bowel obstruction where there is no possibility to place a feeding tube beyond the obstruction, short bowel syndrome, and presence of anastomotic leak or high out-put fistula are some of the common indications for PN in patients with IBD. [4-6].

Exclusive Enteral Nutrition (EEN) in Clinical Practice

EEN has anti-inflammatory effects by modulating gut microbiota, luminal metabolites such as short chain fatty acids (SCFA), reduces luminal antigens and enhances gut barrier function. EEN is effective for inducing remission in Crohn's disease, particularly in children. It serves as a steroid-sparing bridge therapy and superior to steroids in promoting mucosal healing which is a predictor of long-term remission and optimizes nutritional status pre-surgery [4,5].

Comprehensive EEN Protocol

Phase	Components	Monitoring	Success_Indicators
Pre-treatment Assessment	Nutritional status, disease activity, exclusion of obstruction	Weight, blood tests, imaging if indicated	Adequate nutritional status
Initiation (Week 1-2)	Exclusive formula, gradual volume increase, monitor tolerance	Daily symptoms, hydration status, weight	Symptom improvement, weight stabilization
Maintenance (Weeks 3-8)	Full volume, monitor response, manage side effects	Bi-weekly clinical assessment, biomarkers	Clinical remission, biomarker normalization
Reintroduction (Weeks 9-12)	Gradual food reintroduction (1 food every 3-4 days)	Symptom diary, inflammatory markers	Maintained remission with expanded diet
Long-term Maintenance	Maintenance diet + supplements if needed	Quarterly review initially, then 6-12 monthly	Sustained remission, normal growth (pediatrics)

Management of EEN Side Effects

Side_Effect	Incidence	Prevention	Management
Early Satiety/Nausea	30-50%	Slow initiation, overnight feeding	Prokinetics, rate reduction
Diarrhea	20-40%	Isotonic formula, fiber modules	Antidiarrheals, formula change
Constipation	10-20%	Adequate fluids, magnesium supplementation	Laxatives, increased fluids
Regurgitation/Reflux	15-25%	Upright position, slower rate	Rate reduction, proton pump inhibitors
Sweet Taste Fatigue	40-60%	Flavor modules, variety of formulas	Flavoring, temperature variation
Headache	10-15%	Adequate hydration, caffeine if habituated	Analgesics, ensure adequate intake
Hyperglycemia	5-15%	Monitor blood glucose, diabetic formulas	Insulin if needed, formula change

Management of Fiber in IBD

The recommendations for fiber intake in IBD have changed significantly over time. Previously, a low-fiber or low-residue diet was commonly advised to reduce symptoms, however, many international IBD guidelines now promote a different approach of texture modification to allow for inclusion of fiber in certain conditions of IBD, recognizing its important role in gut health as diets low in fiber are associated with increased pathogenic bacteria that degrade the mucous layer resulting in greater dysbiosis and intestinal permeability and mucosal inflammation [7].

It is important to distinguish between different types of fiber. The soluble fiber dissolves in water, forming a gel-like substance. It can help regulate bowel movements and is often better tolerated e.g. oats, beans, and soft fruits. The insoluble fiber like hole grains and the skins of fruits and vegetables add bulk to the stool and can be more difficult to tolerate during flares.

Fiber Management in IBD: Recommendations Based on Disease Status

Fiber Recommendations Based on IBD Disease Status and Phenotype

Disease_Status	Soluble_Fiber	Insoluble_Fiber	Special_Considerations	Practical_Tips
Active Inflammation	Limited, well-cooked	Avoid	Texture modification essential	Peeled fruits, well-cooked vegetables
Mild-Moderate Activity	Gradual introduction	Limited, remove skins/seeds	Monitor for symptom exacerbation	Oats, bananas, peeled apples
Clinical Remission	Encouraged (10-20g/day)	Encouraged with tolerance	Diversity important for microbiome	Whole grains, diverse vegetables
Stricturing Disease	Well-cooked, pureed	Avoid or significant modification	High risk of obstruction	Soups, smoothies, well-cooked
Post-Resection	Gradual introduction	Caution with high amounts	Monitor for bile acid diarrhea	Psyllium for bile acid binding
Ileal Pouch (IPAA)	Encouraged for stool bulk	Individual tolerance	May reduce pouchitis risk	2 fruit servings daily may be protective

Special Considerations in IBD Nutrition

Pediatric-Specific Nutritional Considerations

Pediatric-Specific Nutritional Considerations in Inflammatory Bowel Disease

Aspect	Considerations	Monitoring	Interventions
Growth Assessment	Regular height/weight plotting, bone age assessment	Every 3 months during active disease	Growth hormone assessment if delayed
Energy Requirements	Increased due to catch-up growth + inflammation	Adjust based on growth velocity	High-energy supplements, overnight feeds
Protein Needs	1.5-2.0 g/kg/day for growth and repair	Serum albumin, pre-albumin	Whey protein supplements if needed
Micronutrient Focus	Calcium, vitamin D, zinc, iron for growth	Quarterly during active growth	Aggressive repletion, maintenance supplements
Psychological Aspects	Body image, social eating, family dynamics	Regular psychosocial assessment	Family therapy, peer support groups
Transition to Adult Care	Gradual transition of dietary self-management	Joint pediatric-adult clinics	Education on long-term self-management

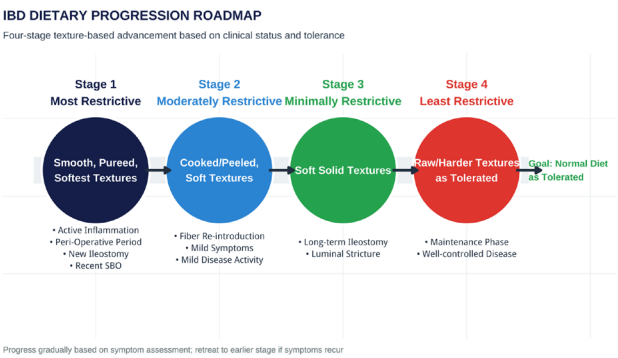
Perioperative Nutritional Management

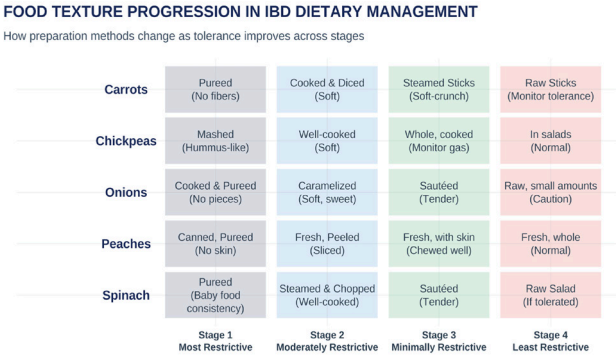
Comprehensive Perioperative Nutritional Management in IBD Surgery

Timeline	Goals	Interventions	Monitoring
4-8 Weeks Pre-op	Optimize nutritional status, correct deficiencies	Oral supplements, enteral nutrition if needed	Weight, albumin, micronutrients
1-2 Weeks Pre-op	Maximize glycogen stores, immunonutrition	Carbohydrate loading, immunonutrition	Glucose control, hydration
Immediate Pre-op (24-48h)	Maintain hydration, minimize catabolism	Clear fluids until NPO, IV hydration	Fluid balance, electrolytes
Post-op Day 1-3	Early enteral nutrition, gut integrity	Tube feeding if oral intake inadequate	Tolerance, electrolyte balance
Post-op Day 4-7	Advance to oral diet, meet requirements	Progressive diet advancement	Oral intake, bowel function
Long-term Post-op	Adapt to anatomical changes, prevent deficiencies	Lifelong B12 if ileal resection, monitor fat absorption	Weight, B12, fat-soluble vitamins, bone density

Transition of diet in patients with IBD

As patients with IBD show clinical improvement—whether spontaneous or treatment-induced—diet should be gradually liberalized in a structured, stepwise manner, balancing gut tolerance, nutritional adequacy, and relapse prevention [7].





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Chapter 19: Anemia in IBD

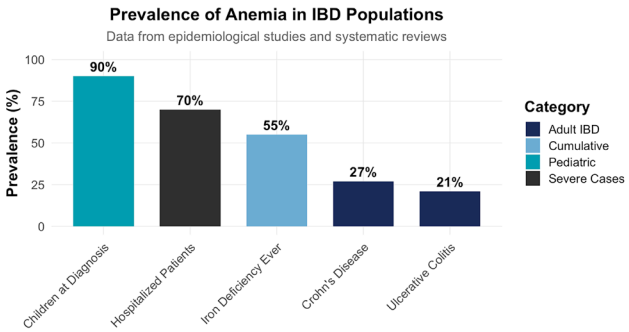
Ebtissam AlMeghaiseeb

Introduction

Anemia is one of the most frequent complications or extraintestinal manifestations (EIMs) in Inflammatory Bowel Disease (IBD). This condition can significantly impact quality of life, contributing to fatigue, reduced physical endurance, and even impaired cognitive function. For healthcare providers caring for IBD patients, recognizing and addressing anemia is essential to holistic disease management [1].

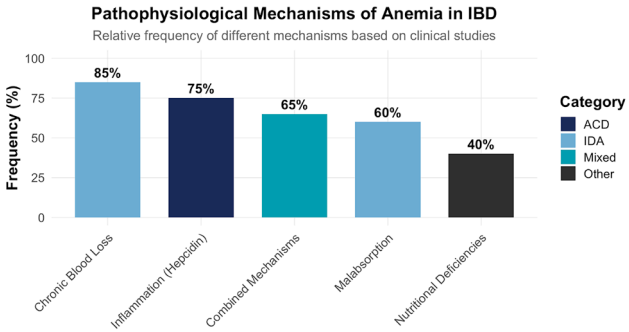
Anemia is common among IBD patients. The World Health Organization (WHO) provides the following age- and gender-specific cut-offs for hemoglobin (Hb) concentration in anemia: <130 g/L for adult men, <120 g/L for adult, non-pregnant women, and <110 g/L for children aged 6-59 months and increasing with age. Studies showed an overall anemia prevalence of 27% in patients with CD and 21% in those with UC [2], with the prevalence in children as high as 90% at diagnosis [3]. Higher rates are typically observed during disease flares and in hospitalized patients, and anemia may be present at diagnosis or develop as the disease progresses. Iron deficiency, in particular, is highly prevalent, affecting over half of IBD patients at some point [4].

Epidemiology and Prevalence



Pathophysiology

Anemia in IBD arises from multiple causes. Iron deficiency anemia (IDA) is the most common type, usually due to chronic blood loss from intestinal inflammation, reduced dietary intake, and malabsorption. Anemia of chronic disease (ACD), or anemia of inflammation, also plays a significant role. Inflammatory cytokines elevate hepcidin levels, which restrict iron availability and impair red blood cell production [3]. Many patients experience a combination of IDA and ACD, and some may have additional contributors like vitamin B12 or folate deficiencies, especially if they have undergone bowel resection [5,6].



Types of Anemia in IBD

Table 1: Comparison of Anemia Types in IBD

Type of Anemia	Cause	Laboratory Findings	Treatment Approach
Iron Deficiency Anemia (IDA)	Chronic blood loss, reduced intake, malabsorption	Low hemoglobin, low serum ferritin (<30 µg/L), low transferrin saturation (<16%)	Oral or IV iron supplementation, address bleeding sources
Anemia of Chronic Disease (ACD)	Inflammation-mediated iron sequestration	Low/normal hemoglobin, normal/high serum ferritin (>100 ug/L) and transferrin saturation<20%, elevated CRP	Treat underlying inflammation, consider IV iron, possible ESA (erythropoiesis-stimulating agent)

Type of Anemia	Cause	Laboratory Findings	Treatment Approach
Mixed Anemia	Combination of IDA and ACD factors	Features of both IDA and ACD	Combined approach: iron supplementation and anti-inflammatory therapy

Diagnostic Approach

Evaluation should begin with a complete blood count (CBC) to confirm anemia. Next steps include:

- Anemia parameters should be evaluated every 6-12 months in patients in remission or with mild disease activity; patients with active disease should be monitored at least every 3 months [1].
- Serum Ferritin: <30 µg/L suggests IDA. In inflammation, levels <100 µg/L may still indicate deficiency [7].
- Transferrin Saturation (TSAT): <16% indicates iron-restricted erythropoiesis [7].
- C-Reactive Protein (CRP): Elevated CRP suggests active inflammation, potentially confounding ferritin interpretation.
- Vitamin B12 & Folate: Generally, presents with normocytic to macrocytic anemia, picture may be mixed if concurrent IDA, consider testing, especially in ileal CD, patients with prior ileal resection, or in patients with restricted diets [5].

Table 2: Structured evaluation to differentiate causes of anemia

Test	Purpose	Interpretation in IBD Context
Complete Blood Count (CBC)	Confirms anemia, assesses MCV and severity	Microcytic = IDA; Normocytic = ACD or mixed
Serum Ferritin	Marker of iron stores	<30 µg/L = IDA; 30–100 µg/L with inflammation = possible deficiency
Transferrin Saturation (TSAT)	Reflects available circulating iron	<16% suggests iron-restricted erythropoiesis[8]
CRP or ESR	Inflammatory markers	Elevated in active IBD, supports ACD diagnosis
Vitamin B12/ Folate	Rule out additional deficiencies	Check in ileal CD or strict vegetarian diets
Reticulocyte Count	Evaluates bone marrow response	Low in IDA/ACD; high in hemolysis or recovery[8]

Management Strategies

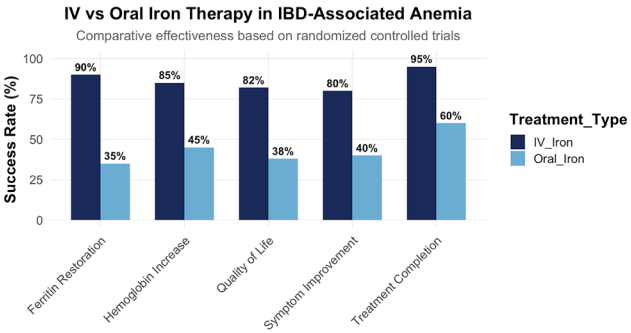
The cornerstone of treating anemia in IBD is identifying the underlying cause(s) and tailoring treatment accordingly. Iron replacement is the most common and crucial intervention [9]. Oral iron remains an option in patients with mild anemia and inactive disease, but gastrointestinal side effects and limited absorption often reduce its utility [8]. In patients who do not respond to iron supplementation or have severe disease, erythropoiesis-stimulating agents (ESAs) can be considered, usually alongside IV iron. Additionally, controlling the underlying IBD inflammation is critical to reducing ongoing iron losses and cytokine-mediated suppression of erythropoiesis [8]. Nutritional deficiencies should also be corrected to support optimal red blood cell production [6].

Intravenous (IV) iron therapy is strongly recommended in patients with moderate-to-severe anemia (hemoglobin <10 g/dL), clinically active IBD, or intolerance or non-responsiveness to oral iron [9]. In these scenarios, inflammation impairs intestinal iron absorption and elevates hepcidin levels, making oral iron ineffective [8]. IV iron bypasses the gastrointestinal tract, delivering iron directly to the bloodstream for efficient use in erythropoiesis. Commonly used IV formulations include ferric carboxymaltose, iron sucrose, and iron isomaltoside, all of which have been shown to safely and rapidly restore iron stores and improve hemoglobin levels [9]. Recent studies suggest ferric carboxymaltose may offer superior efficacy in fewer infusions, with a lower risk of adverse effects compared to older formulations [9]. IV replacement with ferric derisomaltose may increase the risk of hypophosphatemia compared to ferric carboxymaltose.

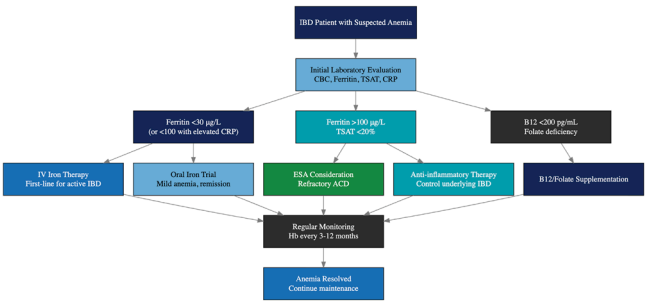
Guidelines such as those from the European Crohn's and Colitis Organization (ECCO) recommend IV iron as first-line therapy in IBD patients who are anemic and have active disease, significant iron deficits, or prior oral iron intolerance [7]. Total iron needs are

calculated based on weight and hemoglobin level, and follow-up is essential to confirm treatment success and prevent recurrence [9].

Role of IV Iron in Managing Anemia in IBD



Management Algorithm



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Ebtissam AlMeghaiseeb

Introduction

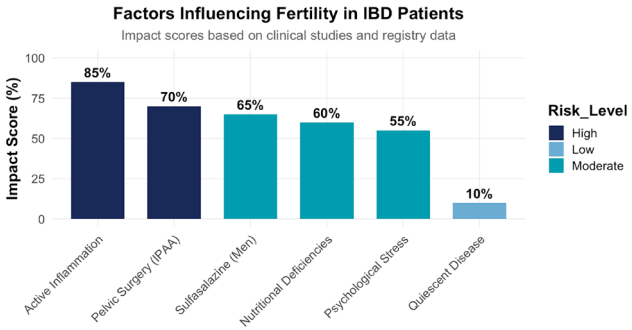
Inflammatory Bowel Disease often manifests during prime reproductive years. Managing IBD in the context of fertility and pregnancy is crucial, given its implications on reproductive health, maternal outcomes, and fetal well-being. Patients with quiescent IBD have fertility rates comparable to the general population. However, active disease, nutritional deficiencies, and psychosocial factors can reduce conception rates [1].

Fertility in IBD

Baseline Fertility and Influencing Factors

Table 1: Factors Influencing Fertility in IBD

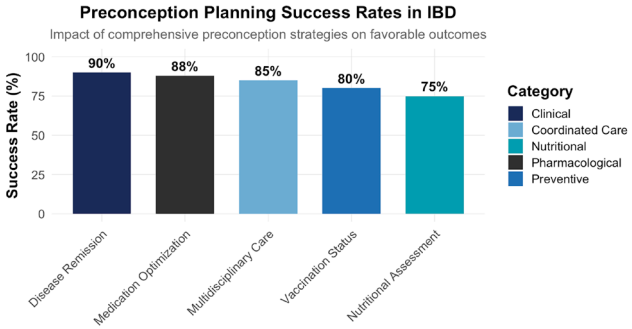
Factor	Effect on Fertility	Notes
Active inflammation	Decreased	Disrupts ovulation, alters hormone levels
Pelvic surgery (e.g., IPAA)	Decreased (up to 3-fold)	Causes adhesions, tubal dysfunction
Sulfasalazine in men	Reversible decrease	Affects sperm count and motility
Nutritional deficiencies	Decreased	Especially iron, folate, vitamin B12
Psychological stress	Decreased	Impacts libido and sexual function



Preconception Counseling and Medication Safety

Preconception Planning

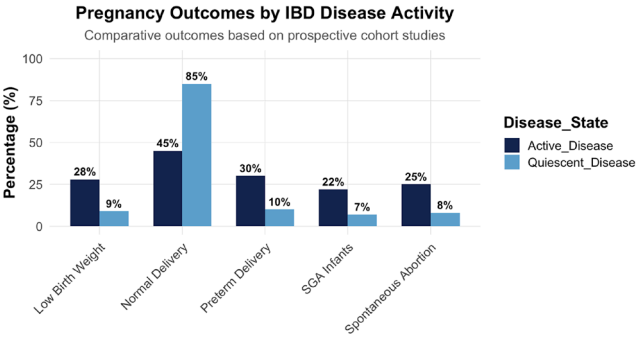
The goal is to achieve deep clinical and endoscopic remission for at least 3-6 months prior to conception. Multidisciplinary counseling should address nutrition, smoking cessation, and vaccinations [2,3]. Education is crucial to reassure patients about the safety of most therapies.



Pregnancy Outcomes and Disease Activity

Women with active IBD at conception are at increased risk of spontaneous abortion, preterm delivery, low birth weight and small for gestational age infants therefore, maintaining remission is critical for optimizing maternal and neonatal outcomes [4].

Impact of Disease Activity on Pregnancy



Medication Safety in Pregnancy

Most IBD medications can be safely continued during pregnancy and lactation, and maintaining disease remission is the strongest predictor of good maternal and fetal outcomes. Aminosalicylates, corticosteroids, thiopurines, and biologics (including anti-TNF agents, vedolizumab, and ustekinumab) are generally considered low risk in pregnancy and compatible with breastfeeding. Anti-TNF agents actively cross the placenta in late pregnancy (except certolizumab pegol, which has minimal transfer), but this has not been associated with adverse neonatal outcomes; breastfeeding remains safe. In contrast, small-molecule agents such as methotrexate, tofacitinib, upadacitinib, and ozanimod are

contraindicated or not recommended in pregnancy and lactation due to teratogenicity or insufficient safety data. Overall, treatment decisions should prioritize sustained disease control using medications with established safety profiles, with multidisciplinary counseling before and during pregnancy

Table 2: Safety of Biologics & Small Molecules in Pregnancy and Lactation

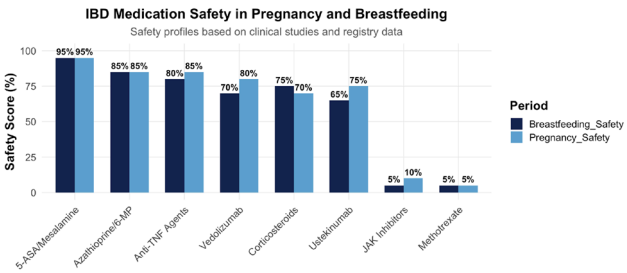
Drug Class	**Example(s)**	**Pregnancy Use**	**Lactation Safety**	**Notes**
Anti-TNF	Infliximab, Adalimumab, Certolizumab pegol	Safe	Safe	Avoid live vaccines in infants up to 6 months (except certolizumab)
Anti-integrin	Vedolizumab	Safe	Safe	
Anti- IL-12/23	Ustekinumab	Safe	Safe	
JAK Inhibitors	Tofacitinib, Upadacitinib	Contraindicated	Contraindicated	Insufficient data to establish safety, stop before conception and switch to biologics.

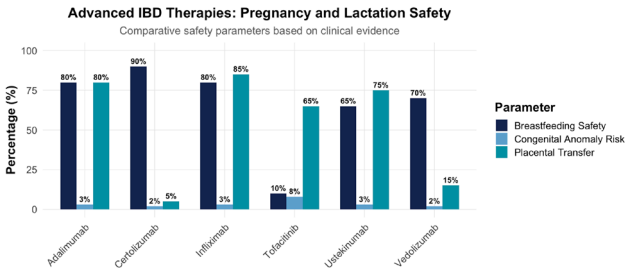
Drug Class	Example(s)	Pregnancy Use	Lactation Safety	Notes
S1P Modulators	Ozanimod	Contraindicated	Contraindicated	Stop > 3 months before attempting conception.

Table 3: Safety of Newer Biologic Therapies and Small Molecules. [5,6]

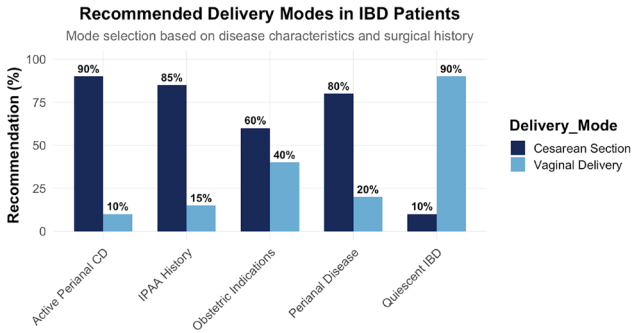
Drug Class	Agent Name	Pregnancy Safety	Breastfeeding Safety	Notes
Anti-IL-23	Risankizumab	Limited human data; animal studies reassuring	Unknown	Avoid unless essential
Anti-IL-23	Mirikizumab	Limited data; caution advised	Unknown	Approved for UC
IL-13/IL-23	Brazikumab	No human data	Unknown	Trial phase
IL-23 (p19)	Guselkumab	Limited data; avoid if possible	Unknown	Crosses placenta in animals

Drug Class	Agent Name	Pregnancy Safety	Breast-feeding Safety	Notes
S1P Modulator	Etrasimod	Contrain-dicated	Unknown	Terato-genic in animals
JAK Inhibitor	Filgotinib	Contrain-dicated	Unknown	Testicular toxicity in preclinical studies but no measura-ble impact on semen parame-ters or sex hormones in men





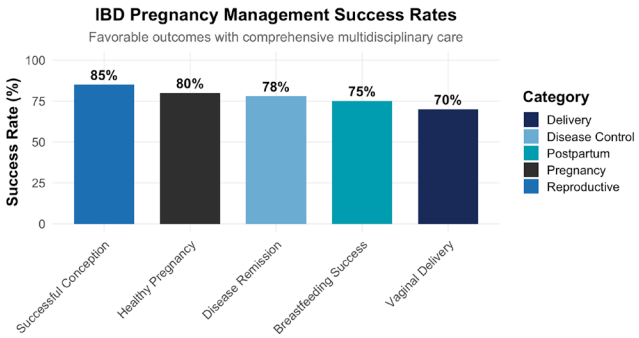
Delivery and Postpartum Management



Other points to consider [7-11]

- IPAA surgery in UC increases infertility risk due to pelvic adhesions and laparoscopic techniques reduce this risk compared to open surgeries.
- Sulfasalazine causes reversible oligospermia in men.
- Azathioprine and 6-mercaptopurine are safe in pregnancy and lactation, but better to avoid initiation during pregnancy.
- Methotrexate does not increase the risk of congenital anomalies when the father is taking it at the time of conception.

• Biologics have not shown adverse effects on sperm parameters.
• Women and men with IBD can successfully conceive and carry healthy pregnancies.
• Medication adherence is critical and most of IBD therapies are safer than active disease during pregnancy.
• Encourage preconception counseling and delivery planning.
• Due to transplacental transfer of IgG1 biologics, avoid live vaccines (e.g. BCG, rotavirus) in infants exposed in the 3rd trimester (except certolizumab that has minimal placental transfer) until 6 months of age.



Comprehensive Management Algorithm

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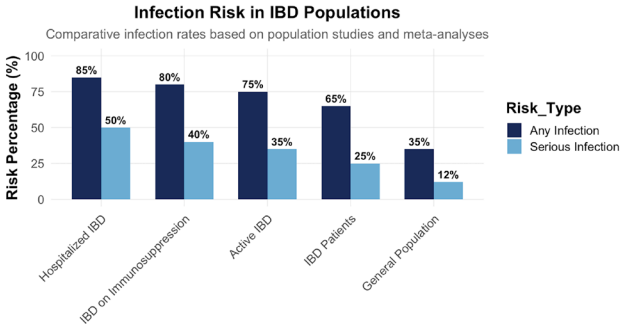
Bashaar AL Ibrahim

Introduction

Patients with Inflammatory Bowel Disease are at an increased risk of infections due to the underlying immune dysregulation, the use of immunosuppressive therapies, and the potential for disruption of the gut barrier [1,2].

