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CROHN'S DISEASE: CURRENT INSIGHTS INTO PATHOGENESIS, DIAGNOSIS AND TREATMENT

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ABSTRACT

Background: Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease with rising global incidence and substantial long-term morbidity. Its heterogeneous clinical course reflects a complex interplay between genetic susceptibility, environmental factors, intestinal dysbiosis, epithelial barrier dysfunction, and dysregulated immune responses. Advances in diagnostics and therapeutics have transformed CD management, yet disease progression and complications remain common.
Methods: This narrative review synthesizes current evidence on the pathophysiology, clinical presentation, diagnostic strategies, and treatment of Crohn's disease. Peer-reviewed literature was examined focusing on genetic and immunological mechanisms, microbiome alterations, diagnostic modalities, conventional and advanced therapies, nutritional and surgical management, and emerging experimental approaches.
Results: Crohn's disease pathogenesis involves polygenic risk factors (e.g., NOD2, ATG16L1, IL23R), impaired autophagy, dysbiosis, and aberrant innate and adaptive immune activation. Diagnosis requires an integrated approach combining biomarkers, endoscopy with histology, and cross-sectional imaging. Therapeutic strategies have shifted toward a treat-to-target model, emphasizing mucosal healing through biologics, small-molecule agents, immunomodulators, and selected nutritional interventions. Novel microbiome and cell-based therapies show promise but remain investigational.
Conclusion: Despite major therapeutic advances, Crohn's disease continues to impose significant disease burden. Early diagnosis, proactive treatment, and personalized, mechanism-based strategies are essential to prevent cumulative bowel damage. Ongoing research into precision medicine and microbiome-targeted therapies may further improve long-term outcomes.

KEYWORDS

Crohn's Disease, Inflammatory Bowel Disease, Pathogenesis, Diagnosis, Treatment, IBD Management

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1.Introduction

Inflammatory bowel diseases (IBD) pose a growing global health challenge. Within this group, Crohn's disease (CD) is a chronic, relapsing and remitting inflammatory bowel disease (IBD) that is increasing in incidence and prevalence globally[1]. The wide spectrum of CD - from mild courses to severe complications - underscores the need for comprehensive understanding of its pathogenesis, diagnosis and management. Epidemiologically, CD's burden is mounting. As noted, the condition is increasing in incidence and prevalence in many parts of the world[2]. This shift hints at the expanding influence of environmental, lifestyle and dietary factors alongside genetic predisposition. The fact that CD often manifests in young adulthood further magnifies its impact on life-long morbidity, productivity and health costs.

The pathophysiology of CD is complex and multifactorial, involving genetic susceptibility, microbial alterations, immune dysregulation and barrier dysfunction. CD is described as a chronic inflammatory bowel disease characterized by transmural inflammation that can affect any part of the gastrointestinal tract[3]. Because of this complexity, clinical presentation and therapeutic responses vary significantly between patients. Accurate diagnosis is essential yet challenging. CD can affect any part of the gastrointestinal tract from the mouth to the anus[4], present with skip lesions, and mimic other gastrointestinal disorders. Recent advances in endoscopy, imaging and biomarkers have improved diagnostic capabilities, yet predicting disease behaviour remains imperfect.

Therapeutically, the landscape of CD has expanded substantially. From traditional anti-inflammatory and immunosuppressive agents to biologics and small-molecule drugs, the armamentarium has grown. Conventional medical therapies - even the most modern - aiming to dampen the inflammatory and immediate disease burden, however, generally fail to improve the long-term course of CD[5].

In light of these developments, the present paper aims to provide an up-to-date overview of Crohn's disease, focusing on the underlying pathogenetic mechanisms, current diagnostic approaches and modern treatment strategies and emerging therapies.

2. Pathophysiology

2.1 Genetics

Genetic susceptibility plays a fundamental role in the development of Crohn's disease, as evidenced by strong familial aggregation and twin studies. Large-scale genomic analyses show that the genetic contribution is substantial[6], highlighting the importance of inherited factors in disease onset. Monozygotic twins demonstrate markedly higher concordance rates for CD compared with dizygotic twins, underscoring the influence of heritable components. Genome-wide association studies (GWAS) have identified more than 200 susceptibility loci associated with inflammatory bowel diseases, many of which are specifically linked to Crohn's disease. CD is driven by multiple genetic variants of small effect[7], emphasising its polygenic nature. These genes influence key biological pathways such as innate immunity, epithelial barrier integrity, autophagy and microbial recognition. Importantly, genetic predisposition alone does not fully determine disease development. Rather, it interacts with environmental exposures and microbial factors to trigger chronic intestinal inflammation.