Epidemiology of Infections in IBD

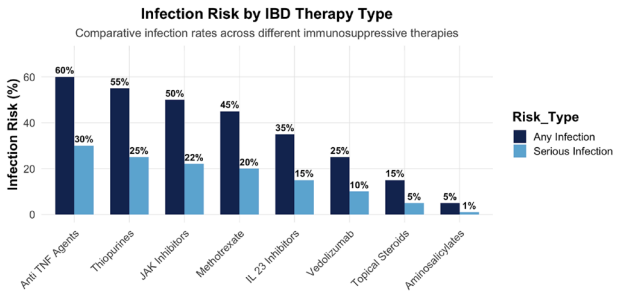


Infections are a significant cause of morbidity and mortality in patients with IBD. Studies have shown that patients with IBD are at a higher risk of both opportunistic and community-acquired infections compared to the general population [3]. The risk of infection is further amplified using immunosuppressive medications, such as corticosteroids, thiopurines, methotrexate, and potentially with some biologic and small molecule therapies [1]. However, it should be noted that multiple registries have demonstrated that uncontrolled or poorly controlled IBD is an important risk factor for infection risk. A large population-based study found that patients with IBD had a 1.5 to 2-fold increased risk of serious infec-

tions compared to the general population [3]. The most common infections in IBD patients include respiratory infections, urinary tract infections, and gastrointestinal infections. Opportunistic infections, such as tuberculosis (TB), cytomegalovirus (CMV), and herpes zoster, are also more prevalent in this population [4].

Risk Factors for Infections in IBD

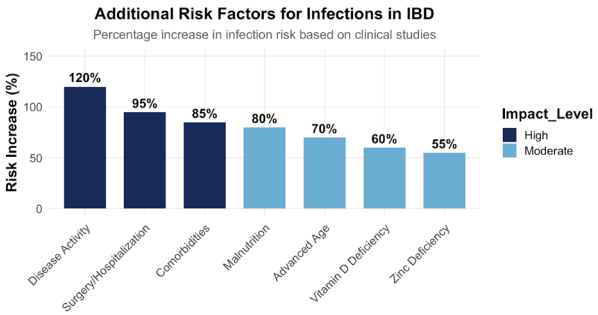
Immunosuppressive Therapy Impact



Several factors contribute to the increased risk of infections in patients with IBD:

1. ***Immunosuppressive Therapy:*** Corticosteroids, immunomodulators and some biologics are independently associated with increased infection risk. Combination therapies, such as anti-tumor necrosis factor (TNF) with thiopurines, further amplify this risk. Recent data suggest lower rates of serious infections with JAK inhibitors and IL-23 inhibitors compared with anti-TNF. Vedolizumab, due to its gut selectivity, has shown a lower rate of non-gastrointestinal infections but may increase the risk of enteric infections such as Clostridioides difficile (C. difficile) [4].

Additional Risk Factors



2. ***Disease severity/activity:*** Patients with severe or active IBD are more susceptible to infections due to the systemic inflammation and mucosal barrier disruption, which can facilitate bacterial translocation. A large cohort study of IBD patients found that patients with active disease were more than twice as likely to develop infections compared to those with quiescent disease [5].

3. ***Malnutrition:*** Malnutrition is common in patients with IBD, particularly in those with CD [6,7]. Nutritional deficiencies, such as low levels of vitamin D and zinc, can impair immune function and increase susceptibility to infections [8].

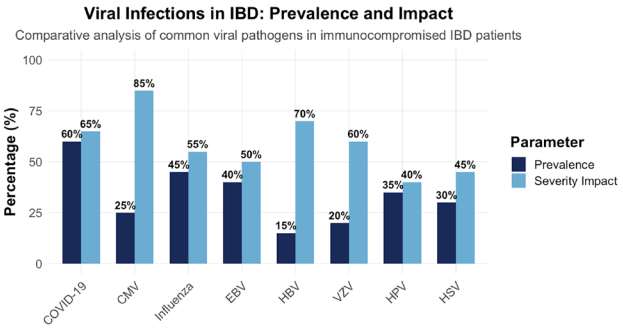
4. ***Surgery and Hospitalization:*** Patients with IBD often require surgical interventions and hospitalizations, which are associated with an increased risk of nosocomial infections, including C. difficile and surgical site infections [9].

5. ***Age and Comorbidities:*** Older patients and those with comorbid conditions, such as diabetes or chronic kidney disease, are at a higher risk of infections. Additionally, the pres-

ence of extraintestinal manifestations of IBD, such as primary sclerosing cholangitis, may further increase infection risk [4,10,11].

Common Infections in IBD

Viral Infections Profile



1. ***Viral Infections:***

o ***Cytomegalovirus (CMV):*** CMV colitis is a serious concern in treatment refractory IBD and is associated with higher rate of hospitalization and colectomy within 12 months. The gold standard for diagnosis involves endoscopic biopsy with immunohistochemistry (IHC) and/or tissue PCR. Treatment includes antiviral therapy (e.g., ganciclovir, valganciclovir), immunosuppressive therapy should not be discontinued except in cases of disseminated infection [12].

o ***Varicella zoster virus (VZV):*** Varicella zoster reactivation is more common in IBD patient, particularly those on JAK inhibitors [13]. Treatment includes acyclovir, valacyclovir or famcyclovir. Intravenous treatment should be considered for severe and complicated infection. Vaccination with the re-

combinant zoster vaccine is recommended for IBD patients [4].

o ***Herpes simplex virus (HSV):*** Primary or recurrent oral and genital herpes may be more frequent and severe in immunosuppressed patient. HSV can cause severe mucocutaneous or systemic infections, including keratitis, retinitis, encephalitis, pneumonia, esophagitis and colitis. Although no vaccine available for HSV, routine prophylaxis with antiviral therapy should be considered for patient with frequent recurrent attacks [4].

o ***Hepatitis virus (A, B, C):***
Hepatitis A virus (HAV): Causes acute hepatitis; vaccination is recommended for non-immune IBD patient before immunosuppressive treatment. Post exposure prophylaxis with immunoglobulin and vaccine is recommended for unvaccinated immunosuppressed patients [14].

Hepatitis B Virus (HBV): Can cause acute or chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Reactivation of HBV can occur with immunosuppression. Screening for HBV is essential before starting immunosuppressive medications. Treatment with nucleoside/nucleotide analogs (e.g., tenofovir, entecavir) is recommended for chronic HBV or as prophylaxis during immunosuppression. Vaccination is recommended for non-immune patients [15].

Hepatitis C Virus (HCV): Can cause chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Reactivation is less common compared to HBV. Treatment with Direct-acting antivirals (e.g., sofosbuvir, ledipasvir) for chronic HCV [4].

o ***Epstein–Barr virus (EBV):*** In most patients, EBV infection is a self-limiting or asymptomatic, even in those receiving immunosuppression. However, EBV is associated with an increased risk of lymphoma in EBV-negative patients on thiopurines. The

Use of thiopurines in EBV-IgG negative patients should be carefully considered. Rare complication of primary viral infection in immunosuppressed patients is hemophagocytic lymph histiocytosis (HLH) and EBV-positive mucocutaneous ulceration. Discontinuation of immunosuppression is the primary therapeutic intervention [4].

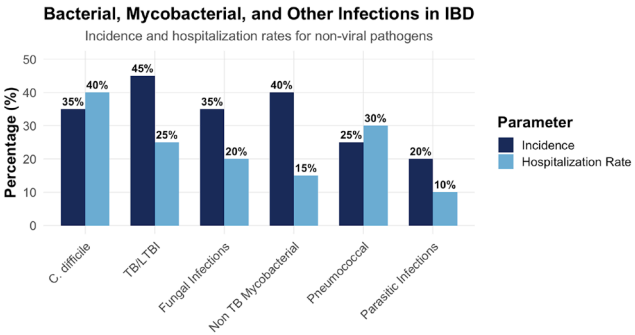
o ***Influenza virus:*** IBD patients have a slightly increased risk of influenza and are more likely to require hospitalization compared to non-IBD patients. Steroid were the only medication independently associated with influenza risk. Annual vaccination is the most effective prevention method and should be recommended for all patients. Immunosuppressive therapy should be withheld in severe cases of influenza [16].

o ***Human papilloma virus (HPV):*** Immunosuppressive therapy increases the risk of persistent HPV infections and cervical cancer. Female IBD patient on immunosuppressive therapy should undergo annual cervical cancer screening. HPV vaccination is recommended for both young male and female patients with IBD [4].

o ***COVID-19:*** Most IBD medications, including anti-TNF agents, vedolizumab, and ustekinumab, do not appear to significantly increase the risk of severe COVID-19. Steroid and thiopurines have been associated with increased risk of severe disease in some studies. In asymptomatic and mild infections, immunosuppressive therapy may be continued. In moderate to severe COVID-19 temporary cessation may be considered. Vaccination is recommended for all IBD patients, prioritizing mRNA or viral vector vaccines. Booster doses are recommended for immunosuppressed patient due to their potentially reduced response to the initial vaccine series [17].

o ***Human immunodeficiency virus (HIV):*** Cohort studies suggest that HIV patients have a less severe course of IBD. Screening for HIV is recommended, especially for high-risk individuals. Immunosuppressives can be used in patients with stable CD4 counts and undetectable viral loads. Close monitoring of CD4 counts is recommended [18].

Bacterial and Other Infections



2. Bacterial infections:

o ***Clostridioides difficile (C. diff):*** IBD patient, particularly those with colonic involvement, are at high risk of C. diff infections. Screening for infection is recommended at every disease flare, as symptoms can mimic or exacerbate an IBD flare. A two-step diagnostic algorithm is recommended, starting with a highly sensitive test (e.g., glutamate dehydrogenase [GDH] or nucleic acid amplification test [NAAT]) followed by highly specific test (e.g., toxin A/B enzyme immunoassay). Treatments include oral vancomycin or fidaxomicin. IV metronidazole is added for severe infections. Recurrent

infections are common; treatment options include vancomycin, fidaxomicin, bezlotoxumab and fecal microbiota transplantation [20].

o ***Salmonella:*** Immunosuppressed IBD patients are at risk of severe Salmonella enteritidis and Salmonella typhimurium infections, including bacteremia, osteomyelitis, and septic arthritis. Treatment include fluroquinolone or third-generation cephalosporins [4].

o ***Escherichia coli (E. coli) and Other Enteric Pathogens:*** Disruption of the gut barrier in IBD increases the risk of infections with enteric pathogens, including E. coli, Campylobacter, and Shigella. These infections can mimic or exacerbate IBD flares. Treatment includes ciprofloxacin or azithromycin [21].

o ***Listeria monocytogenes:*** Listeria can cause severe systemic infections, including meningitis and septicemia, particularly in patients on anti-TNF therapy. Treatment includes ampicillin or trimethoprim-sulfamethoxazole (TMP-SMX) [4]

o ***Pneumococcal Infections:*** IBD patients, even before starting immunosuppressive therapy, have an increased risk of invasive pneumococcal disease (e.g., pneumonia, meningitis). Pneumococcal vaccination is recommended for all IBD patients [4].

o ***Legionella pneumophila infection:*** Immunosuppressed IBD patients, particularly those on anti-TNF therapy, are at risk of Legionella pneumonia. Diagnosis involves urinary antigen testing or PCR on respiratory samples. Treatment includes macrolides or fluroquinolone [4].
o Nocardial infection: Rare but serious opportunistic infections that can occur in patients with IBD, particularly those

on immunosuppressive therapies (e.g., Steroid, Anti-TNF agents). Nocardia species are found in soil and decaying organic matter. Patients with occupational or recreational exposure to soil (e.g., farmers, gardeners) are at higher risk. Clinical presentation includes pulmonary, cutaneous, and disseminated systemic symptoms. Diagnosis involves culture and stain or PCR of affected body fluids or tissue. First line treatment is TMP-SMX [4].

3. Mycobacterium infections:

o ***Mycobacterium TB:*** there is a significant risk of latent TB (LTBI) reactivation with biological therapy and JAK inhibitors, particularly with anti-TNF in combination with immunomodulators. Screening for LTBI is recommended before starting biological treatment and ideally before starting any immunosuppression. Recommended screening tests include Chest x-ray, TB-skin (TST) and/or interferon gamma release assay (IGRA) depending on epidemiological factors and prior BCG vaccination. Periodic rescreening is recommended for patient on biological treatment and JAK inhibitors, especially in endemic areas. Patients with LTBI should receive prophylactic treatment before starting immunosuppressive therapy. Standard treatment includes isoniazid, rifampicin and isoniazid plus rifapentine. Immunosuppressive therapy should be delayed at least one month after starting LTBI treatment [4].

o ***Non-TB mycobacterium (NTM):*** less common than TB but occur in immunosuppressed IBD patients. Symptoms include fever, fatigue and weight loss. Diagnosis involves isolation of the organism from cultures (sputum, blood or tissue biopsies). Treatment involves combination of antibiotics for prolonged period and may require adjustment or discontinuation of immunosuppressive therapy [19].

4. ***Fungal and parasitic infections:***

o ***Pneumocystis jirovecii infection:*** An opportunistic fungal pathogen that causes Pneumocystis pneumonia (PCP), particularly in immunocompromised patients. Prophylaxis with TMP-SMX should be strongly considered for patient on triple immunosuppressive therapy, including steroids, azathioprine, methotrexate and biologics. It may also be considered for those on double immunosuppressive if one agent is a calcineurin inhibitor or a combination of high dose steroid, low lymphocytes count, and JAK inhibitors. Typical presentation includes respiratory symptom and hypoxia. Chest imaging may show bilateral interstitial infiltrates or ground-glass opacities. First line treatment is TMP-SMX. [4].

o ***Candida albicans:*** The most common cause of mucosal infections (e.g., oral thrush, esophageal candidiasis). Invasive infections are uncommon, but mortality is high in IBD patients. Steroid and antibiotics use are the most common risk factors. Treatment includes fluconazole for mucosal infections and echinocandins or amphotericin B for invasive disease [22,23].

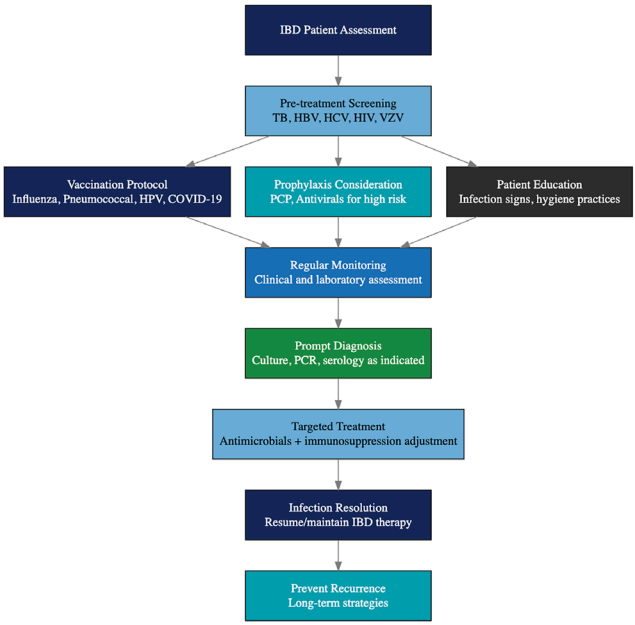
o ***Parasitic infections:*** Parasitic infections in IBD patients can complicate disease management, mimic IBD symptoms, or exacerbate underlying inflammation. Geographic and environmental exposure is an important risk factor.

Protozoal infections: Giardia lamblia, Entamoeba histolytica, Cryptosporidium and Cyclospora species can cause diarrhea in IBD patients.

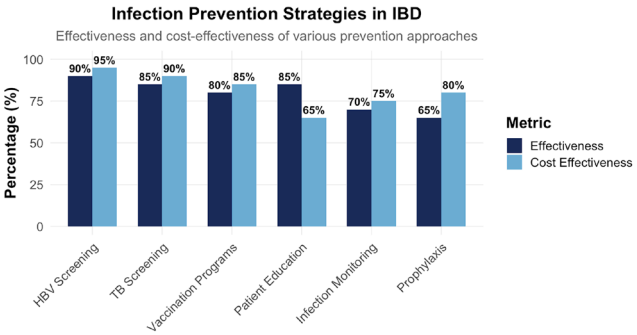
Helminths infections: Strongyloidiasis can cause hyperinfection syndrome in immunocompromised patients, and Schistosomiasis can affect GI tract and liver.

Diagnosis is made through stool examination, supported by serological and molecular testing. Treatment involves antiparasitic therapy according to the isolated species and may require adjustment of immunosuppressive therapy in severe cases [4].

Infection Prevention and Management Algorithm



Key Prevention Strategies



Summary

Infections represent a major challenge in the management of IBD patients, with increased risks driven by both the underlying disease process and immunosuppressive therapies. A comprehensive approach including appropriate screening, vaccination, prophylaxis, and vigilant monitoring is essential for optimal patient outcomes.

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Yaser Meeralam, MD

Introduction

Beyond the intestinal manifestations, patients with IBD face significantly elevated risks of developing various malignancies, particularly gastrointestinal cancers, lymphoma, skin cancers, and cervical cancer [1,2]. The increased cancer risk stems from multiple interconnected factors that include chronic inflammation driving cellular damage, long-term immunosuppressive therapy, environmental risk factors, and potential genetic predispositions [3]. This chapter provides a comprehensive overview of malignancy risks in IBD, focusing on pathogenesis, risk stratification, surveillance strategies, and evidence-based management approaches.

Colorectal Cancer in IBD

Epidemiology and Pathogenesis

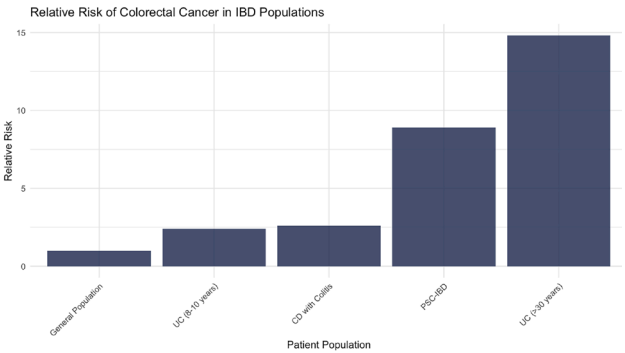

Figure 1: Comparative risk of colorectal cancer in IBD populations versus general population

Patients with long-standing IBD face substantially elevated colorectal cancer (CRC) risks, with UC and Crohn's colitis carrying approximately 2-3 fold increased risk compared to the general population [4]. The cumulative risk increases dramatically with disease duration, reaching 14.8% after 30 years of extensive UC [5]. IBD-associated CRC develops through distinct molecular pathways compared to sporadic CRC, with earlier P53 mutations and later APC mutations in the inflammation-dysplasia-carcinoma sequence [6,7].

Molecular Pathways

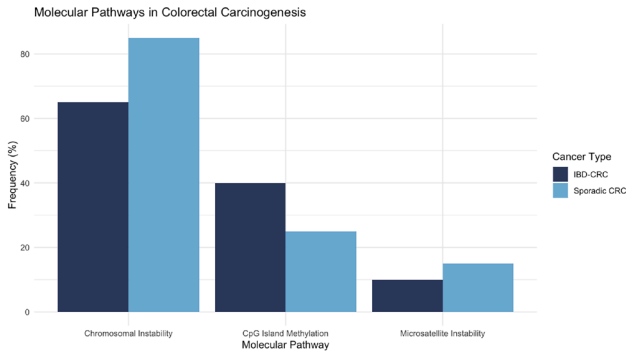

Figure 2: Comparative molecular pathways in sporadic CRC versus IBD-associated CRC

Endoscopic Surveillance

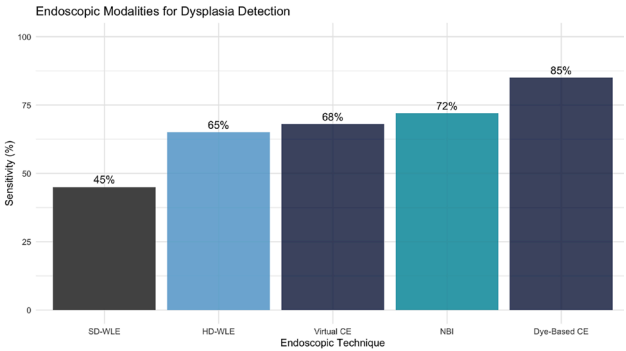

Figure 3: Performance of endoscopic surveillance techniques for dysplasia detection. Abbreviations: SD-WLE: Standard Definition White Light Endoscopy, HD-WLE: High-Definition White Light Endoscopy, Virtual CE: Virtual Chromoendoscopy, NBI: Narrow-Band Imaging, Dye-Based CE: Dye-Based Chromoendoscopy.

Lymphoma Risk in IBD

Therapy-Associated Risk

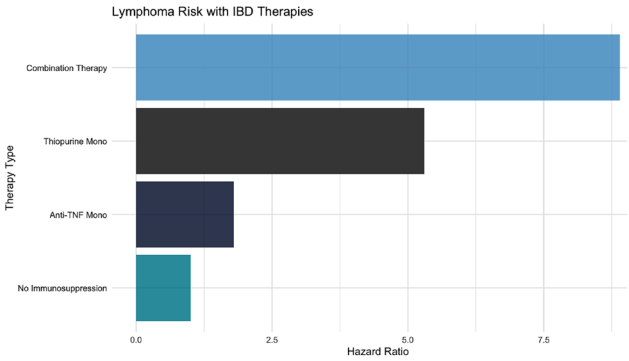

Figure 4: Lymphoma risk associated with different IBD therapies

Lymphoma Subtypes

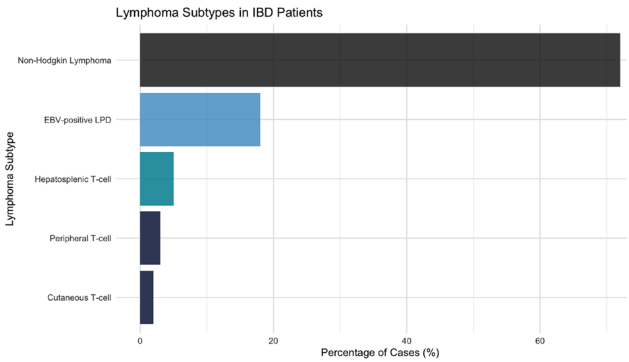

Figure 5: Distribution of lymphoma subtypes in IBD population

Skin Cancer Risks

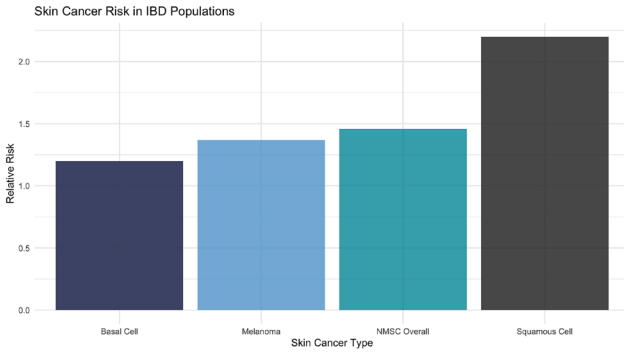

Figure 6: Relative risk of skin cancer in IBD patients

Cervical Cancer Risk

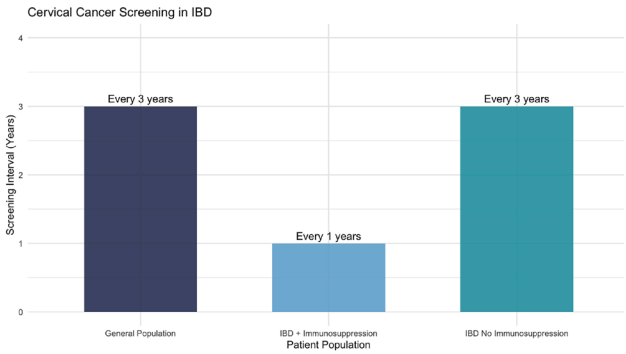

Figure 7: Cervical cancer screening recommendations for IBD patients

Risk Factors and Surveillance

Table 1: Malignancy Risks in IBD

Malignancy	Major Risk Factors	Relative Risk
Colorectal Cancer	Disease duration >8y, PSC, extensive colitis, family history, prior dysplasia	2-3 fold
Lymphoma	Thiopurine use, combination therapy with TNF antagonist, male gender, EBV seronegativity	5.3 fold (thiopurines)
Non-Melanoma Skin Cancer	Thiopurine exposure, chronic UV exposure, fair skin	1.5-2.1 fold
Melanoma	Anti-TNF therapy, family history, intermittent sun exposure	1.4 fold
Cervical Cancer	Immunosuppression, persistent HPV, smoking, reduced screening	1.5-2 fold

Table 2: Surveillance Recommendations

Malignancy	High Risk	Standard Risk	Low Risk
Colorectal Cancer	Annual colonoscopy	1-3 year colonoscopy	5 year colonoscopy
Lymphoma	Clinical monitoring + education	Clinical monitoring	Routine care
Non-Melanoma Skin Cancer	Quarterly dermatology exams	Annual dermatology exams	Sun protection education
Cervical Cancer	Annual Pap smear	1-3 year Pap smear	Routine screening

Management Algorithm

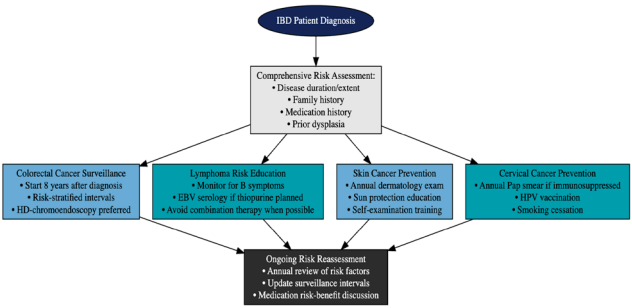

Figure 8: Comprehensive Malignancy Management in IBD

1. Initial Risk Assessment
o Document disease duration and extent
o Review family history and medication exposure
o Assess prior dysplasia history

2. Colorectal Cancer Surveillance
o Begin 8 years after diagnosis for extensive disease
o Use high-definition with either dye spray or virtual chromoendoscopy when available, segmental re-inspection improves detection rate (as opposed to random biopsies)
o Risk-stratified intervals: Annual (high), 1-3 years (intermediate), 5 years (low)

3. Lymphoma Risk Management
o Consider reducing to monotherapy without thiopurine when possible and stable from IBD perspective
o Consider EBV serology before thiopurine initiation (highest risk in patients who seroconvert from EBV negative to positive on thiopurine therapy)
o Educate patients about B symptoms

4. Skin Cancer Prevention
o Annual dermatology exams for immunosuppressed patients
o Sun protection education
o Self-examination training

5. Cervical Cancer Prevention
o Annual Pap smears for women on immunosuppression
o HPV vaccination
o Smoking cessation support

6. Ongoing Monitoring
o Annual review of risk factors
o Adjust surveillance based on new risk factors
o Continuous risk-benefit assessment of medications

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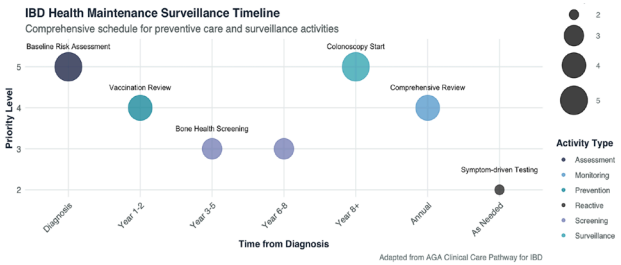
Abdulelah Almutairdi

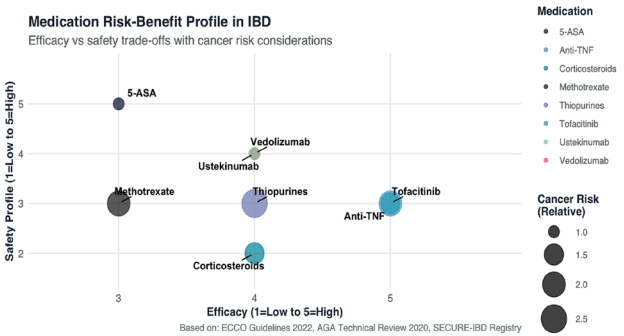
Introduction

Health care maintenance represents a critical component in the comprehensive management of Inflammatory Bowel Disease (IBD), addressing modifiable risk factors, preventive care, and quality of life considerations beyond direct disease control. This chapter provides a comprehensive overview of evidence-based approaches for health maintenance in IBD, including screening protocols, risk stratification, intervention strategies, and specialized care considerations across multiple domains of patient health.

Surveillance Timeline and Intervals



Medication Risk-Benefit Assessment



Smoking and IBD

Impact of Smoking on IBD

Crohn's Disease (CD):

- Disease development and progression: increased disease severity (OR, 1.56).
- Increased risk of disease-related complications (fistulas, strictures).
- Worse medical and surgical outcomes.
- Reduced effectiveness of biologics.
- Increased risk of surgery and higher relapse rates after surgery (OR, 1.97) [1].

Ulcerative Colitis (UC):

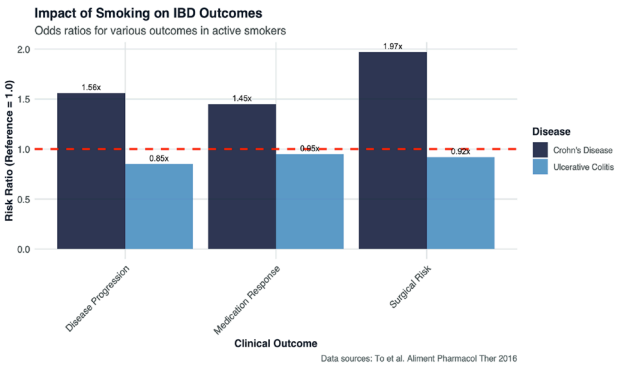
- Paradoxically linked to reduced risk of disease onset in older meta-analyses [2].
- Recent data show no statistically significant impact on natural history [3].
- Quitting smoking may trigger mild flares, but other health benefits of smoking. cessation outweigh risks related to UC.

IBD-associated Colorectal Cancer (CRC):

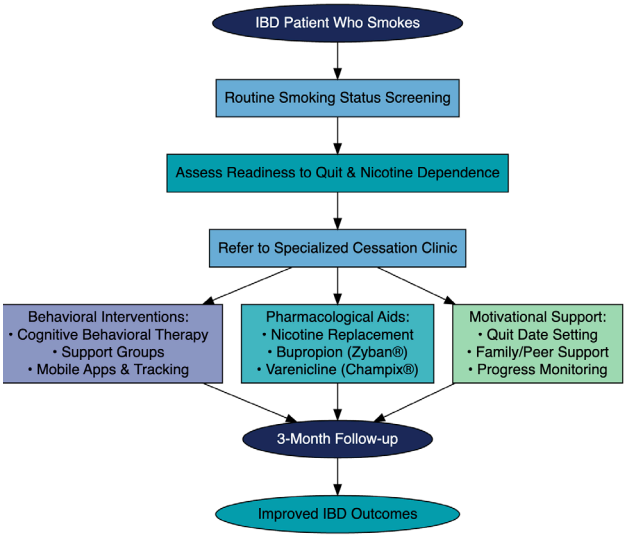
- Retrospective analysis of 1,386 IBD patients showed 11.5% had CRC.
- UC: Higher risk for former smokers (HR 1.73).
- CD: Significantly elevated risk for active smokers (HR 2.20) and passive smoke exposure [4].

Benefits of Quitting Smoking for IBD

- Reduced inflammation and improved treatment response.
- Decreased need for corticosteroids and immunosuppressants.
- Lower risk of post-surgical recurrence in CD [5].



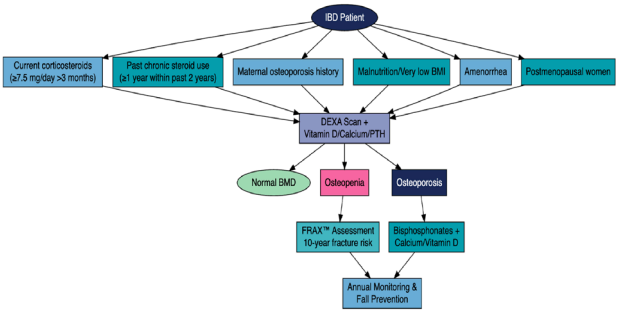
Cessation Strategies



2. Bone Health and IBD

Around 14-42% of IBD patients have osteoporosis, with risk factors including:
- Chronic inflammation.
- Corticosteroid use.
- Low BMI and malnutrition.
- Dietary deficiencies of calcium and vitamin D [6].

Screening Recommendations



Who to screen for osteoporosis:

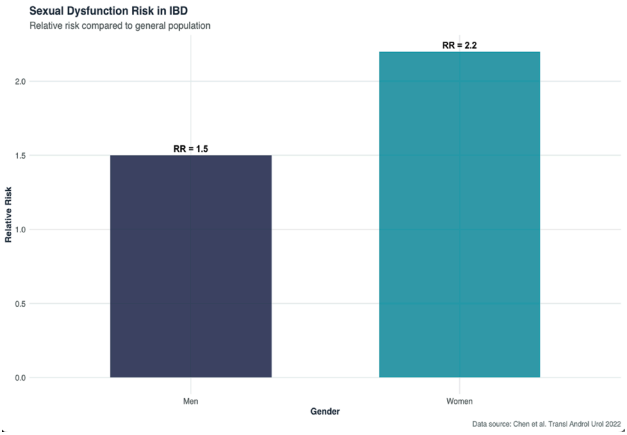
1. Patients starting oral corticosteroid therapy (>3 consecutive months at ≥7.5 mg/day prednisone-equivalent)
2. Inactive disease with past chronic steroid use (≥1 year within past 2 years)
3. Maternal history of osteoporosis
4. Malnourished or very thin patients
5. Amenorrheic patients
6. Postmenopausal women [7,8].

Prevention & Management

- Lifestyle Modifications: Weight-bearing exercise, smoking cessation, alcohol moderation.
- Dietary Support: Calcium intake (1,200 mg/day), vitamin D supplementation (800-2,000 IU/day).
- Medications: Bisphosphonates for diagnosed osteoporosis or high fracture risk, which can be estimated using the FRAXTM Tool [9].

3. Sexual Dysfunction in IBD

Prevalence and Impact



Impact on Men:

- Impaired erectile function (RR = 1.50).
- Poor sexual satisfaction.
- Linked to active disease, fatigue, and corticosteroid use.
- Low testosterone levels in chronic inflammation [10,11].

Impact on Women:

- Increased risk of sexual dysfunction (OR = 2.20).
- Increased dyspareunia [aOR 1.71] and deep dyspareunia [aOR 2.00].
- Fear of pregnancy-related complications [12].

Management Strategies

- Medical: Optimize disease control, manage medication side

effects.
- Psychological: Therapy, address anxiety/depression.
- Physical: Pelvic floor physiotherapy, lubricants, exercise [13].

4. Immunization in IBD

Recommended Vaccination Schedule

Vaccination Recommendations for Immunosuppressed IBD Patients

Vaccine	Schedule	Recommendations
Influenza (Inactivated)	Annual	High-dose if immunosuppressed
Recombinant Zoster (Shingrix)	2-dose series, 2-6 months apart	All ≥50 years and ≥19 if immunosuppressed
Pneumococcal	PCV20/21 once	Age-based recommendations
Hepatitis B	2-3 dose series	Heplisav-B or ENGERIX-B
HPV	3-dose series	18-26 years, consider to 45
Tdap	Per ACIP guidelines	Routine adult vaccination
RSV	Single dose	≥75 years or 60-74 with risk factors

Live Vaccine Considerations

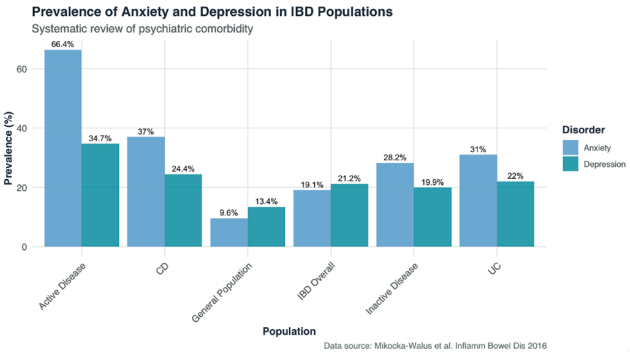
Contraindicated in immunosuppression:
- MMR (Measles, Mumps, Rubella).
- Live Varicella (Chickenpox).

Timing:

- Administer 4 weeks before starting immunosuppressive medication.
- Wait 3 months after discontinuing immunosuppressive medication [14].

5. Mental Health in IBD

Prevalence of Anxiety and Depression



Key Findings:

- Anxiety and depression are 2-3 times more common in IBD patients.
- Both are higher in active disease vs inactive disease.
- Slightly higher prevalence in Crohn's disease vs Ulcerative colitis.
- Poor mental health is linked with increased disease activity, reduced quality of life, treatment non-adherence, and higher hospitalization rates.

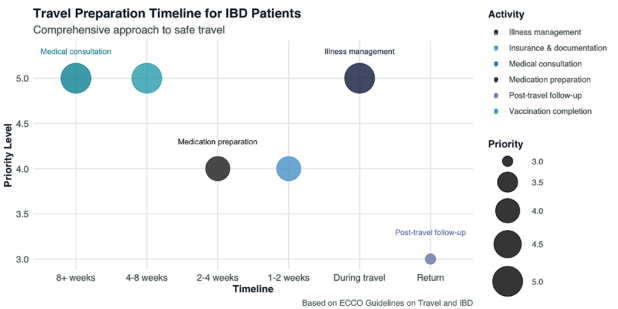
Effective Interventions

- Routine screening with PHQ-9 and GAD-7
- Supportive interventions include psychological therapies (CBT, mindfulness), appropriate medications, and lifestyle measures (exercise, sleep hygiene, social support), online stress reduction programs and integrated psychological care models.
- Referral to psychiatry/psychology should be considered

when mental health significantly impacts function, adherence, or disease activity [15-18].

6. IBD and Travel

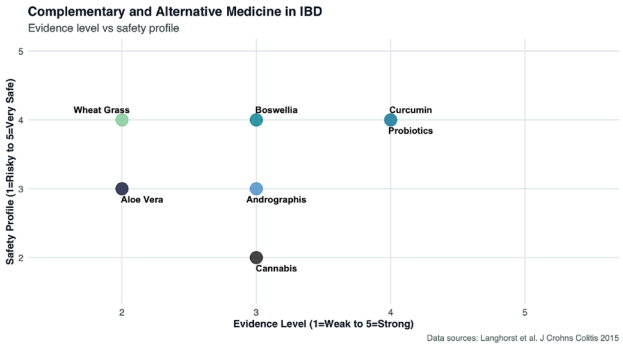
Comprehensive Travel Preparation



Essential Travel Advice:

1. Pre-travel Planning: Consult physician 4-6 weeks before departure.
2. Medications: Carry adequate supply in hand luggage with doctor's letter.
3. Vaccinations: Review status early, avoid live vaccines if immunosuppressed.
4. Insurance: Obtain coverage for pre-existing conditions.
5. Food Safety: Avoid high-risk foods and unsafe water.
6. Emergency Planning: Identify local medical facilities, carry emergency contacts [19].

7. IBD and Complementary and Alternative Medicine (CAM) Evidence-Based CAM Interventions

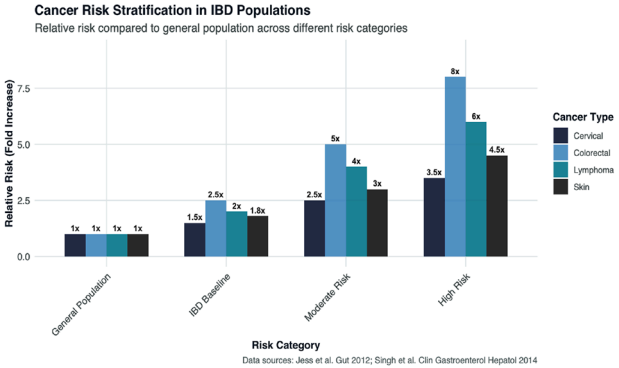


Key Points:

- 30-50% of IBD patients report using CAM.
- Strongest evidence: Curcumin for UC, probiotics for pouchitis.
- Safety concerns: Lack of regulation, potential drug-herb interactions.
- Clinical approach: Supportive, non-judgmental discussion about CAM use [20-29].

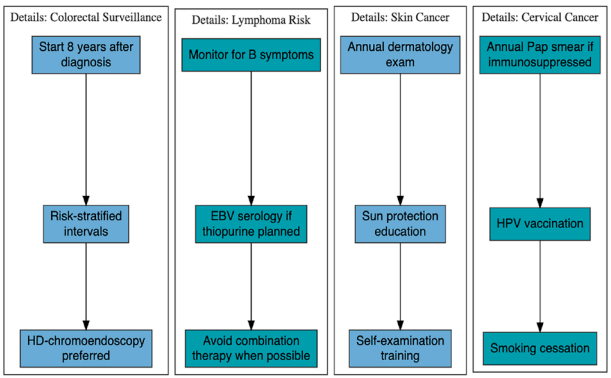
8. Cancer Risk Stratification in IBD

Cancer Risk Stratification in IBD

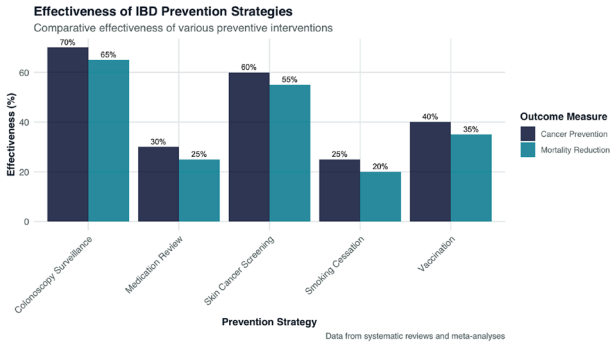


Comprehensive Monitoring Protocol

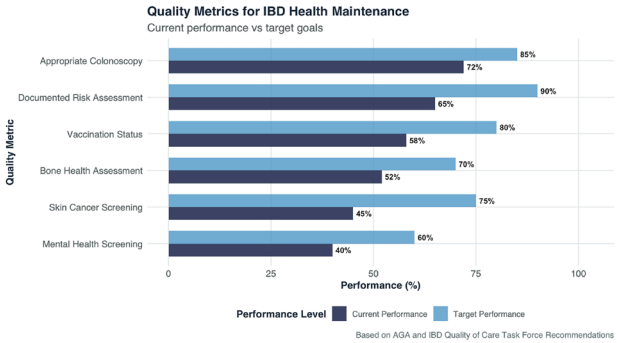
Prevention Strategy Effectiveness



Prevention Strategy Effectiveness



Quality Metrics for IBD Care



Summary and Key Recommendations
Core Principles for IBD Health Maintenance

1. **Comprehensive Baseline Assessment:** Complete evaluation of disease characteristics, family history, and risk factors at diagnosis
2. **Risk-Stratified Surveillance:** Tailor screening intervals and modalities based on individual risk profiles
3. **Multidisciplinary Approach:** Coordinate care between gastroenterology, dermatology, gynecology, and primary care
4. **Patient Education:** Empower patients with knowledge about self-examination and symptom recognition
5. Annual Reassessment: Systematic review and update of surveillance plans based on new data and guidelines

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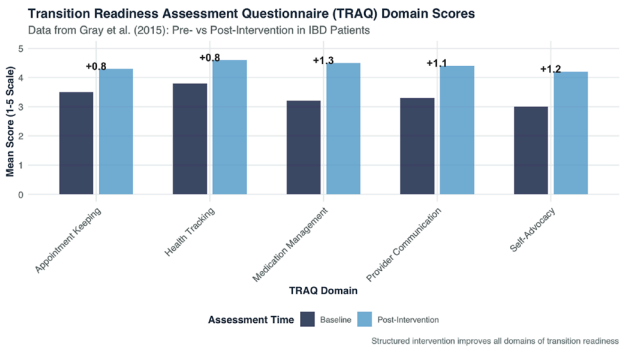
Shakir Bakkari

Introduction

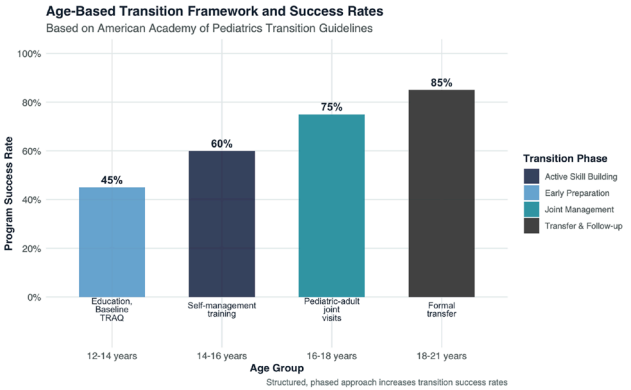
Transition represents the purposeful, planned movement of adolescents and young adults with chronic conditions from child-centered to adult-oriented healthcare systems. In IBD, successful transition is crucial as approximately 25% of patients are diagnosed during childhood/adolescence, facing lifelong disease management. Failed transition correlates with increased emergency department visits (40%), hospitalizations (35%), medication non-adherence (50%), and surgical interventions (20%) compared to structured transition programs. Early introduction and assessment transition planning should commence at age 12-14 years, allowing gradual skill acquisition [1-5].

Transition Readiness Assessment

Transition Readiness Assessment Questionnaire (TRAQ) Scores

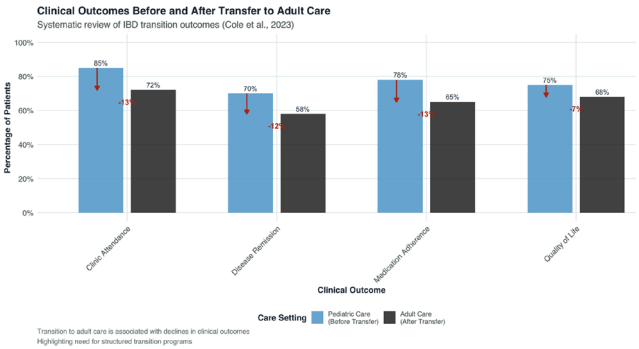


Transition Process Framework

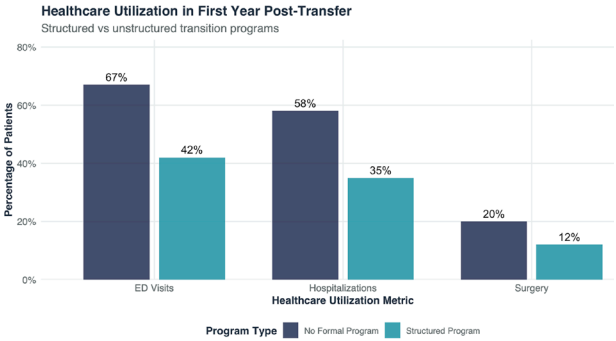


Clinical Outcomes After Transition

Clinical Outcomes



Healthcare Utilization



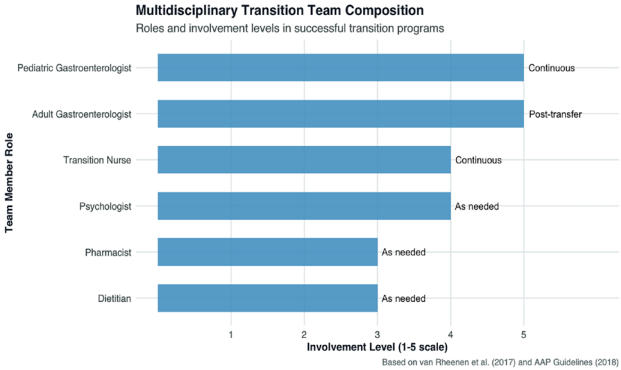
Transition Program Models Comparison

Comparison of Transition Program Models

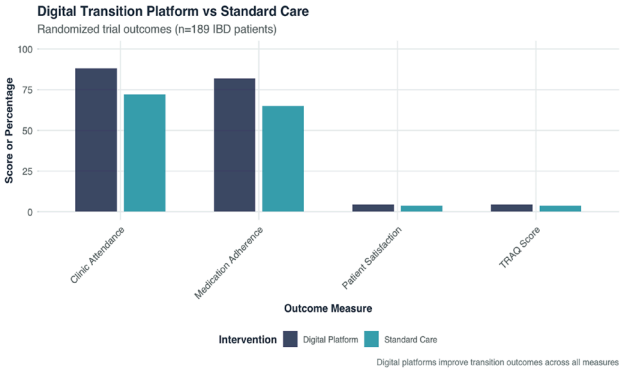
Transition Model	Studies	Patients	Adherence Improvement	Hospitalization Reduction	Patient Satisfaction
Clinic-to-Clinic Transfer	15	1,234	+25%	-15%	3.8/5.0
Joint Transition Clinic	8	567	+45%	-30%	4.5/5.0
Nurse-Led Transition	6	345	+35%	-25%	4.2/5.0
Digital Transition Platform	4	189	+40%	-20%	4.6/5.0

Note:
Data from systematic reviews and meta-analyses

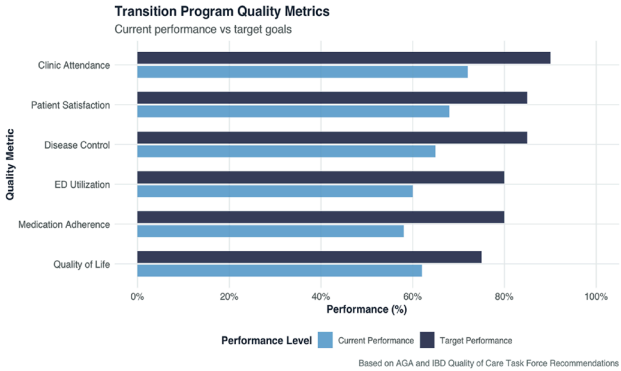
Multidisciplinary Team Approach



Digital Health Interventions

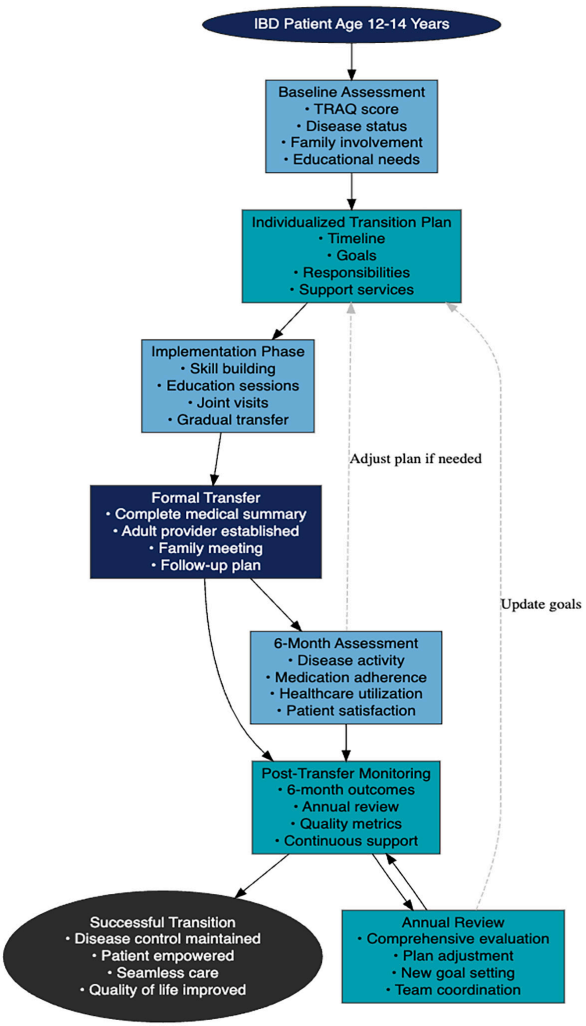


Quality Metrics for Transition Success



Summary and Key Recommendations
Core Principles for Successful IBD Transition [6-20].

1. **Early Introduction:** Begin transition discussions at age 12-14 years to allow adequate preparation time.
2. **Structured Assessment:** Utilize validated tools like TRAQ to evaluate readiness and identify gaps.
3. **Individualized Planning:** Develop personalized transition plans based on patient needs and capabilities.
4. **Multidisciplinary Coordination:** Engage pediatric and adult teams, nurses, psychologists, and social workers.
5. **Gradual Transfer:** Implement joint visits and phased responsibility transfer over 2-3 years when possible.
6. Continuous Monitoring: Track outcomes through 6-month and annual assessments with plan adjustments.
7. **Digital Integration:** Incorporate technology platforms to enhance education and communication.
8. **Family Involvement:** Engage caregivers while gradually shifting responsibility to the patient.
9. **Quality Measurement:** Implement standardized metrics to evaluate program effectiveness.
10. **Ongoing Support:** Provide continuous post-transfer support to ensure long-term success.