Among the identified susceptibility genes, NOD2 remains the most strongly associated with Crohn's disease. NOD2 encodes an intracellular pattern-recognition receptor that detects muramyl dipeptide derived from bacterial cell walls. Mutations in this gene impair microbial sensing and subsequent immune activation. NOD2 regulates host responses to bacterial molecules[8]. Variants such as R702W, G908R and 1007fs have been linked to decreased NF-κB activation and reduced production of antimicrobial peptides, particularly in ileal tissue. These defects contribute to impaired bacterial clearance and increased susceptibility to chronic inflammation. Clinically, NOD2 mutations are associated with ileal disease location and stricturing behaviour, suggesting that genetic variation not only influences risk but also shapes disease phenotype. The functional consequences of NOD2 mutations illustrate how disrupted innate immune recognition forms a cornerstone of Crohn's disease pathogenesis.

Autophagy is an essential cellular process that facilitates the degradation of intracellular pathogens and regulates immune responses. Genetic evidence shows that autophagy dysfunction is a major contributor to Crohn's disease. The ATG16L1 T300A variant is one of the most significant findings in this pathway. ATG16L1 is required for autophagy[9], and its impaired function reduces autophagosome formation. This leads to defective clearance of intracellular bacteria and abnormal Paneth cell granule secretion, both of which are characteristic of CD. Similarly, IRGM (Immunity-Related GTPase Family M Protein) olymorphisms disrupt autophagy initiation and impair microbial degradation. Disruption of autophagy pathways results in increased persistence of intracellular microbes and an exaggerated inflammatory response. Thus, variants in ATG16L1 and IRGM highlight the importance of host cellular homeostasis in maintaining gut immune equilibrium and preventing chronic inflammation.

Variants in immune-related genes further contribute to Crohn's disease by altering cytokine signalling and adaptive immune responses. One of the most important genes in this category is IL23R. The IL-23 signalling pathway plays a central role in the maintenance and activation of Th17 cells. IL23R variants represent a major IBD susceptibility gene[10]. Protective IL23R variants reduce responsiveness to IL-23, thereby limiting Th17-mediated inflammation. Conversely, risk alleles promote sustained cytokine production and chronic intestinal injury. Additional genetic associations include variants in JAK2 and STAT3, which influence downstream cytokine signalling pathways. These molecules are integral to T-cell differentiation and pro-inflammatory cytokine production. Dysregulation of these immune pathways contributes to a persistent imbalance between effector and regulatory responses. Collectively, these findings demonstrate that disruptions in cytokine networks and adaptive immunity represent a key component of Crohn's disease pathophysiology.

2.2 Gut Microbiome

Dysbiosis, defined as an imbalance in the composition and function of the gut microbiota, is a central feature of Crohn's disease. Numerous studies have demonstrated that patients with CD exhibit reduced microbial diversity and significant shifts in bacterial populations. IBD patients have been reported to show a marked decrease in the abundance of Firmicutes and an increased abundance of Proteobacteria[11]. This reduction in beneficial commensals, such as *Faecalibacterium prausnitzii*, weakens the anti-inflammatory capacity of the microbiota and disrupts mucosal homeostasis. Dysbiosis is believed not only to reflect ongoing

inflammation but also to contribute to disease initiation. Frank et al. described this phenomenon as microbial imbalance[12]. The combined loss of protective species and expansion of pro-inflammatory bacteria sets the stage for abnormal immune responses and chronic intestinal inflammation.

Among the microorganisms implicated in Crohn's disease, adherent-invasive *Escherichia coli* (AIEC) has received particular attention. AIEC strains are able to adhere to intestinal epithelial cells, invade them, and survive within macrophages, promoting persistent inflammation. AIEC strains invade intestinal epithelial cells[13]. Their ability to resist intracellular killing leads to sustained activation of pro-inflammatory cytokines, particularly TNF-α and IL-6. Furthermore, hosts with genetic susceptibility—especially variants in NOD2 or ATG16L1—are less able to control AIEC colonisation. This illustrates the tight relationship between microbial composition and host genetic factors. Other pathobionts implicated in CD progression include certain *Ruminococcus gnavus* strains and increased abundance of *Enterobacteriaceae*, which contribute to mucosal inflammation and epithelial damage.