IBD Patient Age 12-14 Years
Baseline Assessment
• TRAQ score
• Disease status
• Family involvement
• Educational needs
Individualized Transition Plan
• Timeline
• Goals
• Responsibilities
• Support services
Implementation Phase
• Skill building
• Education sessions
• Joint visits
• Gradual transfer
Adjust plan if needed
Formal Transfer
• Complete medical summary
• Adult provider established
• Family meeting
• Follow-up plan
Update goals
6-Month Assessment
• Disease activity
• Medication adherence
• Healthcare utilization
• Patient satisfaction
Post-Transfer Monitoring
• 6-month outcomes
• Annual review
• Quality metrics
• Continuous support
Successful Transition
• Disease control maintained
• Patient empowered
• Seamless care
• Quality of life improved
Annual Review
• Comprehensive evaluation
• Plan adjustment
• New goal setting
• Team coordination

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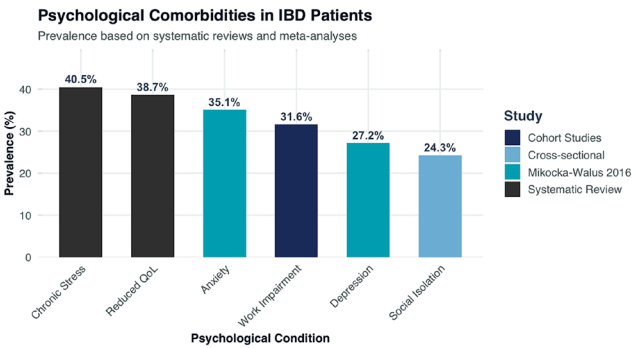
Shakir Bakkari, MD

Introduction

Inflammatory Bowel Disease (IBD) significantly impacts psychological well-being and quality of life. Approximately 30-40% of IBD patients experience anxiety or depression, which can worsen disease outcomes and reduce treatment adherence. Effective counseling and coping strategies are essential components of comprehensive IBD care, addressing the emotional, social, and functional challenges faced by patients [1-4].

Psychological Impact of IBD



Key Psychological Challenges:
Anxiety and Depression: 30-40% prevalence, higher during active disease.

Stress: Chronic stress can trigger symptom flares and worsen disease activity.

Quality of Life Impairment: Physical symptoms significantly impact emotional and social functioning.

Stigma: Embarrassment from symptoms (urgency, incontinence) leads to social withdrawal.

Functional Impairment: Work absenteeism and presenteeism common.

Evidence-Based Counseling Strategies

A. Therapeutic Alliance and Communication

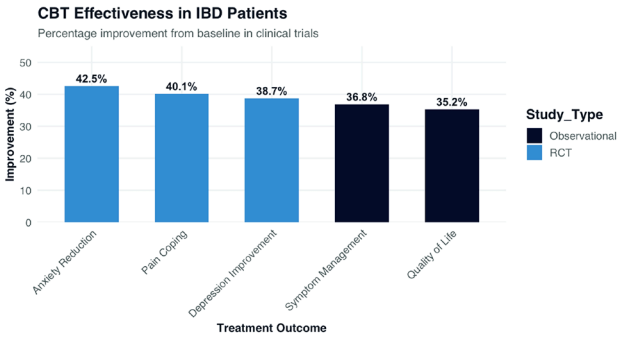
Effective patient-provider relationships are fundamental to IBD care. Key components include:

Therapeutic Alliance Building Strategies

Strategy	Evidence_Level	Impact
Active Listening	Strong	High
Empathetic Communication	Strong	High
Shared Decision Making	Moderate	High
Continuity of Care	Moderate	Moderate
Validation of Concerns	Strong	High

B. Cognitive Behavioral Therapy (CBT) Effectiveness

CBT Components Effective for IBD:
- Cognitive restructuring for illness-related thoughts
- Behavioral activation to counteract withdrawal
- Stress management techniques
- Problem-solving skills training - Relapse prevention planning



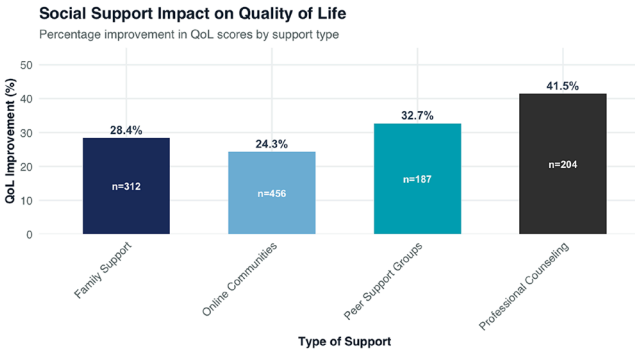
C. Mindfulness-Based Interventions

Mindfulness Interventions for IBD

Technique	Session_Duration	Evidence
Mindfulness-Based Stress Reduction	8 weeks, 2.5 hours/week	Strong (RCTs)
Mindful Breathing	10-20 minutes daily	Moderate
Body Scan Meditation	20-45 minutes, 3x/week	Moderate
Loving-Kindness Meditation	15-20 minutes daily	Limited
Mindful Movement	30 minutes, 3x/week	Moderate

Coping Mechanisms and Self-Management

A. Social Support Systems



B. Stress Management Techniques

Evidence-based stress management strategies include:

Stress Management Techniques for IBD

Technique	Frequency	Evidence_Level	Application
Progressive Muscle Relaxation	15-20 minutes daily	Strong	Muscle tension relief
Deep Breathing	5-10 minutes as needed	Moderate	Acute anxiety reduction
Guided Imagery	10-15 minutes, 3x/week	Moderate	Pain/distraction
Biofeedback	30 minutes, 2x/week	Limited	Symptom awareness
Yoga/Tai Chi	30-60 minutes, 2-3x/week	Moderate	Mind-body integration

C. Lifestyle Modifications

Lifestyle Interventions for IBD Management

Intervention	Impact	Evidence	Recommendation
Regular Exercise	Moderate	Cohort studies	150 min moderate/week
Sleep Hygiene	High	Observational	7-9 hours/night
Balanced Nutrition	High	Systematic reviews	Individualized plans
Smoking Cessation	Critical	Strong (RCTs)	Complete cessation

Addressing Specific Patient Challenges

A. Flare-up Preparedness

Flare-up Preparedness Components and Effectiveness

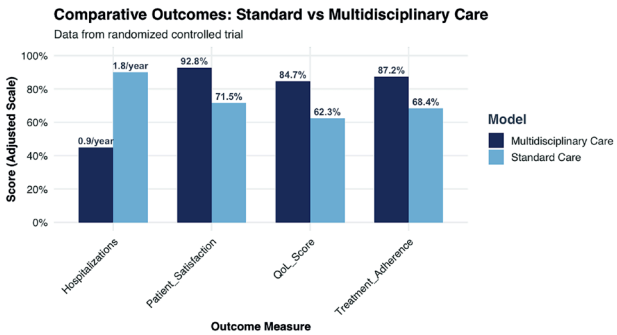
Component	Implementation	Effectiveness
Emergency Medication Kit	>85%	High
Bathroom Access Plan	78%	High
Healthcare Contact List	92%	High
Work/School Accommodation	65%	Moderate
Support Network	71%	High

B. Sexual Health and Body Image

Approximately 40-50% of IBD patients report sexual dysfunction, with higher rates during active disease [5]. Counseling should address:

- Medication effects on sexual function
- Body image concerns related to surgeries/stomas
- Communication strategies with partners
- Fertility concerns and family planning

Multidisciplinary Care Models



Multidisciplinary Team Components [6]:

- **Gastroenterologist:** Medical management leadership
- **IBD Nurse Specialist:** Patient education and coordination
- **Psychologist/Psychiatrist:** Mental health support
- **Dietitian:** Nutritional counseling
- **Social Worker:** Resource navigation and support
- **Primary Care Physician:** Comprehensive health maintenance

Implementation Framework

Counseling Implementation Framework

Step	Tools	Frequency	Responsible
Screening	HADS, PHQ-9, GAD-7	At diagnosis and annually	All providers
Assessment	Clinical interview, QoL measures	As needed	Psychologist/GI
Intervention Planning	Shared decision making, goal setting	Every 3-6 months	Multidisciplinary team
Implementation	CBT, mindfulness, support groups	Weekly to monthly	Therapist/Patient
Monitoring	Regular follow-up, symptom tracking	Monthly to quarterly	GI/Psychologist
Adjustment	Treatment modification based on response	As needed	Multidisciplinary team

Summary and Clinical Recommendations

1. **Routine Screening:** Implement validated tools (PHQ-9, GAD-7) for all IBD patients
2. **Integrated Care:** Develop multidisciplinary care pathways including mental health
3. **Evidence-Based Interventions:** Offer CBT and mindfulness-based interventions
4. **Patient Education:** Provide comprehensive information about disease and coping
5. **Social Support:** Facilitate connections with peer support groups
6. **Regular Follow-up:** Monitor psychological status alongside disease activity
7. **Personalized Approach:** Tailor interventions to individual needs and preferences

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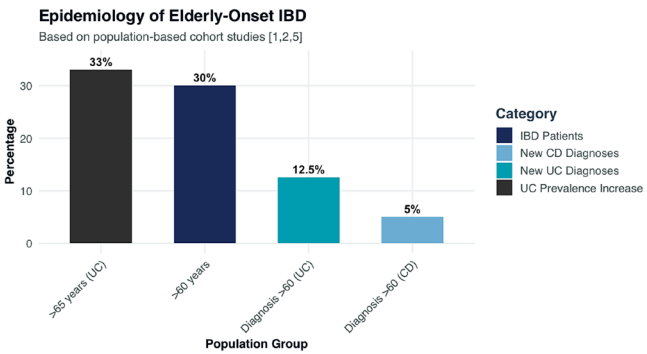
Ahmed Al-Darmaki & Ehab AbuFarhaneh

Introduction

Inflammatory bowel disease (IBD), presents unique diagnostic and therapeutic challenges when it occurs in specific populations such as the elderly and patients with significant comorbidities or immunosuppression. In these groups, disease phenotype, natural history, treatment response, and risk–benefit considerations often differ from the general IBD population, necessitating individualized management strategies. Understanding population-specific factors—including growth and development, frailty, reproductive health, infection risk, and drug safety—is essential to optimize outcomes while minimizing complications.

Inflammatory Bowel Disease in the Elderly

IBD is increasingly prevalent in older populations. While historically considered a disease of young adults, up to 30% of IBD patients are now over 60 years old, and approximately 10-15% of new diagnoses occur after age 60 [1,2].



Clinical Groups in Elderly IBD

1. Elderly-onset IBD (EOIBD): Patients diagnosed with IBD at age ≥ 60 years. It often presents with distinct clinical characteristics, such as more isolated colonic involvement in CD, and a tendency for left-sided disease in UC. Compared to younger patients, elderly individuals with IBD typically have a lower prevalence of extraintestinal manifestations, are less likely to experience disease progression, and are less frequently treated with immunosuppressants or biologics [3,4].

2. Aging with IBD: Patients diagnosed earlier in life now aging with a chronic disease that is typically not associated with high mortality rates, although carries significant morbidity.

Table 1: Comparison of Elderly-Onset vs. Younger-Onset IBD [3,4]

Feature	Elderly_Onset	Younger_Onset
Common Location (CD)	Colonic	Ileal/Ileocolonic
UC Extent	Left-sided/Distal	Pancolitis more common
Disease Behavior (CD)	Inflammatory	Complicated (stricturing/penetrating)
Extraintestinal Manifestations	Less common	More common
Immunosuppressive Use	Less frequent	More frequent
Surgery	Lower cumulative risk	Higher cumulative risk
Diagnostic Delay	More likely	Less likely

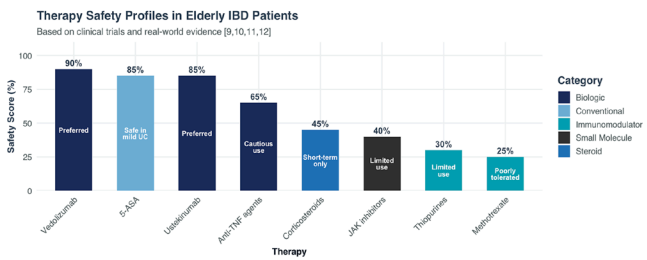


Table 1: Summery of elderly IBD therapies [5-7].

Therapy	Use in Elderly	Comments
Anti-TNF agents	Effective but higher risk of infection, malignancy	Discontinuation common; avoid combination therapy in frail or high-risk patients.
Vedolizumab	Preferred first-line in many centers; safer profile	Lower systemic risk; favourable infection profile; suitable in multimorbid, frail patients
Ustekinumab/IL23	Safe and well-tolerated in older patients	No increase in adverse events compared with placebo in meta-analysis of all RCTs (IBD and non-IBD). Limited data yet re: age-specific risk, suitable in patients ≥70 years.
JAK inhibitors	Use with caution; restricted to select cases	Elevated risk of VTE, CV events, and herpes zoster; requires risk-benefit analysis, give only if no other option.
S1P modulators (e.g., ozanimod)	Limited data; caution in elderly	Monitor for bradycardia, liver enzyme elevations; avoid in CV disease or polypharmacy
Corticosteroids	Short-term only; avoid chronic use	Associated with delirium, infection, fractures; taper early and transition to maintenance. Use enteral coated sterids wherever possible.

Therapy	Use in Elderly	Comments
5-ASA	Safe in mild UC; not for Crohn's	Monitor renal function; watch pill burden in cognitively impaired patients
Thiopurines	Limited use due to toxicity, avoid after age of 60 years.	Risk of lymphoma, skin cancer; avoid unless no alternative; requires age-specific caution
Methotrexate	Poorly tolerated; limited role	Hepatotoxicity and cytopenia risks are high in elderly; often not preferred
Surgery	Consider frailty; elective preferred	Outcomes better with elective surgery; pre-op frailty and nutrition optimization essential

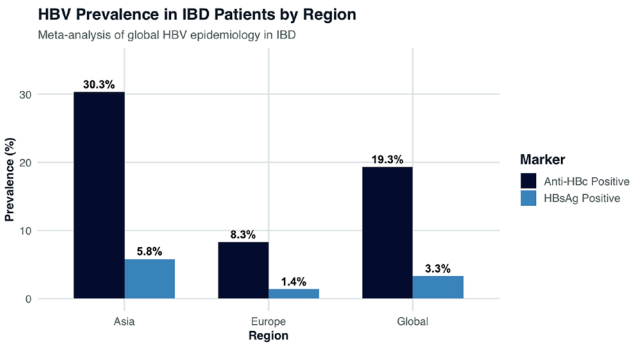
Therapeutic Considerations

• **Assess frailty and functional status** regularly to guide treatment intensity.
• Avoid thiopurines, methotrexate and long-term corticosteroids due to higher risk of adverse effects.
• Consider early biologic initiation in case of steroids need.
• **Simplify regimens, and prefer** vedolizumab or ustekinumab due to better safety in older adults.
• **Use anti-TNFs cautiously**, especially in fit patients with limited alternatives.
• Limit JAK inhibitors to carefully selected cases with close monitoring.
• **Ensure vaccination** against pneumococcus, zoster, and influenza before immunosuppression.
• **Do not undertreat**—active inflammation can lead to worse outcomes than therapy risks.

• **Involve caregivers** and plan for social support, monitoring, and adherence.
• **Tailor surveillance** strategies for cancer, bone density, and malnutrition.

Hepatitis B Virus Management in IBD Patients

HBV prevalence among IBD patients varies significantly by region with global HBsAg positivity of 3.3% in IBD patients, but with marked regional differences. HBV reactivation is defined as reappearance of HBsAg or significant HBV DNA increase in previously inactive infection. Risk depends on baseline serologic status and immunosuppressive regimen:
• **HBsAg-positive patients:** Up to 50% reactivation rate without prophylaxis, especially with anti-TNF agents or corticosteroids.
• **HbsAg-negative, Anti-HBc-positive patients:** 1-10% reactivation risk, reported with thiopurines, anti-TNF agents, and JAK inhibitors.

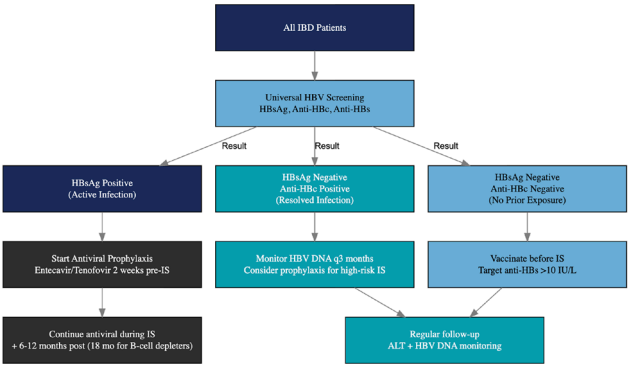


HBV Reactivation Risk by Medication Class [8,9]

Table 2: HBV Reactivation Risk by IBD Medications

Risk_Level	HBsAg_Positive	HBsAg_Negative	Action
High (>10%)	Anti-TNF agents, Corticosteroids (>4 weeks, >20 mg/day), JAK inhibitors	Corticosteroids (>40 mg/day)	Antiviral prophylaxis mandatory
Moderate (1-10%)	Ustekinumab, Other anti-IL23 agents, S1P modulators	Anti-TNF agents, JAK inhibitors, Ustekinumab, Anti-IL23 agents, S1P modulators	Prophylaxis or intensive monitoring (q3 months)
Low (<1%)	Azathioprine, Methotrexate, Mycophenolate, Corticosteroids (low-dose), Vedolizumab	Azathioprine, Methotrexate, Mycophenolate, Corticosteroids (<40 mg/day ≤1 week), Vedolizumab	Regular monitoring may suffice

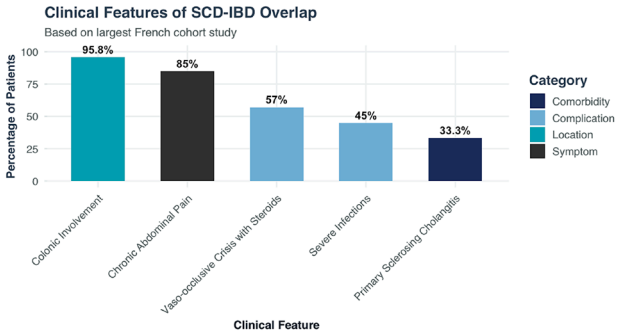
Management Algorithm for HBV in IBD



IBD in Patients with Sickle Cell Disease

The coexistence of sickle cell disease (SCD) and autoimmune diseases like IBD is rare but clinically important as it appears to be associated with both a severe phenotype of autoimmune disease and worsening of SCD [10]. Historically, limited reports have made it difficult to define the true overlap, though both diseases share key immunoinflammatory pathways such as TNF-α, IL-6, and neutrophil extracellular

traps that may contribute to organ injury in both conditions [11,12]. The baseline hyperinflammatory state in SCD can exacerbate IBD activity, while intestinal microvascular occlusion may mimic IBD-related ischemic changes. Clinically, overlapping features such as chronic abdominal pain and anemia complicate diagnosis, often leading to delays in identifying IBD in SCD patients.



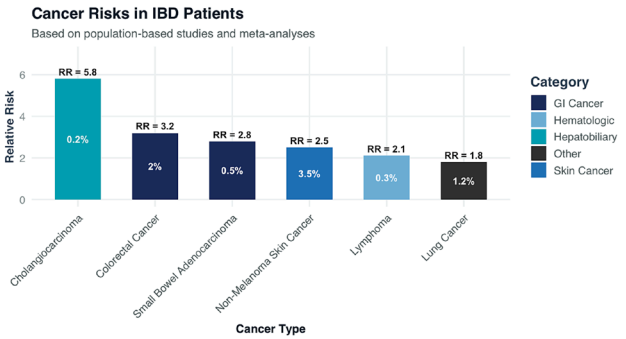
Therapeutic Recommendations for SCD-IBD

Table 3: Therapeutic Considerations in SCD-IBD Patients

Therapy	Recommendation	Risk_Level
Corticosteroids	Limit to short courses; consider VOE prophylaxis	High
Hydroxyurea	May reduce VOC risk when used with steroids	Low
Red Blood Cell Transfusion	Consider with steroids to reduce VOC risk	Low
Vedolizumab	Preferred due to gut-selectivity	Low
Ustekinumab	Preferred due to safety profile	Low
Anti-TNF agents	Use with caution; monitor for infections	Moderate
JAK inhibitors	Use with extreme caution	High

IBD in Patients with Malignancy

IBD patients have an increased risk of malignancies due to chronic inflammation and prolonged immunosuppressive therapy. Colorectal cancer risk in IBD is linked to chronic colonic inflammation, with recent data showing cumulative risks of 1%, 2%, and 5% at 10, 20, and >20 years, respectively, and this risk is more than 3-fold higher in those with PSC. While also increased, small bowel adenocarcinoma, neuroendocrine tumors, intestinal lymphoma, and anal cancers remain rare. Patients with IBD also have increased risks of cholangiocarcinoma, NMSC, hematologic malignancy, and lung cancer. The challenge lies in balancing disease control with minimizing cancer recurrence risk [13].



IBD Drug Management in Patients with Cancer

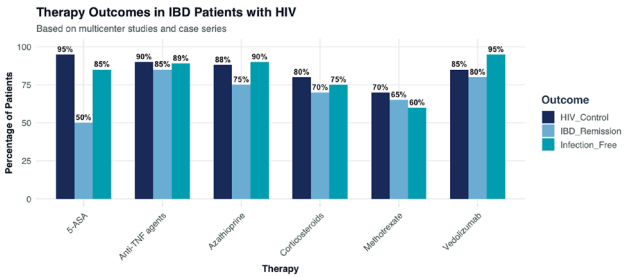
Clinical Box: IBD Drug Management in Patients with Cancer

Cancer_Scenario	Thiopurines	Anti_TNFs	VDZ_UST	JAK_S1P
Lymphoma	Stop (AGA, ECCO)	Consider stopping (AGA)	Acceptable/Preferred (ECCO)	Limited data; use with caution (AGA)
Melanoma	Avoid (ECCO)	Stop (AGA)	Acceptable (AGA, ECCO)	Limited data; avoid if alternatives
Recurrent NMSC	Stop thiopurine (AGA)	Continue (AGA)	Acceptable	Limited data
HPV-related lesions	Avoid thiopurine (ECCO)	No specific restriction	Acceptable (ECCO)	Limited data
Recent high-risk cancer	Avoid for ≥2 years (ECCO)	Cautious use (AGA/ECCO)	Preferred (ECCO)	Not preferred due to safety concerns
Prior low-risk cancer	May resume (AGA/ECCO)	May resume (AGA/ECCO)	Safe and preferred (AGA/ECCO)	Acceptable with close monitoring

Note:
AGA: American Gastroenterological Association; ECCO: European Crohn's and Colitis Organisation

IBD with Concomitant HIV Infection

The relationship between HIV and IBD is complex. HIV infection can influence the course of IBD and may even attenuate its severity. However, IBD can still develop due to the immune imbalance caused by HIV—particularly the reduction in CD4+ T cells and an increase in CD8+ T cells. When managing IBD in patients living with HIV, treatment decisions should be guided by the patient's CD4+ count, HIV viral load, and the presence or risk of opportunistic infections. The goals of therapy are to induce and maintain remission, prevent complications, and improve quality of life—while maintaining immune function and virologic control. A multidisciplinary approach involving gastroenterologists, infectious disease specialists, and pharmacists is essential to optimize outcomes and minimize complications [14,15].



Key Management Principles for HIV-IBD

Management Principles for IBD in HIV Patients

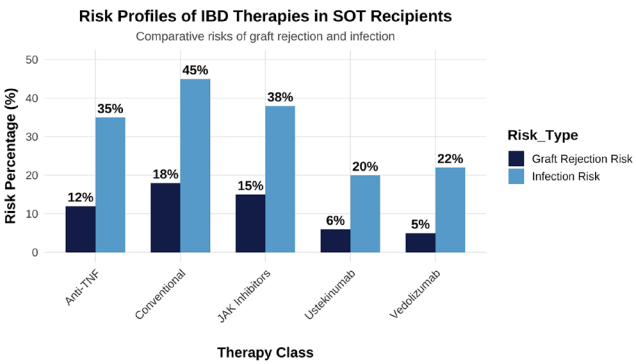
Principle	Importance	Action
CD4+ Count >200	Critical	Required for immunosuppression
Undetectable Viral Load	Critical	Required for immunosuppression
Multidisciplinary Care	Essential	Gastroenterologist + ID specialist
Drug Interaction Review	Essential	Check ART interactions
Vedolizumab Preference	Recommended	Gut-selective mechanism preferred
Monitor for OIs	Essential	Regular screening

IBD Post-Solid Organ Transplant

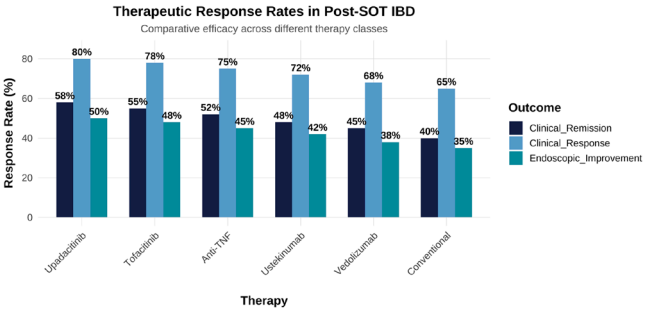
Solid organ transplant (SOT) patients who have undergone heart, kidney, liver, small bowel or lung transplants require lifelong immunosuppression to maintain graft survival, which significantly alters immune system function, thereby possibly modifying the natural history of IBD. As a result, IBD in this population often exhibits itself as an atypical disease, thereby requiring therapeutic decision-making to carefully balance the risk of graft rejection with the need for effective IBD inflammation control.

Past literature shows that historically, therapeutic options for IBD after SOT have been limited due to concerns about complications in the form of infections, drug-to-drug interactions, and the probable risk of graft rejection with the use of additional immunosuppressive agents. However, emerging studies now suggest that modern biologics and small-molecule therapies may be used safely in this population with appropriate monitoring and to individualize therapy according to the type of transplanted organ, baseline immunosuppressive regimen, and infection risk profile [16].

Safety Profiles of IBD Therapies in SOT Recipients

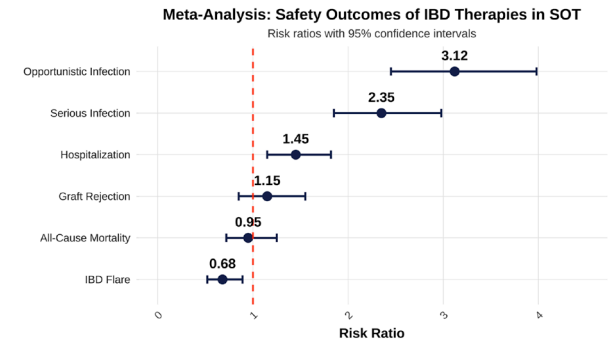


Therapeutic Response Rates



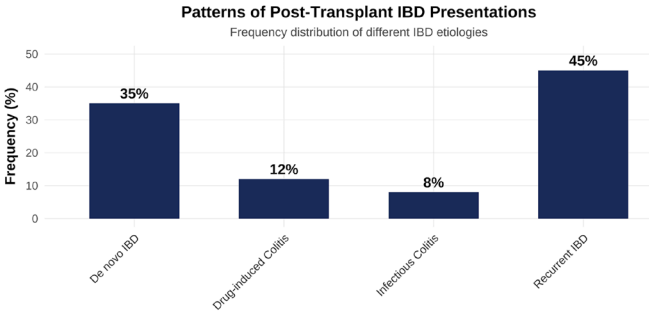
A recent study aimed to analyze the effectiveness and safety of biologic and small molecule therapy for the treatment of IBD among SOT recipients showed that biologic agents were a promising therapy for the treatment of IBD in patients who underwent SOT, since they did not increase the risk of infectious or serious complications [17].

A meta-analysis assessed the safety of biologics such as anti-TNF, anti-integrin, anti-IL12/23, and small molecules, including tofacitinib, Upadacitinib in transplant recipients with IBD. Their pooled analysis demonstrated no statistically significant increase in the risk of mortality or transplant rejection. However, the risk of infections, particularly opportunistic ones, remained elevated compared to non-transplant IBD populations [18].



Clinical Patterns and Disease Course

Post SOT, it is not uncommon to see the co-occurrence of IBD as a de novo disease or as a reactivation and exacerbation of pre-existing IBD [19].



Management Algorithm

Summary

This chapter highli ghts the unique challenges in managing IBD in special populations. Key takeaways include:

1. Elderly IBD: Requires careful consideration of frailty, comorbidities, and polypharmacy with preferential use of vedolizumab/ustekinumab

2. HBV Management: Universal screening and appropriate prophylaxis based on serologic status and immunosuppression risk

3. SCD-IBD: Multidisciplinary approach with caution regarding corticosteroid-induced VOCs

4. Cancer-IBD: Individualized therapy selection based on cancer type, timing, and recurrence risk

5. HIV-IBD: Treat HIV to target CD4+ count >200 and viral suppression with multidisciplinary collaboration

6. **Post SOT:** Multidisciplinary collaboration, infection prophylaxis, and patient monitoring. For regions like Saudi Arabia, where both transplantation and IBD prevalence are rising, establishing national guidelines and collaborative policies could help generate local data, inform practice, and improve patient outcomes.

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Chapter 27: Emerging Technologies, AI and Endoscopic Therapies in IBD

Ahmad Najdat Bazarbashi & Ehab Abufarhaneh

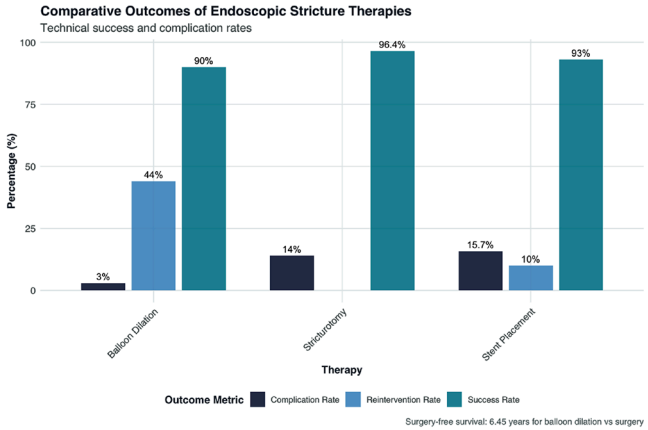
Introduction

Interventional endoscopy has revolutionized IBD management since it was first formalized in 2018 [1]. This minimally invasive subspecialty offers alternatives to surgery for strictures, dysplasia, fistulas, and postoperative complications. Approximately 30-50% of IBD patients develop strictures requiring intervention, while colorectal cancer risk in UC remains 2-5% despite modern therapies [2,3].

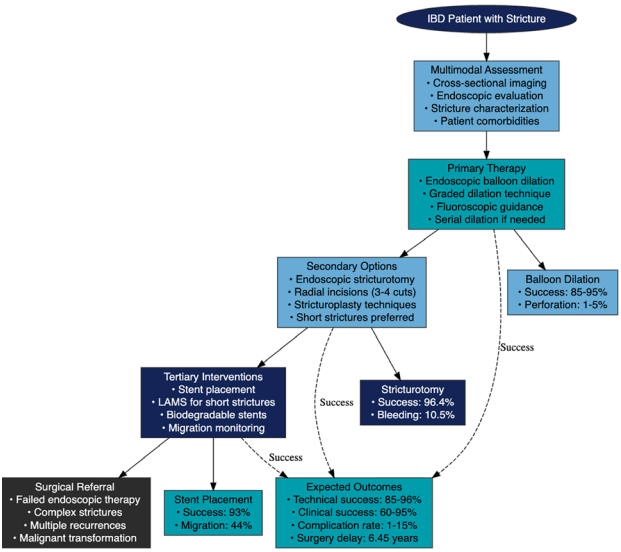
Endoscopic Management of IBD-Related Strictures

Strictures affect up to 70% of Crohn's patients within 10 years. Endoscopic approaches can delay or potentially avoid surgery in 85-95% of cases, although many patients treated endoscopically will require multiple interventions [4-6].

Comparative Efficacy of Stricture Therapies



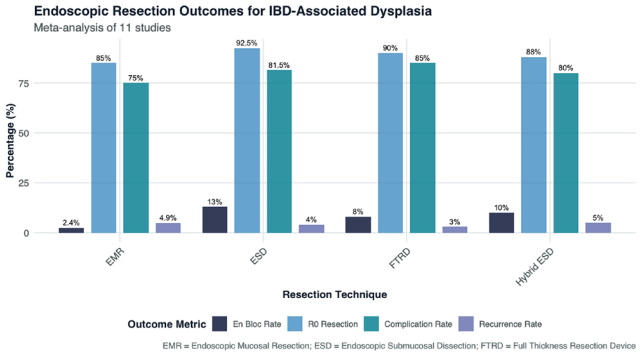
Stricture Management Algorithm



Endoscopic Management of IBD-Associated Dysplasia

Colorectal cancer risk in UC patients is 2-5% with modern surveillance. Endoscopic resection achieves 97.9% success with low complication rates [5-7].

Endoscopic Resection Techniques for Dysplasia



Treatment Selection Guidelines

Endoscopic Treatment Guidelines for IBD-Associated Dysplasia

Lesion Type	Recommended Treatment	Expected Success Rate	Complication Risk
Small, simple (<10 mm, pedunculated)	Standard polypectomy (cold/hot snare)	>95%	Low (<2%)
Polypoid/non-polypoid ≤20 mm, clear borders	En bloc EMR (preferred) or piecemeal EMR	85-90%	Moderate (2-5%)
Non-polypoid >20 mm, clear borders	ESD or hybrid ESD (preferred)	81.5-92.5%	High (5-13%)
Indistinct borders or invasive features	ESD/FTRD for T1; Surgery for T2+	75-85%	Variable

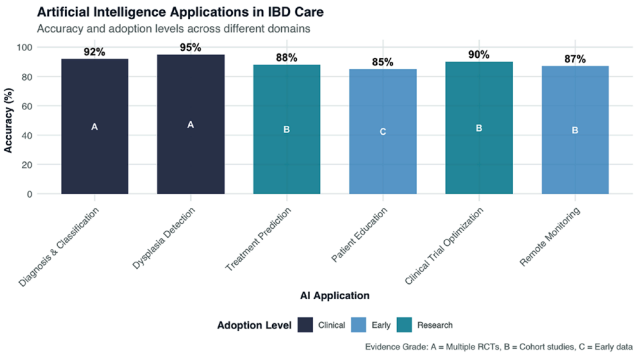
Note:
Based on international consensus and meta-analysis data

Artificial Intelligence in IBD Management

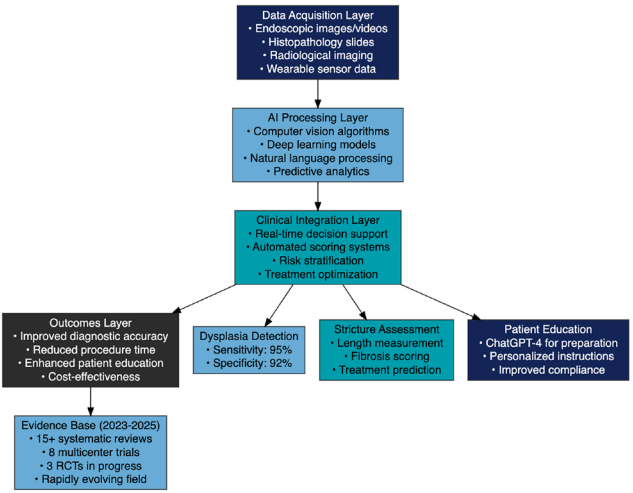
AI encompasses a spectrum of tools, including Machine Learning, deep learning, computer vision AI, and generative AI, all of which are being applied across several stages of IBD care. These range from Diagnosis and Subtype classification via AI-aided imaging, severity assessment by using AI to help read endoscopic image results, using ML-based systems which have enhanced the detection of dysplasia and early cancerous changes in biopsy specimens and simplifying CT and MRI image result. Furthermore, predictive models allow clinicians to anticipate flares and

assess treatment response, while AI-driven patient selection and automated scoring have optimized clinical trial design and reduced costs [8-10].

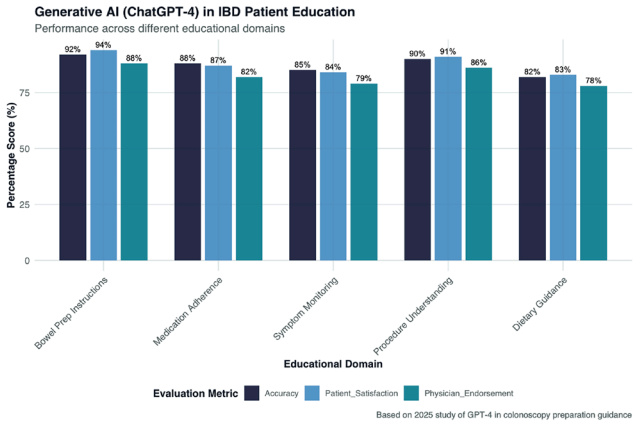
AI Applications Across the IBD Care Continuum



AI Integration Framework for IBD Endoscopy



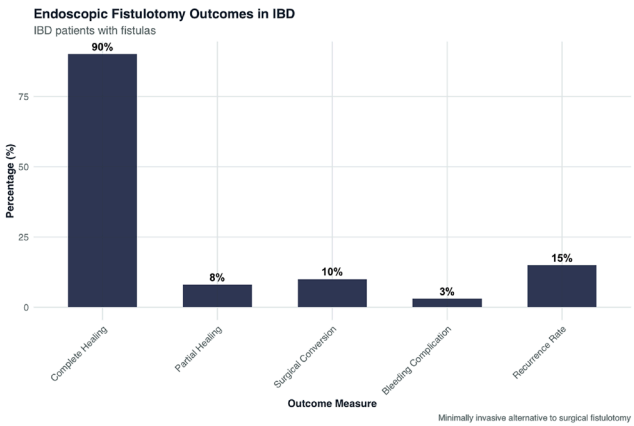
Generative AI in Patient Education



Novel Endoscopic Interventions

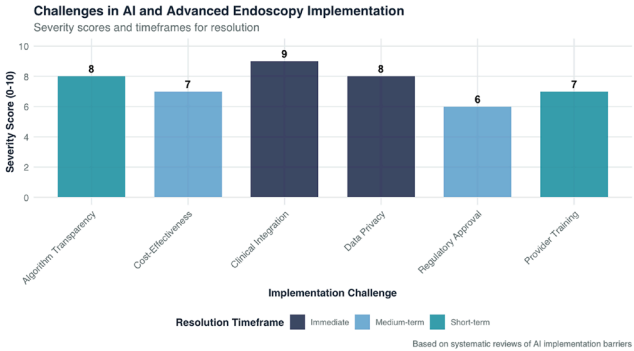
Beyond stricture and dysplasia management, endoscopic techniques address fistulas, leaks, and other IBD complications.

Endoscopic Fistulotomy Outcomes



Future Directions and Challenges

Implementation Challenges



Summary and Key Recommendations

Core Principles of Interventional IBD and AI Integration

1. **Individualized Approach:** Stricture therapy selection based on location, length, fibrosis, and patient factors
2. **Stepped Therapy Algorithm:** Balloon dilation → stricturotomy → stent placement → surgery
3. **Dysplasia Management:** En bloc resection preferred; ESD for lesions >20mm or poor lifting
4. **AI as Augmentation:** Computer-aided detection supports but doesn't replace clinician judgment
5. **Multidisciplinary Integration:** AI tools integrated into existing IBD care pathways
6. **Patient-Centered Education:** Generative AI for personalized preparation and instruction
7. **Validation and Standardization:** Multicenter validation of AI algorithms before clinical use
8. **Ethical Considerations:** Transparent algorithms, data privacy, and equitable access
9. **Continuous Learning:** AI systems that adapt to new data and clinical experience

10. **Cost-Benefit Analysis:** Evaluate AI implementation against clinical outcomes and resource use

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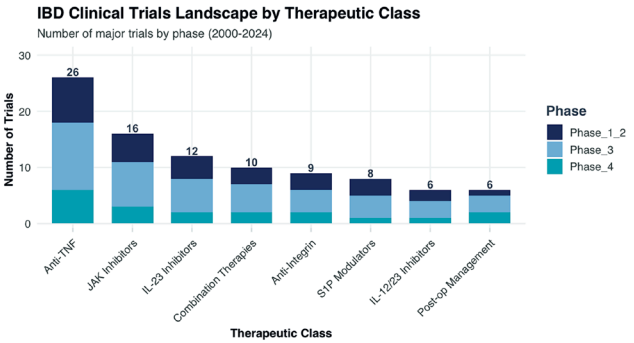
Chapter 28: Clinical Trials in IBD

Hend Almuhaya & Turki AlAmeel

Introduction

Clinical trials form the cornerstone of evidence-based management in inflammatory bowel disease (IBD). This chapter systematically reviews landmark and contemporary trials across therapeutic domains, providing a comprehensive evidence base for clinical decision-making in Crohn's disease (CD) and ulcerative colitis (UC). The trials are organized by therapeutic class and clinical scenario, with emphasis on comparative effectiveness, safety, and practical implications.



A. Head-to-Head Comparative Trials

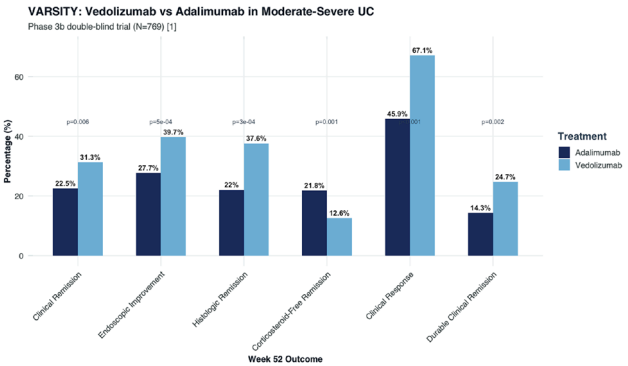
1. VARSITY Trial

Vedolizumab vs Adalimumab for Moderate-to-Severe UC

Study Design: Phase 3b, double-blind, double-dummy, randomized trial

- **Primary endpoint:** Clinical remission at week 52
- **Secondary endpoint:** Endoscopic improvement, steroid-free remission at week 52 which was assessed only in patients who were receiving corticosteroids at baseline.

Result:



Conclusion:
Vedolizumab was superior to Adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Comment:
Dose escalation not allowed during the trial. Some TNF non-responders were permitted. Some outcomes achieved with vedolizumab by week 6 were already superior to adalimumab. Post-hoc analyses have demonstrated consistent effects across other endpoints including histological response.

Reference: Sands BE et al. N Engl J Med 2019;381:1215-1226

2. SEAVUE Trial

Ustekinumab vs Adalimumab in patients with Moderate-to-Severe CD

Study Design: Randomized, double-blind, parallel-group, active-comparator, phase 3b trial

- Biologic-naive adults (≥18 years) with moderate-to-severe Crohn's disease, unresponsive or intolerant to conventional therapy (or corticosteroid-dependent), and at least one ulcer on baseline endoscopy.
- Patients were randomly assigned to receive:
  o Ustekinumab (~6 mg/kg IV on day 0, then 90 mg SC q8 weeks) vs Adalimumab (160 mg on day 0, 80 mg at 2 weeks, then 40 mg once q2 weeks, SC) through week 56
- **Primary endpoint:** Clinical remission (CDAI score <150) at week 52
- **Secondary endpoints:** Corticosteroid-free remission, clinical response, endoscopic improvement, endoscopic remission at week 52 and clinical remission at week 16.

Result:

Table 1: SEAVUE Trial - Comprehensive Outcomes (Biologic-Naïve CD) [2]

Timepoint	Endpoint	Ustekinumab	Adalimumab	Difference	p_value
Early Response (Week 16)					
Week 16	**Clinical Remission**	57.1%	60.0%	-2.9%	0.58
Week 16	**Clinical Response**	72.9%	70.0%	+2.9%	0.52
Maintenance (Week 52)					
Week 52	**Clinical Remission**	64.9%	61.0%	+3.9%	0.42
Week 52	**Endoscopic Remission**	28.5%	30.7%	-2.2%	0.68
Week 52	**Steroid-Free Remission**	60.7%	57.4%	+3.3%	0.56
Week 52	**Clinical Response**	72.3%	66.2%	+6.1%	0.18

Conclusion:
There was no significant difference in the primary outcome between the treatments, although both were effective in this population of biologic-naïve patients with CD.
Reference: Sands BE et al. Lancet 2022;399:2200-2211

3. LYRIC Trial

Laparoscopic ileocaecal resection vs Infliximab for terminal ileitis in CD

Study Design: Randomized, controlled, open-label, multicenter trial.

- Adults aged 18–80 years with non-stricturing, ileocaecal Crohn's disease unresponsive to at least 3 months of conventional therapy (corticosteroids, thiopurines, or methotrexate) were randomized to either Infliximab vs ileocaecal resection.
- Exclusion criteria: Diseased terminal ileum >40 cm or presence of abdominal abscesses
- **Primary endpoint:** Quality of life on the Inflammatory Bowel Disease Questionnaire at 1year
- **Secondary endpoint:** General quality of life (SF-36) health survey and its physical and mental component subscales, days unable to participate in social life, days on sick leave, morbidity and body image and cosmesis.

Result:

Domain	Resection	Infliximab	p_value	Clinical_Implication
Quality of Life (IBDQ)	No difference	No difference	0.82	Comparable
Quality of Life (SF-36 Physical)	No difference	No difference	0.67	Comparable
Quality of Life (SF-36 Mental)	No difference	No difference	0.91	Comparable
Days on Sick Leave	3.4 days	1.4 days	<0.0001	Significant difference
Hospital Readmissions	6%	4%	0.45	Comparable
Surgical Complications	12%	8%	0.31	Comparable

Conclusion:

Laparoscopic resection in patients with limited (diseased terminal ileum <40 cm), non-stricturing, ileocaecal Crohn's disease in whom conventional therapy has failed, could be considered a reasonable alternative to infliximab therapy.

Reference: Ponsioen CY et al. Lancet Gastroenterol Hepatol 2017;2:785-792

4. SEQUENCE Trial

Risankizumab vs Ustekinumab in Moderate-to-Severe CD

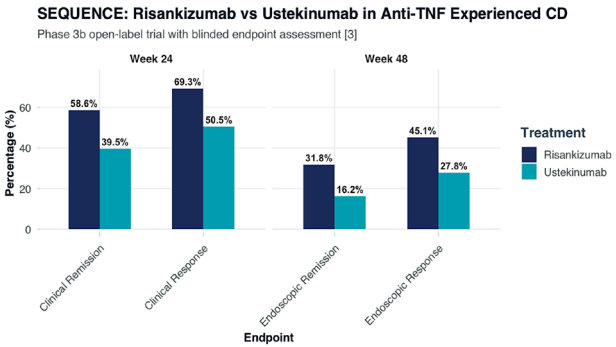
Study Design: Phase 3b, multicenter, open-label, randomized, controlled trial with blinded assessment of end points.

- Patients with moderate-to-severe Crohn's disease who had had an inadequate response to

Anti TNF therapy or unacceptable side effects with such therapy were randomly assigned to receive Risankizumab or Ustekinumab at standard doses for 48 weeks

- **Primary endpoint:** Non-inferiority for Clinical remission at week 24 (CDAI score <150) & superiority for endoscopic remission at week 48

Result:



Conclusion:

In this head-to-head clinical trial of Risankizumab and Ustekinumab involving patients with moderate-to-severe Crohn's disease who had had unacceptable side effects with anti-TNF therapy or an inadequate response to such therapy, Risankizumab was noninferior to Ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48.

Reference: Ferrante M et al. N Engl J Med 2024;390:1270-1281

B. Combination Therapy studies

1. SONIC Trial

Infliximab, Azathioprine, or Combination Therapy for CD

Study Design: Randomized, double-blind

• Patient with moderate-to-severe Crohn's disease with no prior immunosuppressive or biologic therapy were randomly assigned to receive either:

o IV Infliximab (IFX) 5mg/kg induction dose then q8weeks

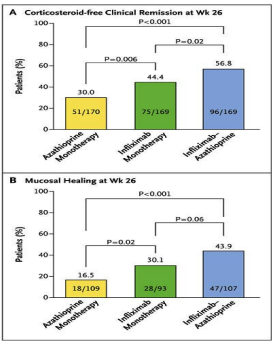
o Azathioprine (AZA) 2.5mg/kg

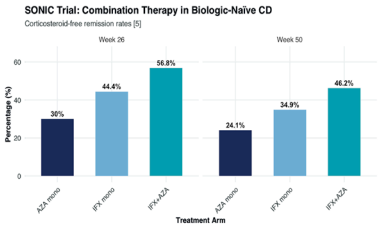
o Combination therapy (IFX+AZA)

• **Primary endpoint:** Rate of corticosteroid-free clinical remission at week 26.

• **Secondary endpoint:** Mucosal healing at week 26, the rate of any remission, response-70, response-100, the IBDQ score, corticosteroid dose at each data-collection time point, CRP level from baseline to week 26.

Result:





Conclusion:

Combination therapy superior to monotherapies for steroid-free remission.

Antibodies to infliximab were detected in 0.9% receiving combination therapy vs 14.6% receiving infliximab.

Reference: Colombel JF et al. N Engl J Med 2010;362:1383-1395

2. DIAMOND Trial

Adalimumab Monotherapy and Combination with Azathioprine for CD

Study Design: Multicenter, randomized, prospective, open-labelled study.

- **Primary endpoint:** Clinical remission at week 26.
- **Secondary endpoint:** The rates of clinical remission at the other time points, the rate of a clinical response at each time point and rates of mucosal improvement at Weeks 26 and 52.

Result:

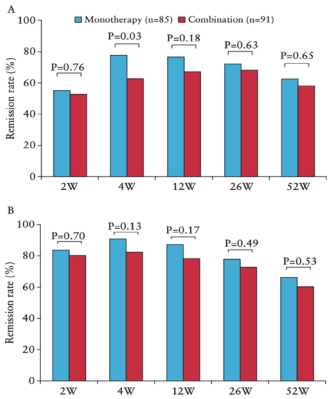


Figure 3. Rates of clinical remission [A] and clinical response [B].

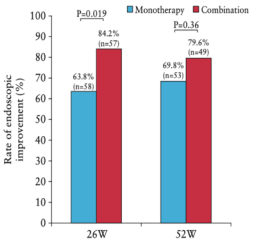


Figure 4. Comparison of the rates of endoscopic improvement at Weeks 26 and 52.

Conclusion:

The clinical efficacy of a combination of adalimumab and azathioprine at Week 26 did not differ from that of adalimumab monotherapy in patients with Crohn's disease naïve to both medications.

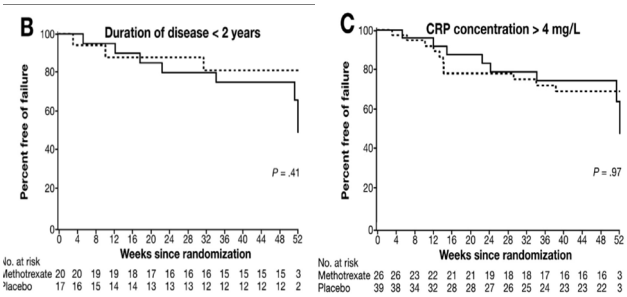
Reference: J Crohns Colitis. 2016 Nov;10(11):1259-1266.

3. COMMIT Trial

Infliximab vs Combination Infliximab and Methotrexate in Moderate-to-Severe CD

• **Primary endpoint:** Time to treatment failure, defined as a lack of prednisone-free remission (CD Activity Index, <150) at week 14 or failure to maintain remission through week 50.
• **Secondary endpoint:** Proportion of patients who achieved overall treatment success (defined by achieving prednisone-free remission at week 14 and maintenance of this remission through week 50), the proportion of patients who achieved prednisone-free remission at week 14, the mean change in the CDAI and SF-36 scores, the median change in serum CRP, the median serum infliximab concentration, the proportion of patients who developed antibodies to infliximab.

Result:



Conclusion:
The combination of infliximab and methotrexate, although safe, was no more effective than infliximab alone in patients with CD receiving treatment with prednisone. No clinically meaningful differences were observed in secondary outcomes and combination therapy was well tolerated.
Reference: Gastroenterology. 2014 Mar;146(3):681-688.e1.

4. SUCCESS Trial

Infliximab vs Azathioprine vs Combination Therapy in Moderate-to-Severe UC

Study Design: Randomized double-blind trial

• Patient with Moderate to Severe UC, anti-TNF naive and AZA-naive or off AZA for 3 months.