Microbial metabolites exert profound effects on gut homeostasis, immune modulation and inflammation. Short-chain fatty acids (SCFAs), especially butyrate, are critical for epithelial integrity, yet their levels are markedly decreased in Crohn's disease. As one metabolic analysis noted, the reduction of the intracellular availability of butyrate in colonocytes may decrease its protective effects toward cancer in IBD patients[14]. Reduced SCFA availability weakens the mucosal barrier and diminishes regulatory T-cell function. Conversely, pro-inflammatory metabolites such as lipopolysaccharides (LPS) stimulate toll-like receptors and enhance cytokine production. The response to bacterial LPS provides a superb illustration of innate immune function[15]. Bile acid metabolites also influence inflammation: dysbiosis alters bile acid conversion, fostering an environment that favours Th17 expansion. These metabolic disturbances illustrate how shifts in microbial function—not just composition—drive chronic inflammation in Crohn's disease.

2.3 Immune System

The innate immune system plays a central role in the early recognition of microbes and the initiation of inflammatory responses in Crohn's disease. Defects in innate immunity contribute to impaired bacterial clearance and sustained activation of pro-inflammatory pathways. Macrophages and dendritic cells in CD often exhibit abnormal cytokine secretion, leading to excessive stimulation of adaptive immunity. A hallmark of innate immune activation in CD is the response to bacterial components such as lipopolysaccharides (LPS). Bacterial LPS act as extremely strong stimulators of innate immunity[16]. This heightened responsiveness reflects dysregulated pattern-recognition receptor (PRR) signalling, particularly involving TLR4 and NOD2. Because NOD2 variants impair microbial sensing, patients exhibit reduced antimicrobial peptide production and increased mucosal bacterial load. Collectively, innate immune defects provide a foundation for chronic inflammation in Crohn's disease.

Adaptive immune responses in Crohn's disease are characterised by dysregulated T-cell activity, particularly skewing toward Th1 and Th17 phenotypes. These subsets promote chronic inflammation by secreting pro-inflammatory cytokines including TNF-α, IFN-γ, IL-12 and IL-23. Patients with CD have been shown to have increased Th17 cells[17]. This imbalance results in persistent mucosal immune stimulation and tissue destruction. Reduced function of regulatory T cells further aggravates inflammation, as tolerance toward commensal bacteria is compromised. Cytokine signalling pathways, including IL-23R–STAT3 and JAK2-mediated cascades, amplify T-cell activation. Together, these immune deviations sustain the chronicity and relapse-prone course of Crohn's disease.

Loss of tolerance to commensal gut bacteria is a defining feature of Crohn's disease. In a healthy gut, immune responses against resident microbes are tightly controlled, but in CD this equilibrium becomes disrupted. CD involves chronic, immune-mediated inflammation [18]. Genetic susceptibility, epithelial barrier defects and dysbiosis all contribute to misdirected immune activation. When regulatory mechanisms fail, harmless microbial antigens trigger exaggerated inflammatory responses, perpetuated by both innate and adaptive immunity. Persistent exposure to luminal antigens promotes cytokine overproduction, granuloma formation and progressive tissue injury. The resulting cycle of dysregulated host-microbe interactions drives the characteristic chronicity of Crohn's disease.

2.4 Autophagy Dysfunction

Autophagy is an essential cellular mechanism responsible for maintaining intestinal homeostasis through the elimination of intracellular pathogens and regulation of immune processes. Autophagy eliminates intracellular microbes and provides host defence against bacterial infection[19]. Through xenophagy, intestinal epithelial cells and macrophages identify and degrade bacteria that breach the mucosal barrier, preventing uncontrolled inflammation. Autophagy also participates in the antigen presentation process[20]. Together, these functions ensure that microbial exposure is controlled, epithelial integrity is maintained, and immune activation remains appropriately regulated. When autophagy is impaired, pathogenic bacteria survive longer within host cells, increasing antigenic stimulation and promoting chronic inflammation characteristic of Crohn's disease.