• Randomized to receive:

o IFX monotherapy (5 mg/kg IV)

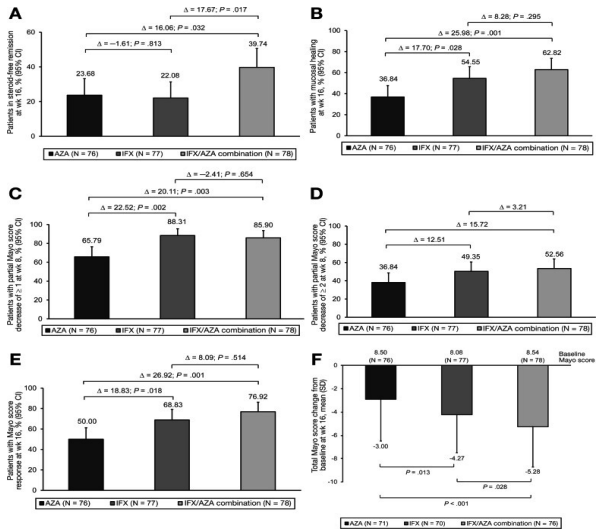
o AZA monotherapy (2.5 mg/kg daily)

o Combination therapy (5 mg/kg IFX + 2.5 mg/kg AZA daily)

• **Primary endpoint:** Corticosteroids-free remission at week 16.

• **Secondary endpoint:** Partial Mayo response at week 8, total Mayo score response at week16 (defined as a decrease in the total Mayo score of ≥3 points and at least a 30% decrease from baseline Mayo score), Mucosal healing (Mayo endoscopy subscore of 0 or 1) at week16, and changes in mean Mayo score.

Result:



Conclusion:
Anti-TNF naive patients with moderate to severe UC treated with IFX-+AZA were more likely to achieve corticosteroid free remission at 16 weeks than those receiving either monotherapy. Combination therapy led to significantly better mucosal healing than AZA monotherapy.
Reference: Panaccione et al. Gastroenterology, Volume 146, Issue 2, 392 - 400.e3

Summary: DIAMOND, COMMIT, and SUCCESS Trials

Table 3: Comparative Analysis of Combination Therapy Trials

Trial	Design	Population	Combination	Primary_Endpoint	Result	Key_Message
DIAMOND (CD)	Open-label, randomized	Immunosuppressant-naïve CD	ADA + AZA	Clinical remission week 26	No difference (71.8% vs 68.1%)	No added benefit of combination
COMMIT (CD)	Double-blind, placebo-controlled	Moderate-severe CD on prednisone	IFX + MTX	Time to treatment failure week 50	No difference (30.6% vs 29.8%)	MTX adds no benefit with IFX+steroids
SUCCESS (UC)	Double-blind, randomized	Moderate-severe UC, anti-TNF naïve	IFX + AZA	Steroid-free remission week 16	Superior (39.7% vs 22.1%)	Combination superior to monotherapy

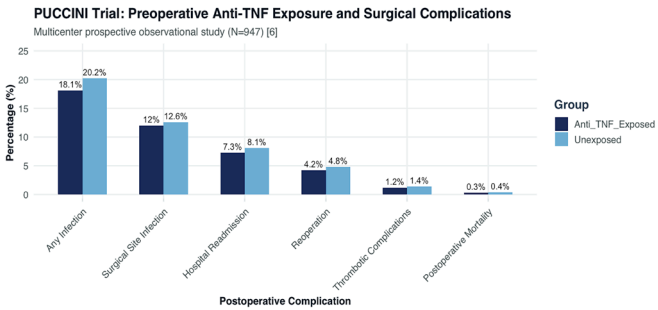
1. PUCCINI

Safety of Preoperative Anti-TNF Exposure in Patients with IBD Undergoing Intra-abdominal Surgery

Study Design: Prospective, multicenter observational study

- A total of 947 patients with IBD, more than two-thirds had CD
- **Primary endpoint:** Occurrence of any infection within 30 days of surgery.
- **Secondary endpoint:** Hospital readmission within 30 days of surgery, reoperation within 30 days of surgery, 30-day postoperative mortality, duration of postoperative hospitalization, thrombotic complication within 30 days of surgery, and hypomotility complication (ileus >5 days or small-bowel obstruction).

Result:



Conclusion: No association between preoperative anti-TNF exposure and postoperative infections. Detectable drug levels not associated with increased complications and this supports the safety of continuing biologics perioperatively.

Reference: Cohen B et al. Gastroenterology 2022;163:1011-1022

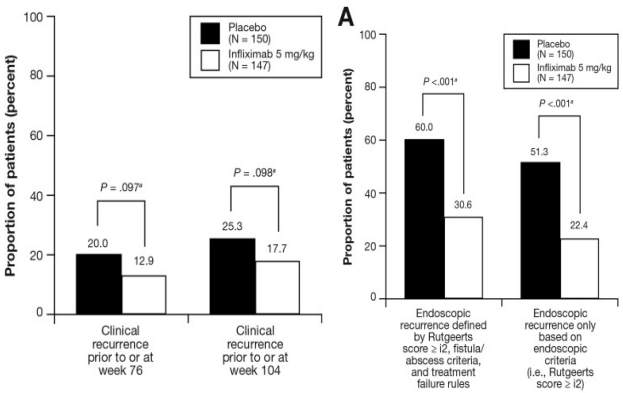
2. PREVENT Trial

Infliximab vs Placebo to Prevent CD Recurrence

Study Design: Randomized, double-blind

- **Primary endpoint:** Clinical recurrence before or at week 76.
- **Secondary endpoint:** Endoscopic recurrence by Rutgeert score.

Result:



Conclusion:

Infliximab is not superior to placebo in preventing clinical recurrence after CD-related resection. However, infliximab does reduce endoscopic recurrence. Risk factors for clinical recurrence were patients previously treated with anti-TNF or those who had more than one resection.

Reference: Regueiro M et al. Gastroenterology. 2016 Jun;150(7):1568-1578

3. REPREVIO Trial

Vedolizumab to Prevent Postoperative Recurrence of CD

Study Design: Randomized, double-blind, placebo-controlled trial

- Patients aged 18 or older with Crohn's disease who underwent ileocolonic resection and had one or more risk factors for recurrence were randomized to vedolizumab 300 mg at weeks 0,8,16 and 24 vs placebo.
- Patients were stratified based on disease behavior
- **Primary endpoint:** The distribution of modified Rutgeerts scores between treatment groups at week 26
- **Secondary endpoint:**

o The proportion of patients with severe endoscopic recurrence of Crohn's disease (defined as a modified Rutgeerts score ≥i2b) at week 26.

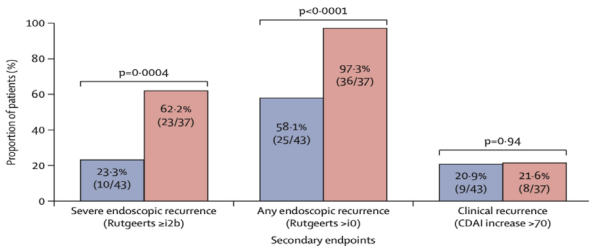
o Proportion of patients with any endoscopic recurrence of Crohn's disease (defined as a modified Rutgeerts score >i0) at week 26

o Clinical recurrence

o Adverse events and serious adverse events

Result:

- Primary endpoint: patients in the vedolizumab group had a 77·8% (95% CI 66·4–86·3, p<0·0001) probability of having a lower modified Rutgeerts score than patients in the placebo group.



- **Secondary endpoint:**

Conclusion:

Vedolizumab treatment within 4 weeks of ileocolonic resection was more likely to prevent endoscopic CD recurrence than placebo.

Reference: D'Haens G et al. Lancet Gastroenterol Hepatol. 2025 Jan;10(1):26-33.

4. POCER Trial

CD Management after Intestinal Resection

Study Design: Randomized, double-blind

- **Initial drug therapy for both groups:** all patients received 3 months of metronidazole.
- Further therapy was stratified according to the predicted risk of recurrence:
  - o High-risk patients received thiopurine and if intolerant, received adalimumab.
  - o Low-risk patients only completed the metronidazole without additional therapy.
- All patients had colonoscopy at 18 months
- **Primary endpoint:** Presence and severity of endoscopic recurrence at 18 months after surgery using the Rutgeerts score.

Result:

Endoscopic recurrence at 18 months was lower in the active care group (49%) than the standard of care group (67%), p=0.03. Complete mucosal normality was maintained in (22%) in the active care group versus (8%) in the standard care group (p=0·03). The incidence and type of adverse and severe adverse events did not differ significantly between patients in the active care and standard care groups

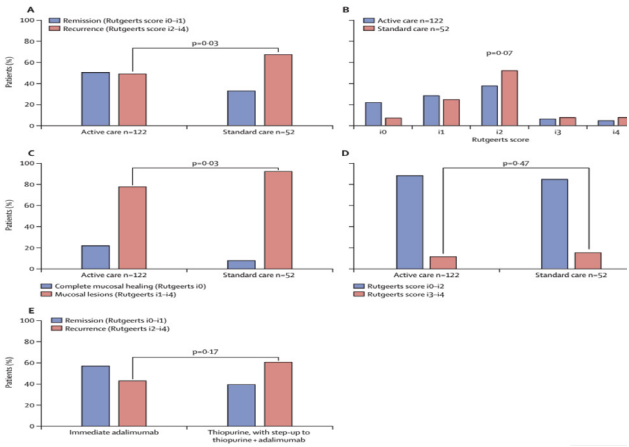


Figure: Endoscopic outcomes at 18 months postoperatively in modified intention-to-treat analysis

Conclusion: Treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of postoperative CD recurrence.
Reference: De Cruz P et al. Lancet. 2015 Apr 11;385(9976):1406-17.

Summary: Postoperative Recurrence Prevention Trials

Table 4: Postoperative Recurrence Prevention Trials in CD

Trial	Agent	Design	Population	Primary_Endpoint	Result	Reference
PREVENT	Infliximab	Double-blind, RCT	CD post-resection with ≥1 risk factor	Clinical recurrence week 76	No diff in clinical recurrence (12.9% vs 20.0%, p=0.97); Endoscopic recurrence lower (30.6% vs 60.0%, p<0.001)	[7]
REPREVIO	Vedolizumab	Double-blind, RCT	CD post-ileocolonic resection with ≥1 risk factor	Modified Rutgeerts score distribution week 26	Vedolizumab superior (p<0.0001)	[8]
POCER	Risk-stratified management	Randomized, controlled	CD post-resection	Endoscopic recurrence week 18	Active care superior (49% vs 67%, p=0.03)	[9]

D. ASUC Rescue Therapy Studies

1. CONSTRUCT Trial

Infliximab vs Cyclosporin in ASUC

Study Design: Randomized trial

- **Primary endpoint:** Quality-adjusted survival
- **Secondary endpoint:** Change in Crohn's and Ulcerative Colitis Questionnaire (CUCQ) and change in two generic quality-of-life measures, mortality, incidence of colectomy, both emergency and planned, and length of stay.

Result:

No Significant Difference in terms of quality-adjusted survival, colectomy rates, secondary outcome including time to colectomy between infliximab and cyclosporin groups and no differences in serious adverse events

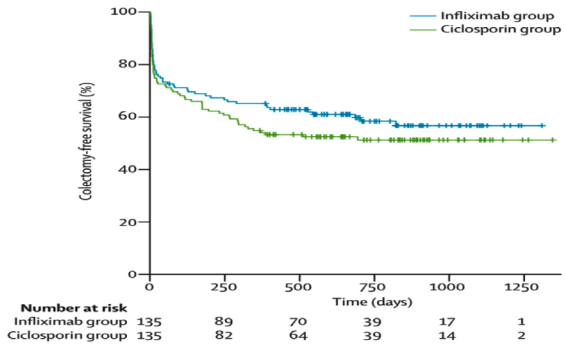


Figure: Time to colectomy

Conclusion:

There was no significant difference between ciclosporin (cyclosporine) and infliximab in clinical effectiveness

Reference: Williams JG et al. Lancet Gastroenterol Hepatol. 2016 Sep;1(1):15-24.

2. CYSIF Trial

Infliximab vs Cyclosporin in ASUC

Study Design: Open-label, randomized controlled trial

• **Primary endpoint:** Treatment failure defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy, or death,

Result:

No significant differences in clinical response in day 7 (cyclosporin (86%) versus IFX (84%)), treatment failure day 98 (60%) cyclosporin versus (54%) infliximab and adverse events (16%) cyclosporin versus (25%) infliximab.

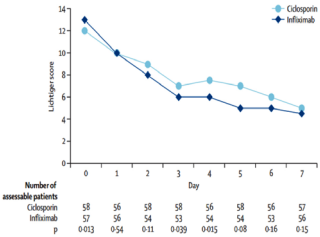


Figure 1: Lichtiger scores from day 0 to day 7, by treatment

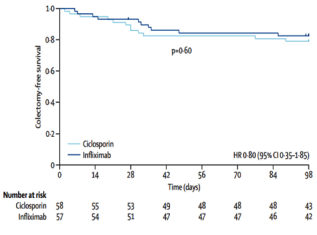


Figure 2: Kaplan-Meier curves for colectomy-free survival

Conclusion:

Cyclosporin was not more effective than Infliximab in patients with ASUC refractory to intravenous steroids. In clinical practice, treatment choice should be guided by physician and center experience.

Reference: The Lancet, Volume 380, Issue 9857, 1909 - 1915

3. TACOS Trial
Tofacitinib versus Placebo in ASUC

Study Design: single-center, double-blind, placebo-controlled trial randomized
• Adult patients admitted with ASUC were randomized to receive tofacitinib 10 mg q8h or matching placebo for 7 days while continuing IV steroids
• After day 7 the study was unblinded as an open label. All patients received tapering steroids, those in tofacitinib arm continued tofacitinib 10 mg BD and the placebo arm on 5 ASA +thiopurine"
• **Primary endpoint:** Response to treatment
• **Secondary endpoint:** Cumulative probability of requiring initiation of infliximab or undergoing colectomy within 90 days following randomization.

Result:

Table 5: TACOS Trial - Tofacitinib in ASUC [10]

Timepoint	Outcome	Tofacitinib	Placebo	Effect_Size	p_value
Day 7	Treatment Response	83.0%	58.8%	OR 3.42	0.007
Day 7	Need for Rescue Therapy	11.3%	31.4%	OR 0.27	0.01
Day 90	Cumulative Rescue Probability	13%	38%	HR 0.31	0.003
Day 90	Colectomy Rate	6.3%	17.6%	RR 0.36	0.04

Conclusion:
In patients with ASUC, combination of tofacitinib and corticosteroids improved treatment responsiveness and decreased the need for rescue therapy
Reference: Singh A et al. Am J Gastroenterol. 2024 Jul 1;119(7):1365-1372.

4. PREDICT-UC Trial

Intensified vs standard dose Infliximab induction therapy for ASUC

Study Design: Open-label, multicenter randomized controlled trial in Australia with 138 patients.
Compared standard (5 mg/kg) vs. intensified (10 mg/kg or accelerated 5 mg/kg at weeks 0, 1, 3) infliximab induction.
Primary endpoint: Clinical response by Day 7
Secondary endpoint: Remission/colectomy rates at 3 months.
o Patients aged ≥18 years with intravenous steroid-refractory ASUC were randomized to receive a first dose of 10mg/kg (Intensified induction strategy (IIS)) or 5 mg/kg IFX (standard induction strategy (SIS)) or (accelerated induction strategy (AIS))

IIS (10 mg/kg):
o First dose of 10 mg/kg at week 0.
o Second dose at day 7 (or earlier) if no response

Patients receiving 5 mg/Kg were randomized between:
SIS (5 mg/kg):
• 5 mg/kg at weeks 0, 2, and 6.
• Extra 5 mg/kg dose between day 3 and day 7 if no response.
AIS (5 mg/kg):
• 5 mg/kg at weeks 0, 1, and 3.
• Week 1 dose increased to 10 mg/kg if no response by day 7.
• **Primary endpoint:** Clinical response by day 7
• **Secondary endpoint:** Assessed outcomes to day 7 and exploratory outcomes compared induction regimens until month 3.

Result:
o Clinical response at day 7: ***10 mg/kg Infliximab (IIS)*** (65%) vs ***5 mg/kg Infliximab (SIS & AIS)*** (61%) , p=0.32
o After 2nd randomization, clinical response at day 14 was 74% IIS group vs 73% AIS group vs 68% SIS group, p=0.81
o No significant differences in clinical remission, steroid free, endoscopic remission, and colectomy at months 3 in all groups

Conclusion:
In steroid-refractory ASUC, a first dose of 10 mg/kg IFX was not superior to 5 mg/kg IFX in achieving clinical response by day 7. Intensi-

fied, accelerated, and standard induction regimens did not result in a significant difference in clinical response by day 14 or in remission or colectomy rates by month 3.

Comment:
In 5mg/kg initial dose, 22% lower response rate seen with low albumin <25 Vs ≥ 25g/L, similar result with CRP ≥ 50 mg/L. Proactive Intensified induction strategies may benefit in patient with low Albumin <25 or high CRP ≥ 50
Reference: Choy MC et al. Gastroenterol Hepatol. 2024 Nov;9(11):981-996.

E. Advanced Therapy for Pouchitis

EARNEST Trial

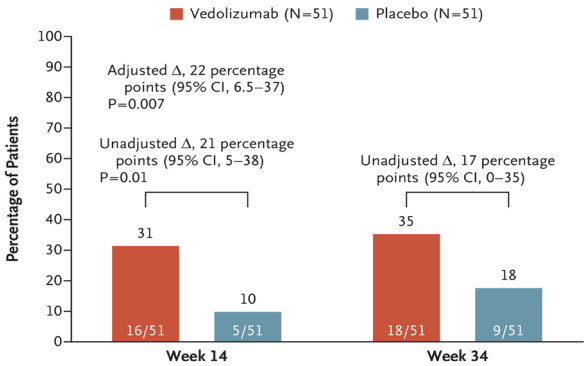
Vedolizumab in patients with UC who underwent IPAA

Study Design: A phase 4 randomized, double-blind trial aimed to evaluate vedolizumab in adult patients in whom chronic pouchitis had developed after undergoing IPAA for UC

• Patients were assigned (in a 1:1 ratio) to receive vedolizumab intravenously at a dose of 300 mg or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. All the patients received concomitant ciprofloxacin from weeks 1 to 4.

Primary endpoint: Modified Pouchitis Disease Activity Index (mPDAI)–defined remission (an mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the mPDAI total score; scores range from 0 to 12, with higher scores indicating more severe pouchitis) at week 14. The mPDAI is based on clinical symptoms and endoscopic findings.

Result:



Conclusion:

Treatment with vedolizumab was more effective than placebo in inducing remission in patients who had chronic pouchitis after undergoing IPAA for UC.

Reference: Travis S et al. N Engl J Med. 2023 Mar 30;388(13):1191-1200

F. Small Molecules

1. OCTAVE Trial

Tofacitinib as Induction and Maintenance Therapy for UC

Study Design: Randomized, double-blind, placebo-controlled trials
Induction: OCTAVE Induction 1 and 2.
Maintenance: OCTAVE Sustain.

• ***OCTAVE Induction 1 and 2;***
• Adults with moderately to severely active UC, with history of Inadequate response or intolerance to conventional therapy or Anti-TNF were randomly assigned to tofacitinib (10 mg twice daily) or placebo for 8 weeks
• **Primary endpoint:** Remission at week 8

Result:
• **OCTAVE Induction 1:** (18.5%) Tofacitinib group Vs (8.2%) placebo group (P=0.007)
• **OCTAVE Induction 2:** (16.6%) Tofacitinib group Vs (3,6%) placebo group (P<0.001)
• The rates of overall infection and serious infection were higher with tofacitinib than with placebo

• O**CTAVE sustain:** Patients who achieved a clinical response to induction therapy randomized to 5mg BD or 10mg BD or placebo

• **Primary endpoint:** Remission at week 52

Result:
• **OCTAVE Sustain:** (34.3%) in 5-mg tofacitinib group and (40.6%) in 10mg tofacitinib group Vs (11.1%) in the placebo group (P<0.001 for both comparisons with placebo)
• The rate of serious infection was similar across the three treatment groups
• Overall infection and herpes zoster infection were higher with tofacitinib than with placebo

Conclusion:
In patients with moderately to severely active UC, tofacitinib was more effective as induction and maintenance therapy than placebo.
Comment:
Increased risk of infection, especially herpes zoster, and higher cholesterol levels in tofacitinib than placebo
Reference: Sandborn WJ et al. N Engl J Med. 2017 May 4;376(18):1723-1736

2. U-ACHIEVE/ U-ACCOMPLISH Trial

Upadacitinib as Induction and Maintenance Therapy for Moderate-to-Severe UC

Study Design: Phase 3, Randomized, double-blind, placebo-controlled
Induction Studies: U-ACHIEVE and U-ACCOMPLISH.
Maintenance Study: (U-ACHIEVE).
• Patients with mod-severe UC were randomized to 45mg/day of UPA vs placebo for 8 weeks(induction).
• Patients achieving a clinical response during the induction phase were re-randomized (1:1:1) to 15 mg UPA vs 30 mg UPA vs placebo for 52 weeks.
• Proctitis alone and previous JAKi exposure excluded.

U-ACHIEVE (UC1) Induction /U-ACCOMPLISH (UC2)
• **Primary endpoint:** Clinical remission at week 8
Result:
• **UC1:** (26%) Upadacitinib vs (5%) Placebo (p<0.0001).
• **UC2**: (34%) Upadacitinib vs (4%) placebo (p<0.0001).
• The most reported adverse events in UC1 and UC2: nasopharyngitis, High CK and acne

In both induction studies, serious adverse events and adverse events leading to discontinuation of treatment were less frequent in the upadacitinib 45 mg group than in the placebo group

U-ACHIEVE Maintenance (UC3)
• **Primary endpoint:** Clinical remission at week52

Result:
• Clinical remission at w52: (52%) Upadacitinib 30 mg, (42%) Upadacitinib 15 mg Vs (12%) Placebo, (p<0.0001)
• The most reported adverse events in UC3: Upper respiratory tract infection, nasopharyngitis, CK elevation, and arthralgia

Cancer, adjudicated major adverse cardiac events, and venous thromboembolism were rare

Conclusion:
Upadacitinib is more effective than placebo for both induction and maintenance of remission.
Reference: Danese S et al. Lancet. 2022 Sep 24;400(10357):996

3. U-EXCEL & U-EXCEED / U-ENDURE Trial
Upadacitinib as Induction and Maintenance Therapy for CD

Study Design: Two phase 3 induction trials (U-EXCEL and U-EXCEED), and & maintenance (U-ENDURE)
• Induction trial: patients with moderate-to-severe CD randomly assigned to receive 45 mg of upadacitinib Vs placebo for 12 weeks.
• **Maintenance trial:** Patients achieving clinical response to upadacitinib during induction were re-randomized in the maintenance trial (1:1:1 ratio) to one of three groups: Upadacitinib 15 mg, Upadacitinib 30 mg, or placebo once daily for 52 weeks.
• **Primary endpoint:** Co-primary endpoints of clinical remission (CDAI <150) and endoscopic response at week 12 and week 52.

Result:
• **Clinical remission after induction:**
o **U-EXCEL:** (49.5%) 45 mg Upadacitinib vs (29.1%) placebo, (p<0.0001)
o **U-EXCEED:** (38.9%) 45 mg upadacitinib vs (21.1%) placebo, (p<0.0001)
• **Endoscopic response after induction:**
o **U-EXCEL:** (45.5%) 45 mg upadacitinib vs (13.1%) placebo, (p<0.000)
o **U-EXCEED:** (34.6%) 45 mg upadacitinib vs placebo (3.5%), (p<0.0001)

Result:
• **Clinical remission in maintenance at week 52:**
o **U-ENDURE :** 37.3% UPA15 vs 47.6% UPA30 vs 15.1% placebo, p<0.0001
• **Endoscopic remission in maintenance at w52:**
o **U-ENDURE:** 27.6% UPA15 vs 40.1% UPA30 vs 7.3% placebo, p<0.0001
• Herpes zoster more frequent in UPA than placebo
• Hepatic Disorders & Neutropenia: More frequent in the 30 mg upadacitinib group compared to the 15 mg

Conclusion:
Upadacitinib induction & maintenance treatment was superior to placebo in patients with moderate-to-severe CD
Reference: Loftus EV et al. N Engl J Med. 2023 May 25;388(21):1966-1980.

4. SELECTION Trial

Filgotinib as Induction and Maintenance Therapy for UC

Study Design: phase 2b/3, double-blind, randomized, placebo-controlled trial

- **Induction Study A** (Biologic-Naïve No prior TNF antagonist or Vedolizumab use)

o Inadequate response, loss of response, or intolerance to corticosteroids or immunosuppressants

- **Induction Study B** (Biologic-Experienced, No TNF antagonist or Vedolizumab use within 8 weeks before screening)

o Inadequate response, loss of response, or intolerance to any TNF antagonist or Vedolizumab

- Randomization (2:2:1) to Filgotinib 200 mg, Filgotinib 100 mg, or placebo once. Patients achieving clinical remission or Mayo Clinic Score response at week 10 entered the maintenance study.
- **Maintenance Phase:**

o Patients on Filgotinib (induction) were re-randomized (2:1) to continue their Filgotinib dose or switch to placebo.

o Patients on placebo (induction) continued placebo.

- **Primary endpoint:** Clinical remission (based on Mayo endoscopic, rectal bleeding, and stool frequency subscores) at weeks 10 and 58.

Result:

- **Clinical Remission at week 10 (Filgotinib 200 mg vs Placebo):**

o Induction Study A: 26.1% vs 15.3% (95% CI 2.1–19.5, p=0.0157)

o Induction Study B: 11.5% vs 4.2% (95% CI 1.6–12.8, p=0.0103)

- **Clinical Remission at week 58 (Filgotinib 200 mg vs Placebo):**

o 37.2% vs 11.2% (95% CI 16.0–35.9, p<0.0001)

- **Filgotinib 100 mg vs Placebo:**

o Week 10: No significant difference

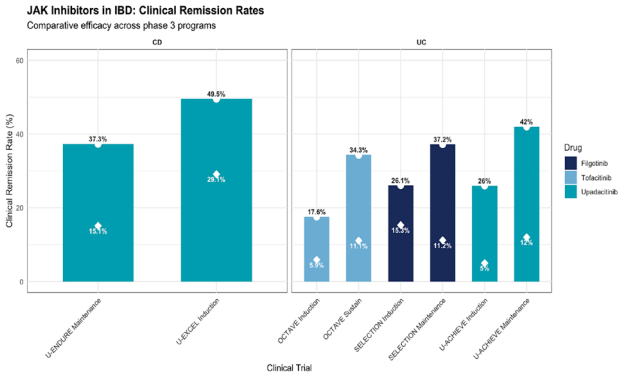
o Week 58: 23.8% vs 13.5% (95% CI 0.0–20.7, p=0.0420)

Conclusion:

Filgotinib 200 mg was well tolerated, and efficacious in inducing and maintaining clinical remission compared with placebo in patients with moderately to severely active UC.

Reference: Feagan BG et al. Lancet. 2021 Jun 19;397(10292):2372-2384.

Summary: JAK Inhibitors: Comprehensive Program Results



5. TRUE NORTH Trial
Ozanimod in UC Induction & Maintenance

Study Design: Double-blind, randomized trial
Induction period (10 weeks)
• Cohort 1: patients were Randomized, double-blind assignment to receive oral
ozanimod hydrochloride 1 mg or placebo once daily.
• Cohort 2: Patient received open-label ozanimod at the same daily dose.
Maintenance period (Through Week 52): Patients who achieved a clinical response to ozanimod during the induction period were randomized again to Double-blind ozanimod or placebo.
• **Primary endpoint:**
Induction period: Clinical remission at week 10.
Maintenance period: Clinical remission week 52.
• **Secondary endpoint:**
Induction period: Clinical response, endoscopic improvement, and mucosal healing plus histologic remission,
Maintenance period: Clinical response, endoscopic improvement, maintenance of clinical remission, glucocorticoid-free remission mucosal healing, and durable clinical remission.
Result:
• All secondary end points were significantly improved with ozanimod as compared with placebo in both periods. Clinical remission met for naïve to anti-TNF, but not for anti-TNF exposed.
• Infection with ozanimod was similar to that with placebo during induction and higher than that with placebo during maintenance.
• Serious infection occurred in less than 2% of the patients in each group during the 52-week trial.
• Elevated liver aminotransferase levels were more common with ozanimod.

Efficacy	*Clinical Remission Ozanimod vs Placebo*	*Clinical Response Ozanimod vs Placebo*	*Endoscopic Improvement Ozanimod vs Placebo*	*Mucosal Healing Ozanimod vs Placebo*
Induction Period	18% vs. 6%, P<0.001	48% vs. 26%, P<0.001	27% vs. 12%, P<0.001	13% vs. 4%, P<0.001
Maintenance Period	37% vs. 19%, P<0.001	60% vs. 41%, P<0.001	46% vs. 26%, P<0.001	30% vs. 14%, P<0.001

Conclusion:
Ozanimod was more effective than placebo as induction and maintenance therapy in patients with moderately to severely active UC.
Original study: Sandborn WJ et al. N Engl J Med. 2021 Sep 30;385(14):1280-1291.

ELEVATE Trial

Etrasimod as Induction and Maintenance Therapy for UC

Study Design: Two independent randomized, multicenter, double-blind, placebo-controlled, phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12.

• Adults with moderate-to-severe active UC who had an inadequate/loss of response or intolerance to at least one approved therapy were randomly assigned to once-daily oral Etrasimod 2 mg or placebo.

• **ELEVATE UC 52**: 12-week induction + 40 week maintenance (treat-through design).

• **ELEVATE UC 12:** Independently assessed induction at week 12.

• **Primary endpoint:**

• **ELEVATE UC 52:** Clinical remission at week 12 (induction) and Clinical remission at week 52 (maintenance).

• **ELEVATE UC 12:** Clinical remission at week 12 (induction).

• **Key Secondary Endpoints:**

• **ELEVATE UC 52:** endoscopic improvement, symptomatic remission, and endoscopic improvement–histological remission with histological remission at week 12 and at week 52. Corticosteroid-free and sustained clinical remission were additional key secondary endpoints assessed at week 52

• **ELEVATE UC 12 (Week 12)**: Endoscopic improvement, Symptomatic remission and Endoscopic improvement–histological remission.

Result:

Clinical Remission Rates:

• ELEVATE UC 52:

o Week 12 (Induction): 27% Etrasimod vs. 7% placebo ($p < 0.0001$)

o Week 52 (Maintenance): 32% Etrasimod vs. 7% placebo ($p < 0.0001$)

• ELEVATE UC 12:

o Week 12: 25% Etrasimod vs. 15% placebo ($p = 0.026$)

Safety & Adverse Events:

• ELEVATE UC 52: 71% Etrasimod vs. 56% placebo

• ELEVATE UC 12: 47% Etrasimod vs. 47% placebo

• No deaths or malignancies reported in either trial.

• No signal for infection or malignancy

Conclusion:
Etrasimod was effective and well tolerated as an induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.
Reference: Sandborn WJ et al. Lancet. 2023 Mar 25;401(10381):1000

Summary: S1P Receptor Modulators

Table 6: S1P Receptor Modulators in Ulcerative Colitis

Drug	Trial	Population	Clinical_Remission	Endoscopic_Improvement	Histologic_Remission	Safety	Reference
Ozanimod	TRUE NORTH Induction	Moderate-severe UC	18.4% vs 6.0%	27.3% vs 11.6%	12.6% vs 5.8%	Favorable	[11]
Ozanimod	TRUE NORTH Maintenance	Induction responders	37.0% vs 18.5%	45.7% vs 23.8%	30.4% vs 11.9%	Favorable	[11]
Etrasimod	ELEVATE UC 52	Moderate-severe UC	27% vs 7%	39% vs 15%	28% vs 7%	Well tolerated	[12]
Etrasimod	ELEVATE UC 12	Moderate-severe UC	25% vs 15%	36% vs 24%	24% vs 14%	Well tolerated	[12]

G. Interleukin inhibitor-23

COMMAND & INSPIRE Trial

Risankizumab for Moderate-to-Severe UC

Study Design: Phase 3, multicenter, double-blind, randomized trial
• Adult patients with Moderately to severely active UC and history of intolerance or inadequate response to one or more conventional therapies or advanced therapies, and no prior exposure to Risankizumab.
Induction Trial: Randomization to receive: Risankizumab 1200 mg IV or placebo at week 0,4,8
Maintenance Trial: Patients with clinical response after Risankizumab during the induction trial were randomized
to Risankizumab 180 mg SC or Risankizumab 360 mg SC or placebo every 8 weeks for 52 weeks
• **Primary endpoint:** Clinical remission at week 12 for the induction trial, and at week 52 for the maintenance trial.

Result:
• **Clinical remission rates at week 12:** (20.3%) 1200 mg Risankizumab, and (6.2%) for placebo; $p < .001$
• **Clinical remission rates at week 52:** (40.2%) 180 mg of Risankizumab, (37.6%) 360 mg of Risankizumab,
and (25.1%) for placebo; $p<0.001$
• No new safety risks were detected in the treatment groups.
Conclusion:
Compared with placebo, Risankizumab improved clinical remission rates in an induction trial and in a maintenance trial for patients with moderately to severely active UC.
Reference: Louis E et al. JAMA. 2024 Nov 19;332(19):1676.

ADVANCE & MOTIVATE Trial

Risankizumab as Induction Therapy for CD

Study Design: 2 randomized, double-masked, placebo-controlled, phase 3 trials.

- Aged 16–80 years with moderately to severely active CD, previously showing intolerance or inadequate response to one or more biologics or conventional therapy (ADVANCE) or to biologics (MOTIVATE) were randomly assigned to receive:

IV Risankizumab single dose of 600mg or 1200mg or placebo at weeks 0, 4, and 8

- **Co-primary endpoint:** Clinical remission and endoscopic response w12.

Result:

- ***All coprimary endpoints at week 12 were met in both trials with both doses of Risankizumab (p values ≤0·0001).***

In ADVANCE:	*In MOTIVATE*
• Clinical remission rate: (45%) in Risankizumab 600mg, (42%) in Risankizumab 1200 mg Vs (25%) placebo (p<0.0001)	**• Clinical remission rate:** (42%) in Risankizumab 600mg, (40%) in Risankizumab 1200 mg Vs (20%) placebo (p<0.0001)
• Eendoscopic response rate: (40%) in Risankizumab 600 mg, (32%) in Risankizumab 1200 mg Vs (12%) placebo (p<0.0001)	**• Eendoscopic response rate:** (29%) in Risankizumab 600 mg, (34%) in Risankizumab 1200 mg Vs (11%) placebo (p<0.0001)

Conclusion:

Risankizumab was effective and well tolerated as induction therapy in patients with moderately to severely active Crohn's disease.

Reference:D'Haens G et al. Lancet. 2022 May 28;399(10340):2015-2030

FORTIFY Trial

Risankizumab as maintenance therapy for moderately to severely active CD

Study Design: Phase 3, multicenter, double-blind, randomized trial
• Patients aged 16–80 years with moderately to severely active CD who achieved clinical response to Risankizumab during the ADVANCE or MOTIVATE induction trials were allowed to enter the FORTIFY maintenance trial.
• Patients were randomly assigned to:
o **Subcutaneous Risankizumab 180 mg** (every 8 weeks).
o **Subcutaneous Risankizumab 360 mg** (every 8 weeks).
o **Withdrawal receiving placebo** (every 8 weeks).
• **Co-primary endpoints at Week 52:** Clinical remission and endoscopic response

Result:
• Risankizumab 360 mg showed significant efficacy over placebo CDAI clinical remission, Stool frequency/abdominal pain remission, and endoscopic response.
• Risankizumab 180 mg was effective for CDAI clinical remission and endoscopic response
but not significantly better for stool frequency/abdominal pain remission.

Efficacy	*Clinical Remission at week 52*	*Stool frequency/abdominal pain remission*	*Endoscopic response*
Risankizumab 360 mg vs. Placebo	52% vs 41% (P=0.0054)	52% vs 40% (P=0.0037)	47% vs 22% (P=0.0001)
Risankizumab 180 mg vs. Placebo	55% vs 41% (P=0.0031)	44% vs 40% (P=0.12)	47% vs 22%(P=0.0001)

Conclusion:
• Risankizumab is a safe and efficacious treatment for maintenance of remission in mod-severe CD.
• The study confirmed a dose-dependent response and demonstrated that Risankizumab was safe and well tolerated.
Reference: Ferrante M et al. Lancet. 2022 May 28;399(10340):2031-2046.

GALAXI-1 Trial

Efficacy and Safety of Guselkumab for patients with CD

Study Design: phase 2, randomized, multicenter, double-blind trial
Adult patients with moderately to severely active CD were randomized to receive one of five treatment groups, with regimens consisting of an intravenous induction phase (0,4,8) transitioning to a subcutaneous.
(1) Guselkumab 200mg IV →100 mg group
(2) Guselkumab 600mg IV→200 mg group
(3) Guselkumab 1200→200 mg group
(4) Ustekinumab group (6 mg/kg intravenous at week 0, then 90 mg subcutaneous every 8 weeks)
(5) Placebo group
• **Endpoint: Assessed at w 48 included:** CDAI remission (CDAI score <150), endoscopic response (≥50% improvement from baseline in SES-CD or SES-CD score ≤2), and endoscopic remission (SES-CD score ≤2)

Result:
• CDAI Clinical Remission at w48:
o Guselkumab 200→100 mg: 64% (39/61)
o Guselkumab 600→200 mg: 73% (46/63)
o Guselkumab 1200→200 mg: 57% (35/61)
o Ustekinumab: 59% (37/63)
o Placebo (continued): 60% (9/15) >> At week 12, 24.6% (15/61) of placebo patients achieved CDAI remission. Of these:15 patients continued placebo: 60% (9/15) were in clinical remission at week 48.
o Placebo (crossed to ustekinumab): 59% (26/44). The remaining 46 patients did not achieve CDAI clinical response at week 12 and were switched to ustekinumab of these; 59% achieved CDAI clinical remission at week 48.
• Endoscopic Response at w48: Guselkumab 200→100mg: 44%, Guselkumab 600→200mg: 46%, Guselkumab 1200→200 mg: 44%, Ustekinumab: 30%
• Endoscopic Remission: Guselkumab 200→100 mg: 18%, Guselkumab 600→200 mg: 17%, Guselkumab 1200→200 mg: 33%, Ustekinumab: 6%.
Conclusion:
Patients receiving Guselkumab intravenous induction and subcutaneous maintenance treatment achieved high rates of clinical and endoscopic efficacy up to week 48. No new safety concerns were identified.
Reference: Danese S et al. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):133-146.

QUASAR Trial

Guselkumab for patients with Moderate-to-Severely active UC

Study Design: Two phase 3, randomized, double-blind, placebo-controlled studies

• Primary Endpoint: Clinical remission at Week 12 and week 44 (induction + Maintenance Study)

• Secondary Endpoint: Clinical response, endoscopic improvement, histo-endoscopic

mucosal improvement, endoscopic remission, IBDQ remission at week 12 (induction study)

Result:

• Induction Study (Table 1).

• Maintenance Study, Clinical Remission at Week 44:

o Guselkumab 200 mg SC every 4 weeks: 50% vs. Placebo: 19% (P<0.0001).

o Guselkumab 100 mg SC every 8 weeks: 45% vs. Placebo: 19% (P<0.0001).

Table 1: Primary, major secondary and histological endpoints, at induction Week 12

Domain	Endpoint	Placebo (%)	Guselkumab IV 200 mg (%)	Δ vs Placebo	p-value
Clinical	Clinical remission at Week 12	8%	23%	+15%	<0.0001
	Clinical response	28%	62%	+34%	<0.0001
Endoscopic	Endoscopic improvement	11%	27%	+16%	<0.0001
	Endoscopic remission	5%	15%	+10%	<0.0001
Deep Healing	Histo-endoscopic mucosal improvement	8%	24%	+16%	<0.0001
Histological	Histological improvement	21%	45%	+24%	<0.0001
	Histological remission	19%	40%	+22%	<0.0001
Patient-Reported Outcome	IBDQ remission	30%	51%	+22%	<0.0001
	Fatigue response	21%	41%	+20%	<0.0001
Symptomatic	Symptomatic response (Week 12)	35%	72%	+37%	<0.0001
	Symptomatic remission (Week 12)	21%	50%	+29%	<0.0001

Conclusion:
Guselkumab was effective and safe as induction and maintenance therapy in patients with moderately
to severely active ulcerative colitis. Guselkumab efficacy was shown in both biologic- naive and JAK inhibitor-naive patients, and in patients with a history of inadequate response or intolerance to biologics or JAK inhibitors
Reference: Rubin DT et al. Lancet. 2025 Jan 4;405(10472):33-49.

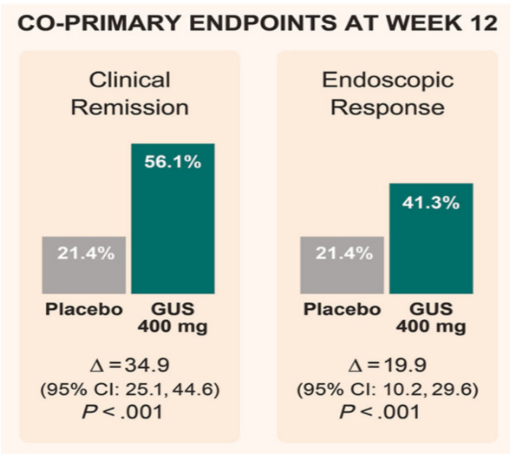
GRAVITI trial

Efficacy and Safety of Guselkumab Subcutaneous Induction and Maintenance in Moderate-to-Severe CD

Study Design: A Phase 3 double-blind, placebo-controlled, treat-through trial to evaluate subcutaneous induction and maintenance with Guselkumab in adult patients with moderately to severely active CD

Primary endpoint: The co-primary endpoints were clinical remission (CDAI score <150) at week 12 and endoscopic response (≥50% improvement from baseline in the SES-CD score) at week 12.

Result:



Reference: Hart A et al. Gastroenterology. 2025 Aug;169(2):308-325

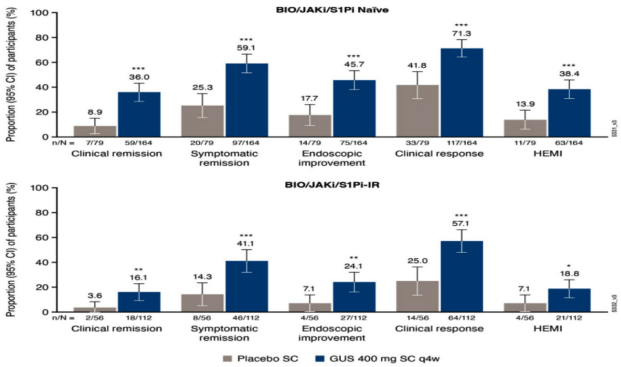
ASTRO trial

Efficacy and Safety of Guselkumab Induction Therapy in patients with UC

Study Design: A Phase 3 double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate subcutaneous (SC) induction and maintenance with Guselkumab in patients with moderately to severely active UC.
Primary endpoint: clinical remission (Mayo stool frequency subscore 0/1 not increased from baseline, rectal bleeding subscore 0, MES 0/1 with no friability) at week 12.

Result:

Figure. Primary Endpoint and Week 12 Secondary Endpoints by Biologic, JAK Inhibitor, and/or S1P Inhibitor History



*Nominal P<0.05, **Nominal P<0.01, ***Nominal P<0.001.

Reference: Long M et al. Lancet Gastroenterol Hepatol. 2026 Jan 13:S2468-1253(25)

LUCENT Trial

Mirikizumab as induction and maintenance in UC

Study Design: Phase 3, randomized, double-blind, placebo-controlled trials
Induction Trial: Patients were randomly assigned to Mirikizumab 300 mg IV Q4 weeks for 12 weeks vs Placebo
Maintenance Trial: Patients who responded to the induction therapy were randomly assigned to Mirikizumab 200 mg SC q4 weeks for 40 weeks vs placebo
• Primary endpoint: Clinical remission at week 12 and week 40
• Secondary endpoint: Clinical response, endoscopic remission, and improvement in bowel-movement urgency

Result:
• **Clinical Remission:**
• Induction Trial (Week 12): Mirikizumab (24.2%) vs Placebo (13.3%), significant difference
($P < 0.001$).
• Maintenance Trial (Week 40): Mirikizumab (49.9%) vs Placebo (25.1%), significant difference
($P < 0.001$).
• The criteria for all the major secondary end points were met in both trials
• Adverse events: nasopharyngitis and arthralgia more frequent in Mirikizumab than in placebo
• In Mirikizumab group, 15 experienced an opportunistic infection (6 with herpes zoster) and 8 had cancer (3 with colorectal cancer)
• In contrast, among those who received placebo in the induction trial, 1 patient had herpes zoster infection, and no patients developed cancer.
Conclusion:
Mirikizumab was more effective than placebo in inducing and maintaining clinical remission in patients with moderately to severely active UC. Opportunistic infection or cancer occurred in a small number of patients treated with Mirikizumab.
Reference: D'Haens G et al. N Engl J Med. 2023 Aug 24;389(8):772

VIVID-1 Trial

Efficacy and safety of Mirikizumab in patients with Moderate-to-Severe CD

Study Design: Phase 3, randomized, double-blind, double-dummy, placebo-controlled and active-controlled, treat-through study

• Adult patients with moderately-to-severely active CD and previous inadequate response, loss of response, or intolerance to one or more approved biological therapies or conventional therapies were randomly assigned (6:3:2) to receive:

o **Mirikizumab** 900 mg IV (weeks 0, 4, 8), then 300 mg SC every 4 weeks (weeks 12–52)

o **Ustekinumab** 6 mg/kg IV (week 0), then 90 mg SC every 8 weeks (weeks 8–52).

o **Placebo**

• Co-primary endpoint (assessing superiority of Mirikizumab over placebo were composite endpoints):

• patient-reported outcome (PRO) clinical response at week 12 and endoscopic response at week 52 (endoscopic response-composite)

• PRO clinical response at week 12 and Crohn's Disease Activity Index (CDAI) clinical remission at week 52 (CDAI clinical remission-composite)

Result:

• Endoscopic response-composite: (38·0%) Mirikizumab vs (9·0%) placebo (99·5% CI 20·6–36·8; p<0·0001)

• CDAI clinical remission-composite: (45·4%) Mirikizumab vs (19·6%) placebo (99·5% CI 15·9–35·6; p<0·0001

• The incidence rates of overall adverse events and discontinuations in patients treated with Mirikizumab were lower compared with placebo.

• The most common adverse event across the three groups was COVID-19.

• Serious adverse events: (10·3%) Mirikizumab, (10·7%) ustekinumab, and (17·1%) of 211 patients on placebo

Conclusion:
Mirikizumab was safe and effective as induction and maintenance treatment for patients with moderately-to-severely active CD who had intolerance, inadequate response, or loss of response to standard therapy.

Reference: Ferrante M et al. Lancet. 2025 Apr 12;405(10486):1230

Summary: Risankizumab: Complete Phase 3 Program

Table 7: Risankizumab Comprehensive Phase 3 Program

Disease	Study_Phase	Trial	Population	Dose	Clinical_Remission	Endoscopic_Resp
CD	Induction	**ADVANCE**	Bio-naïve/experienced	600mg/1200mg IV	45%/42% vs 25%	40%/32% vs 12%
CD	Induction	**MOTIVATE**	Bio-experienced	600mg/1200mg IV	42%/40% vs 20%	29%/34% vs 11%
CD	Maintenance	**FORTIFY**	Induction responders	180mg/360mg SC	55%/52% vs 41%	47%/47% vs 22%
UC	Induction	**COMMAND/INSPIRE**	Advanced therapy experienced	1200mg IV	20.3% vs 6.2%	Improved
UC	Maintenance	**COMMAND/INSPIRE**	Induction responders	180mg/360mg SC	40.2%/37.6% vs 25.1%	Improved

Table 8: IL-23 Inhibitors - Recent Clinical Trials

Drug	Disease	Trial	Design	Clinical_Remission	Key_Finding	Reference
Guselkumab	CD	GALAXI-1	Phase 2, dose-ranging	64-73% at week 48	High rates of endoscopic response	[16]
Guselkumab	UC	QUASAR Induction	Phase 3, RCT	23% vs 8% at week 12	Effective induction therapy	[17]
Guselkumab	UC	QUASAR Maintenance	Phase 3, RCT	45-50% vs 19% at week 44	Effective maintenance with both regimens	[17]
Mirikizumab	UC	LUCENT Induction	Phase 3, RCT	24.2% vs 13.3% at week 12	Superior to placebo	[18]
Mirikizumab	CD	VIVID-1	Phase 3, RCT	38.0% vs 9.0% endoscopic response composite	Superior to placebo and non-inferior to ustekinumab	[19]

H. Therapeutic Monitoring and Treatment Optimization

CALM Trial

Effect of tight control management on CD

Study Design: Open-label, randomized, controlled phase 3 trial

• Patients with CD were randomized to:

1. Tight control: Treatment escalation based on these failure criteria: fecal calprotectin ≥ 250 µg/g, C-reactive protein ≥ 5mg/L, CDAI ≥ 150, or prednisone use during the previous week.
2. Clinical management: Treatment escalation based on CDAI scores and prednisone use.

• Treatment was escalated if the failure criteria were met.

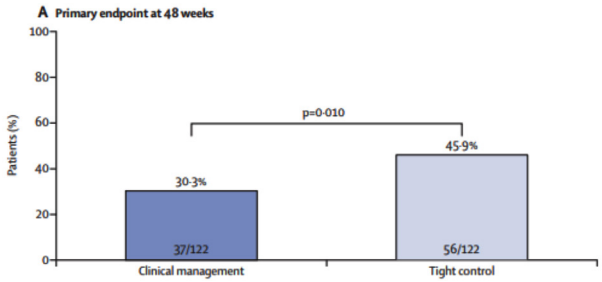
• Escalation was performed stepwise as follows:

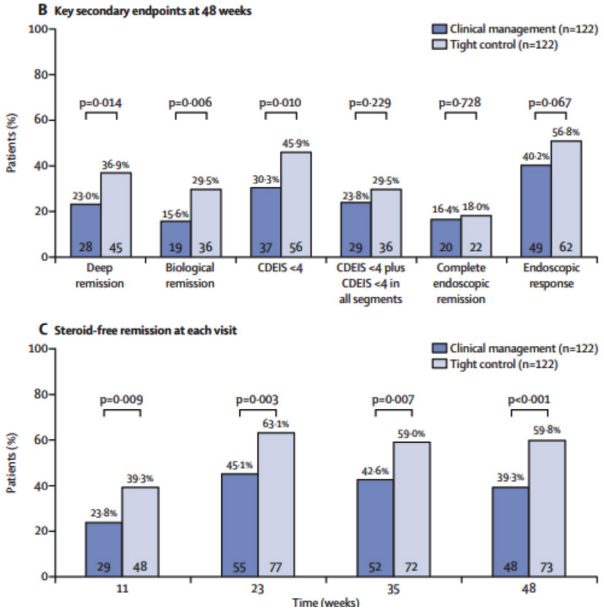
No treatment > Adalimumab induction then Adalimumab q2weeks > Adalimumab q1 week >
adalimumab q1week+AZA.

• **Primary endpoint:** Mucosal healing (CDEIS<4) at week 48

• **Secondary endpoint:** Deep remission; biological remission; CDEIS<4; complete endoscopic remission; endoscopic response; steroid free remission, clinical remission.

Result:





Conclusion:
Management of active CD based on concentrations of fecal calprotectin and CRP in addition to clinical symptoms leads to better outcomes compared to clinical management alone.

Reference: Colombel JF et al. Lancet. 2018 Dec 23;390

REACT Trial
Early combined immunosuppression for the management of CD

Study Design: Open-label cluster randomized controlled trial
• Patients were randomly assigned (1:1) to either early combined immunosuppression vs
conventional management

• **Intervention:**
• Early Combined Immunosuppression (ECI) Group:
o Patients with active disease (Harvey-Bradshaw Index [HBI] >4) after corticosteroid initiation received early combination therapy: TNF antagonist (adalimumab or infliximab) and Antimetabolite (azathioprine, 6-mercaptopurine, or methotrexate)
o Disease activity was reassessed every 12 weeks, with stepwise treatment escalation:
▪ If active disease persisted (HBI ≥7) → TNF antagonist dose intensification
▪ If still active after intensification → Switch TNF antagonist or antimetabolite
▪ Surgery was considered only after all medical options failed
• Conventional Management Group:
o Physicians unaware of ECI algorithm details provided standard-of-care treatment at their discretion.
• **Follow-Up and Monitoring:**
o Patients were followed for 24 months with scheduled visits at months 0, 6, 12, 18, and 24, assessing HBI scores, medication use, hospitalizations, surgeries, and adverse outcomes.
o Escalation in the ECI group was protocol-driven, whereas in conventional management, escalation was at the treating physician's discretion.

• **Primary endpoint:** Proportion of patients in corticosteroid-free remission at 12 months
• **Secondary endpoint**: Mean proportion of patients in remission and differences in mean HBI scores at months 6, 18, and 24, time to occurrence of the first major adverse outcome, time to introduction of and the proportion of patients treated with specific CD medications, serious drug, and disease-related events; & mortality.

Result:
• 12-Months Corticosteroid-Free Remission: No significant difference.
• 24-month patient-level composite rate of major adverse outcomes (surgery, hospital admission, or serious disease- related complications): lower at ECI practices vs conventional management practices (27·7% vs 35·1%, HR 0·73, 95% CI 0·62 to 0·86, p=0·0003)

Conclusion:
ECI was not more effective than conventional management for controlling Crohn's disease symptoms, however the risk of major adverse outcomes was lower. ECI was not associated with an increased risk of serious drug-related adverse events or mortality.

Reference: Khanna R et al. Lancet. 2015 Nov 7;386 (10006):1825-34.

PROFILE Trial

Top-down versus accelerated step-up treatment strategies for patients with newly diagnosed CD

Study Design: Open-label, randomized controlled trial enrolled adults with newly diagnosed active CD to top-down or accelerated step-up treatment

- **Primary endpoint:** Sustained steroid-free and surgery-free remission to week 48
- **Secondary endpoint:** Endoscopic remission at week 48, quality of life assessment, number of flares requiring treatment escalation by week 48, and number of CD related hospital admissions and surgeries by week 48.

Result:

- There was no biomarker–treatment interaction effect
- Sustained steroid-free and surgery-free remission: (79%) Top-down group vs (15%) accelerated step-up group (95% CI 57 to 72; p<0·0001)
- There were fewer adverse events and serious adverse events in the top-down group than in the accelerated step-up group with fewer complications requiring abdominal surgery and no difference in serious infections.

Conclusion:

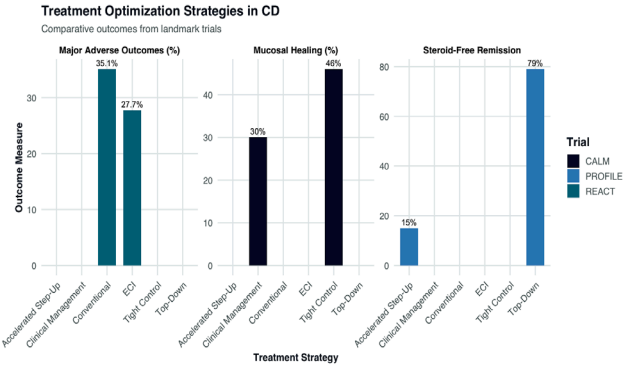
Top-down treatment with combination IFX plus immunomodulator achieved substantially better outcomes at 1 year than accelerated step-up treatment. The biomarker did not show clinical utility. Top-down treatment should be considered standard of care for patients with newly diagnosed active CD.

Comment:

Patients with mild CD were not included in the study.

Reference: Noor NM et al. Lancet Gastroenterol Hepatol. 2025 Aug;10(8):e10.

Summary: CALM, REACT, and PROFILE Trials



PANTS

Mechanisms and management of loss of response to anti-TNF therapy for patients with CD

Study Design: Multicenter, prospective observational cohort study reporting the rates of effectiveness of infliximab and adalimumab in anti-TNF-naive patients with active luminal CD aged 6 years and older.

Aim: To assess the rates of effectiveness of Infliximab and Adalimumab in anti-TNF-naive patients with active luminal CD

- **Primary endpoint:**
- **Treatment failure endpoints were:**

o Primary non-response, defined as exit before week 14 because of treatment failure including IBD related surgery, corticosteroid use at week 14 new prescriptions or if previous dose had not been stopped, or Patients whose CRP concentration did not decrease to 3 mg/L or less or by 50% or more from baseline at week 0)

o Non-remission at weeks 54, 102, and 150,

o Adverse events leading to drug withdrawal

- **Loss of response:**

o Loss of response was defined in patients who initially responded to anti-TNF therapy at the end of induction and who subsequently developed symptomatic activity that warranted an escalation of steroid, immunomodulatory, or anti-TNF therapy, resectional surgery, or exit from study due to treatment failure

Result:

Table 9: PANTS Study - Key Findings on Anti-TNF Therapy [20]

Aspect	Infliximab	Adalimumab	Implication
Remission at Year 3	34.7%	28.9%	Moderate long-term efficacy
Loss of Response by Year 3	60.0%	68.4%	High loss of response rate
Optimal Drug Levels	6.1-10.0 mg/L (week 14)	10.1-12.0 mg/L (week 14)	Therapeutic drug monitoring guide
ADA Development by Year 3	44.0%	20.3%	Higher with infliximab
HLA-DQA1*05 Risk	HR 1.46 (p=0.003)	HR 1.60 (p=0.10)	Genetic risk factor
Immunomodulator Protection	HR 0.40 (p<0.001)	HR 0.42 (p=0.003)	Reduces immunogenicity

Conclusion:
• Only around a third of patients with active luminal CD treated with an anti-TNF drug were in remission at the end of 3 years of treatment.
• Low drug concentrations at the end of the induction period predict loss of response by year 3 of treatment, suggesting higher drug concentrations during the first year of treatment, particularly during induction, might lead to better long-term outcomes.
• Anti-drug antibodies associated with undetectable drug concentrations of infliximab, but not adalimumab, Infliximab had a higher rate of ADA development (44.0%) compared to adalimumab (20.3%). Can be predicted by carriage of **HLA-DQA1*05** and mitigated by concomitant immunomodulator use for both drugs.

Reference: Chanchlani N et al. Lancet Gastroenterol Hepatol. 2024 Jun;9(6):521-538.

ENTERPRET Trial

Vedolizumab Dose Optimization in Patients with UC

Study Design: Phase 4, open-label, randomized, controlled trial for patients with moderate to severe UC who had high drug clearance at week 5 (serum concentration, <50 µg/mL) and nonresponse to standard Vedolizumab treatment at week 6. At week 6, eligible patients were randomized 1:1 to receive standard dosing (300 mg every 8 weeks) or dose-optimized vedolizumab (600 mg at week 6, then 300 mg every 4 weeks; or 600 mg at week 6, then 600 mg every 4 weeks [based on week 5 serum concentration]).

- **Primary endpoint:** Endoscopic improvement at week 30.
- **Secondary endpoint:** Clinical remission at week 30, clinical response at week 14 & 30

Result:

- At week 6 (47.5%) had a clinical response.
- Patients with nonresponse at week 6, 86.5% had high drug clearance.
- At week 30, (18.9%) who received standard Vedolizumab had endoscopic improvement vs (14.5%) who received dose-optimized Vedolizumab, 9.4% who received standard Vedolizumab had clinical remission at week 30 vs 9.1% who received dose-optimized Vedolizumab and clinical response was observed in 32.1% and 30.9%, respectively.
- Safety event rates were similar among treatment groups.

Table 10: ENTERPRET Trial - Vedolizumab Dose Optimization [21]

Group	Description	Endoscopic_Improvement	Clinical_Remission	Conclusion
Standard Dosing	300 mg IV at weeks 0, 2, 6, then q8w	18.9%	Similar across groups	Reference
Dose Optimized (Regimen A)	Week 5 level 30-50 µg/mL → 600 mg at week 6, then 300 mg q4w	No significant difference	Similar across groups	No advantage over standard
Dose Optimized (Regimen B)	Week 5 level <30 µg/mL → 600 mg at weeks 6, 10, 14, 18, 22, 26	No significant difference	Similar across groups	No advantage over standard

Conclusion:

In patients with early nonresponse and high drug clearance, Vedolizumab dose optimization is probably not required. A proportion of patients benefited from continued treatment irrespective of the dose received.

Reference: Jairath V et al. CGH, Volume 22, Issue 5, 1077 - 1086.e13

I. Pregnancy

PIANO Registry

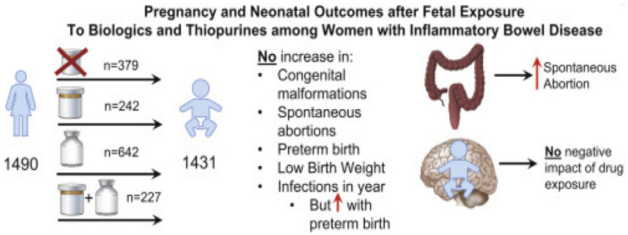
Pregnancy and Neonatal Outcomes after Fetal Exposure to Biologics and Thiopurines among Women with IBD

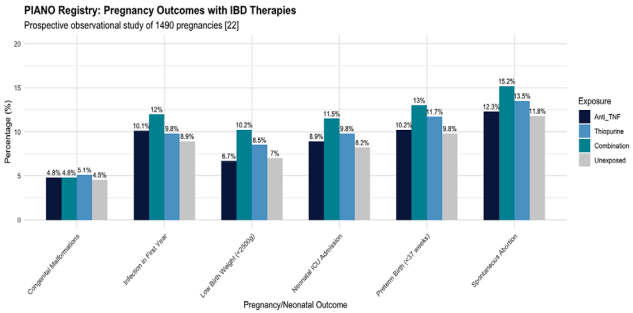
Study Design: Observational study. Pregnant woman with IBD on biologics and/or thiopurine.

- **Primary endpoint:** comparison of 5 outcomes (congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infant infections) among pregnancies exposed vs unexposed in utero to biologics, thiopurines, or a combination

Result:

- Drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infections during the first year of life.
- Higher disease activity was associated with risk of spontaneous abortion (HR, 3.41; 95% CI 1.51–7.69) and preterm birth with increased infant infection (OR, 1.73; 95% CL, 1.19–2.51).





Conclusion:

Biologic, thiopurine, or combination therapy exposure during pregnancy was not associated with increased adverse maternal or fetal outcomes at birth or in the first year of life. Therapy with these agents can be continued throughout pregnancy in women with IBD to maintain disease control and reduce pregnancy-related adverse events

Reference: Mahadevan U et al: Gastroenterology. 2021 Mar;160(4):1131-1139.

J. Switching from Intravenous to Subcutaneous

VISIBLE 1 Trial

Subcutaneous Vedolizumab as maintenance therapy in patients with Moderate-to-Severe UC

Study design: Phase 3, double-blind, double-dummy trial. Patients with moderately to severely active ulcerative colitis received open-label treatment with intravenous Vedolizumab 300 mg at weeks 0 and 2. At week 6, patients with clinical response were randomly assigned maintenance treatment with subcutaneous Vedolizumab 108 mg every 2 weeks, intravenous Vedolizumab 300 mg every 8 weeks, or placebo.
Primary endpoint: Clinical remission at week 52 (Mayo score of ≤2 and no subscore >1).

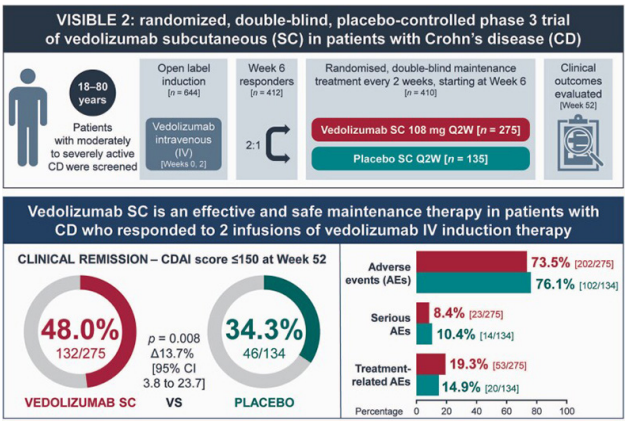
Result: Efficacy Results (Week 52)
- **Clinical Remission Placebo:** 14%, Vedolizumab SC: 46%, Vedolizumab IV: 43% ($P < 0.001$).
- **Endoscopic Improvement: Placebo:** 21%, Vedolizumab SC: 57%, Vedolizumab IV: 54% ($P < 0.001$).
- **Durable Clinical Response: Placebo:** 29%, Vedolizumab SC: 64%, Vedolizumab IV: 72% ($P < 0.001$).
- **Adverse events:** (77%, 65%, 76%), serios adverse events (5%, 6%, 2%), infections (5%,4%,2%) and injection site reaction (0%,10%,2%) occured in placebo, SC Vedolizumab and IV Vedolizumab. respectively.

Conclusions
SC Vedolizumab is effective as maintenance therapy in patients with moderately to severely active UC who had a clinical response to intravenous Vedolizumab induction therapy. It has a favorable safety and tolerability profile.
Reference: Sandborn WJ et al. Gastroenterology. 2025 Aug;169(2):390

VISIBLE 2 Trial

Vedolizumab SC as Maintenance Therapy in CD

Study design: Randomized, double-blind, placebo-controlled, phase 3 trial evaluating a SC Vedolizumab as maintenance treatment in adults with moderately to severely active CD



Conclusions: Vedolizumab SC is an effective and safe maintenance therapy in patients with CD who responded to two infusions of vedolizumab intravenous induction therapy.

Reference:

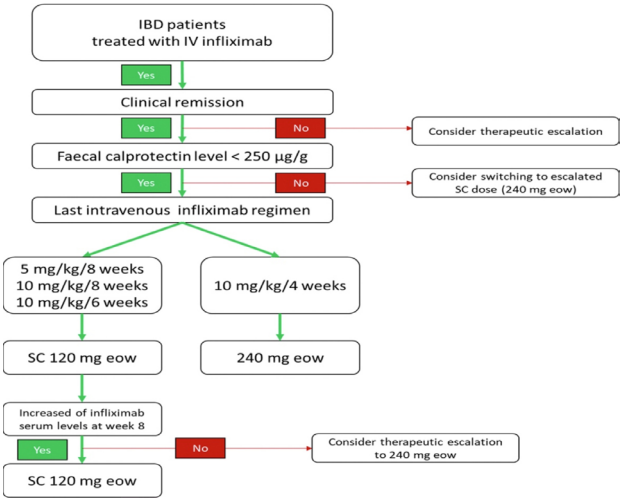
Vermeire S et al. J Crohns Colitis. 2022 Jan 28;16(1):27-38

REMSWITCH Trial

Effectiveness of Switching from IV to SC Infliximab in Patients With IBD

Study Design: Observational multicenter study. IBD patients in clinical remission (partial Mayo score ≤2 or Harvey-Bradshaw index ≤4) were switched to a unique dose of subcutaneous infliximab (120 mg every other week). Pharmacological and biological data were collected at baseline, visit 1 (4–8 weeks post switch), visit 2 (8–16 weeks post switch), and visit 3 (16–24 weeks post switch).

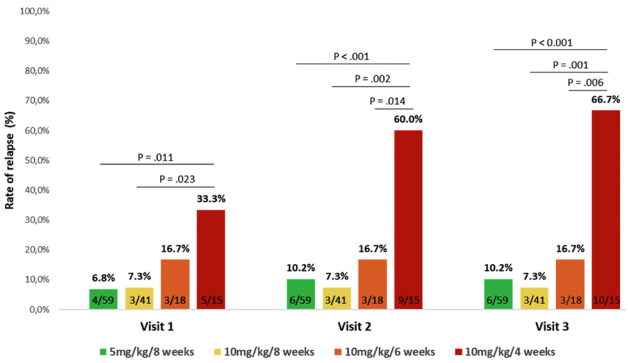
• Primary endpoint: Relapse was defined as clinical relapse or fecal calprotectin increase ≥150 µg/g compared with baseline

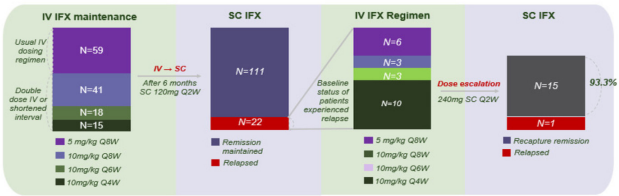


Result:

At visit 3 (16 and 24 weeks after the switch), relapse occurred in:

• 5 mg/kg every 8 weeks: 10.2%
• 10 mg/kg every 8 weeks: 7.3%
• 10 mg/kg every 6 weeks: 16.7%
• 10 mg/kg every 4 weeks: 66.7% (P < .001)





- Dose escalation to 240 mg every other week led to recapture clinical remission in 93.3% (n = 14 of 15)
- IFX serum levels increased after the switch (P < .0001) except for patients receiving 10 mg/kg q4w

Higher Risk of Relapse:

- Patients on 10 mg/kg every 4 weeks (odds ratio [OR]: 12.4; P = .017).
- Baseline fecal calprotectin >250 µg/g (OR: 5.4; P = .042).
- Reduced (41.7%) or stable (36.8%) infliximab serum levels after the switch, compared with increased levels (12.7%) (P = .020 and P = .019).

Conclusions:

Switching from intravenous to subcutaneous infliximab 120 mg every other week is safe and well accepted, leading to a low risk of relapse in IBD patients except for those receiving 10 mg/kg every 4 weeks requiring 240 mg every other week.

Reference: Buisson A et al. Clin Gastroenterol Hepatol. 2023 Aug;21(9):2338-2346.e3.

LIBERTY Trial

Subcutaneous Infliximab as Maintenance Therapy for IBD

Study Design: Two randomized, placebo-controlled, double-blind studies

• Induction Phase: All patients received CT-P13 (Infliximab) IV 5 mg/kg at weeks 0, 2, and 6

• At week 10 (before the first treatment in the maintenance phase), clinical responders were randomized (2:1) to receive CT-P13 SC 120 mg vs placebo every 2 weeks.

• **Primary endpoint:** Clinical Remission and Endoscopic Response at week 54 in CD, and Clinical Remission at week 54 in UC

• **Secondary endpoint:** CDAI Score Decrease ≥100-point reduction, Endoscopic and Corticosteroid-Free Remission at week 54 in CD, and Clinical Response, Endoscopic–Histologic Mucosal Improvement and Corticosteroid-Free Remission at week 54 in UC

Result:

• **Primary Endpoints at Week 54**

• CD Study:

o Clinical Remission: 62.3% (IFX SC) vs 32.1% (placebo), P < .0001.

o Endoscopic Response: 51.1% (IFX SC) vs 17.9% (placebo), P < .0001.

• UC Study: Clinical Remission: 43.2% (IFX SC) vs 20.8% (placebo), P < .0001.

• **Secondary Endpoints at week 54:** was significantly higher with IFX SC vs placebo in both studies

• IFX SC was well tolerated with no new safety signals identified.

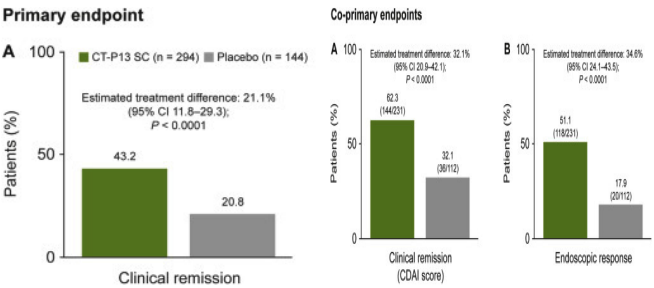
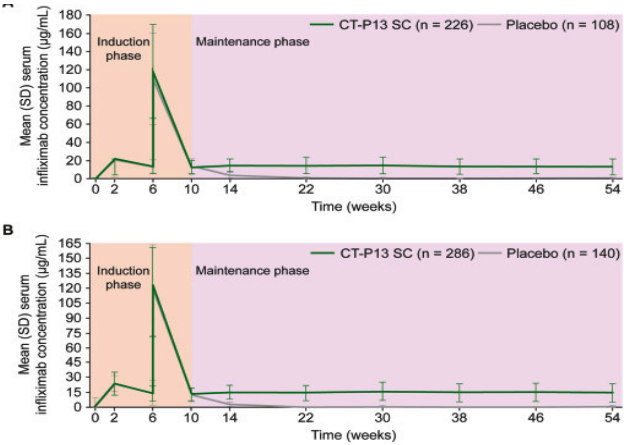


Figure: Linear scale mean (SD) serum infliximab concentrations up to week 54 (PK population) in the CD (A) and UC (B)



Anti-Drug Antibodies (ADAs) Positivity Rates:
o CD Study: IFX SC (65.1%) vs Placebo (76.2%)
o UC Study: IFX SC (63.8%) vs Placebo (91.8%)
o In the IFX SC groups, rates of ADA positivity increased up to week 30, before remaining relatively consistent until week 54. Dose adjustment did not noticeably impact rates of ADA positivity.

Impact of ADAs on Efficacy
• CD Study:
o Slightly lower clinical remission and endoscopic response rates at week 54 in ADA-positive patients vs ADA-negative patients.
o ADA-positive patients on IFX SC still had better outcomes than placebo.
o No clear trend in co-primary endpoints based on ADA titer quartiles.
• UC Study:
o Clinical remission rates at week 54 were comparable between ADA-positive and ADA-negative patients.
o Higher ADA titer quartiles were associated with lower remission rates, but the sample size was limited.

Conclusion:
Infliximab SC was more effective than placebo as maintenance therapy and was well tolerated in patients with moderately to severely active CD or UC who responded to Infliximab IV induction
Reference: Hanauer SB et al. Gastroenterology. 2024 Oct;167(5):919-933

Summary: IV to SC Switching Trials

Table 11: IV to SC Switching Trials - Efficacy and Safety

Drug	Trial	Design	Population	SC_Regimen	Efficacy	Relapse_Rate	Reference
Vedolizumab	VISIBLE 1 (UC)	Phase 3, RCT	IV induction responders	108 mg q2w	Non-inferior to IV	Low, comparable to IV	[23]
Vedolizumab	VISIBLE 2 (CD)	Phase 3, RCT	IV induction responders	108 mg q2w	Non-inferior to IV	Low, comparable to IV	[24]
Infliximab	REMSWITCH	Observational	IV maintenance in remission	120 mg q2w	93% remission maintenance	10-67% (dose-dependent)	[25]
Infliximab	LIBERTY	Phase 3, RCT	IV induction responders	120 mg q2w	Superior to placebo	Significantly lower vs placebo	[26]

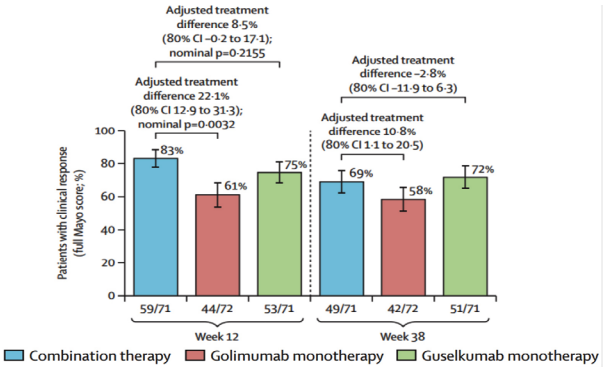
K. Dual Advanced Therapies

VEGA Trial

Guselkumab plus Golimumab combination therapy vs Guselkumab or Golimumab monotherapy in patients with UC

Study Design: Randomized, double-blind, controlled, phase 2, proof-of-concept trial aimed to compare the efficacy and safety of Guselkumab plus Golimumab combination therapy with either monotherapy in patients with moderately-to-severely active UC.
Primary endpoint: clinical response at week 12 (defined as ≥30% decrease from baseline in the full Mayo score and a decrease of ≥3 points with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1). The major secondary endpoint was clinical remission at week 12 (defined as a full Mayo score of ≤2 with no individual subscore of >1).

Result:

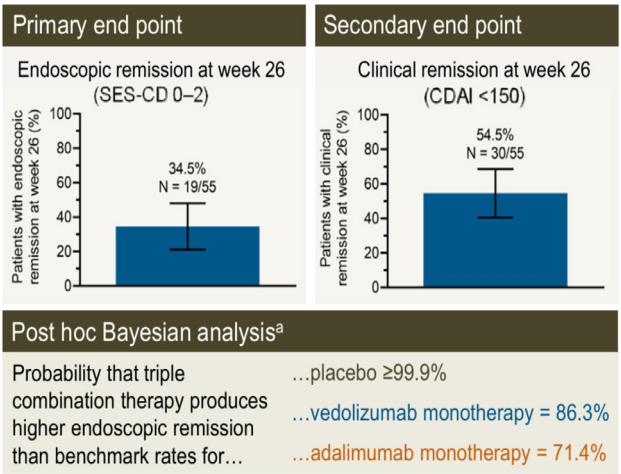


Conclusion:
Combination therapy with Guselkumab and Golimumab might be more effective for UC than therapy with either drug alone. These findings require confirmation in larger trials.
Reference: Feagan BG et al. Lancet Gastroenterol Hepatol. 2023 Apr;8(4):307-320

EXPLORER Trial

Vedolizumab, Adalimumab, and Methotrexate Combination Therapy in CD

Study Design: Prospective, phase 4, single-arm, open-label, multicenter study to assess the efficacy and safety of triple combination therapy in patients with moderate to severe CD. All patients received intravenous Vedolizumab until week 102; subcutaneous Adalimumab until week 26; and oral Methotrexate 15 mg weekly until week 34.
Primary endpoint: Endoscopic remission (defined as SES-CD 2) at week 26.
Secondary end points: Clinical remission (CDAI score response (100-point decrease in CDAI score from baseline) at weeks 10 and 26, the proportion of patients achieving endoscopic response (50% reduction in SES CD from baseline) at week 26, and the proportion of patients achieving endoscopic healing (SES-CD 4 with a reduction from baseline of 2 points and no individual subscore >1) at week 26.
Result:
At week 26, (34.5%) were in endoscopic remission.
At week 26, (54.5%) were in clinical remission.
Six patients had serious adverse events



Conclusions

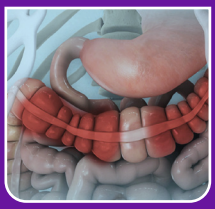
Combination therapy resulted in endoscopic and clinical remission at week 26 in 34.5% and 54.5% of patients, respectively, with no safety signal related to the treatment regimen. This supports further evaluation of combination therapy in CD.

Reference: Colombel JF et al. Clin Gastroenterol Hepatol. 2024 Jul;22(7):1487-1496.e12.

Summary: Dual Advanced Therapies

Table 12: Dual Advanced Therapy Trials in IBD

Trial	Combination	Disease	Phase	Design	N	Clinical_Response	Endoscopic_Remission	Safety	Status	Reference
VEGA	Guselkumab + Golimumab	UC	Phase 2	Randomized, double-blind	214	83.3% (combo) vs 61.1-66.7% (mono) at week 12	47.2% (combo) vs 22.2-27.8% (mono) at week 12	Similar to monotherapy	Proof-of-concept	[27]
EXPLORER	Vedolizumab + Adalimumab + Methotrexate	CD	Phase 4	Single-arm, open-label	45	65% at week 26	40% at week 26	Acceptable, no new safety signals	Ongoing	[28]



Inflammatory Bowel Disease (IBD) remains one of the most complex and rapidly evolving fields in gastroenterology. This book "Essential Guide to Inflammatory Bowel Disease" is written by experts to provides a concise yet comprehensive guide tailored for medical professionals, offering up-to-date insights into diagnosis, clinical management, and emerging therapies to achieve the best patient outcome in day-to-day practice.

With a focus on practical application, it bridges the gap between evidence-based medicine and real-world patient care. Whether you are a gastroenterologist, internist, surgeon, or trainee, this resource serves as a reliable companion in understanding and managing the challenges of IBD in clinical practice.

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