Genetic studies highlight autophagy dysfunction as a key component of Crohn's disease pathogenesis, particularly involving ATG16L1 and NOD2. One of the most significant findings is the ATG16L1 T300A variant. Cells expressing this risk allele show impaired bacterial handling[21]. This impairment compromises the formation of autophagosomes and reduces the ability of epithelial and immune cells to clear intracellular bacteria. Moreover, ATG16L1 deficiency affects the function of Paneth cells - specialised intestinal epithelial cells responsible for secreting antimicrobial peptides. ATG16L1-deficient Paneth cells exhibit striking abnormalities in the granule exocytosis pathway[9], resulting in reduced defensin secretion and impaired mucosal defence.

Similarly, mutations in NOD2, the first Crohn's-associated gene identified, alter innate immune sensing of bacterial muramyl dipeptide. NOD2 in susceptibility to CD, and suggest a link between an innate response to bacterial components and development of disease[8], NOD2 normally cooperates with ATG16L1 in recruiting autophagy machinery. When either gene is mutated, bacteria persist within host cells, leading to chronic immune activation.

Taken together, defects in ATG16L1 and NOD2 create a synergistic vulnerability: impaired xenophagy, defective antimicrobial peptide secretion, and exaggerated immune responses. These abnormalities support persistent bacterial survival in the mucosa, driving the chronic inflammation characteristic of Crohn's disease.

2.5 Epithelial barrier

The intestinal mucosal barrier is composed of a monolayer of columnar epithelial cells [22] which is overlaid by mucus and antimicrobial products; together these elements separate the luminal microbiota from host tissues and maintain mucosal homeostasis.. Paneth cells, located at the base of small-intestinal crypts, secrete granules rich in antimicrobial peptides (α-defensins and lysozyme) that contribute to luminal sterility and shape microbial composition - indeed, Paneth cells secrete these microbicidal granules[23]. The mucus layer itself is stratified, providing a largely sterile inner layer and a looser outer layer that hosts commensals; tight junction proteins (occludin, claudins, ZO-1) dynamically regulate paracellular permeability and are central to barrier integrity.

Loss of barrier integrity - often referred to as increased intestinal permeability or "leaky gut" - permits translocation of microbial products and whole bacteria, which can trigger and perpetuate mucosal inflammation. Clinical and mechanistic reviews note that increased permeability is linked to stress, immune activation and epithelial injury, and that it facilitates the passage of luminal antigens into the mucosa. A defective mucosal barrier may result in increased intestinal permeability[24] in multiple conditions including IBD. In Crohn's disease specifically, dysfunction of Paneth cells is a well-documented contributor: patients with ileal CD show reduced antimicrobial activity and reduced Paneth cell α-defensins[25], findings that compromise mucosal defence and correlate with bacterial adherence. Mechanistically, genetic or autophagy-related defects (e.g., ATG16L1 variants) produce Paneth cell secretory abnormalities. The resulting increase in luminal antigen load and paracellular leak drives innate and adaptive immune activation, forming a feed-forward loop that sustains chronic inflammation in Crohn's disease.

2.6 Environmental factors

Dietary patterns strongly influence intestinal homeostasis and have been linked to the risk and course of Crohn's disease. In particular, a Westernised dietary pattern - high in saturated fats, refined sugars and ultra-processed foods, and low in fibre - has been associated with an increased risk of IBD and with pro-inflammatory changes in the gut microbiota. Also, food preparation methods may affect the risk of IBD development. Processed foods, frequently seen in Western diets, include the use of preservatives and emulsifiers[26]. Dietary additives such as emulsifiers and other ultra-processed food components have been

proposed to disrupt the mucous layer and epithelial barrier, promoting low-grade inflammation and microbial shifts; in conclusion, these components promote gut inflammation[27].

Smoking is one of the most consistently identified environmental risk factors for Crohn's disease and is associated with a more aggressive disease course. Cigarette smoking is considered an important risk factor for developing Crohn's disease (CD)[28]. Smoking increases the likelihood of flares, the need for immunosuppression, surgical intervention and postoperative recurrence. Smoking also alters mucosal immune responses and the gut microbiome, thereby worsening clinical outcomes in CD patients.

Early-life exposures and broader societal changes influence Crohn's disease risk through effects on the developing microbiome and immune system. Epidemiological studies and meta-analyses indicate that early-life antibiotic exposure is associated with a higher risk of later IBD - notably Crohn's disease - with conclusions such as antibiotic use in the first year of life is associated with a modestly increased risk for CD[29]. Recurrent infections and excessive antibiotic use perturb microbial diversity and reduce colonisation resistance, facilitating expansion of opportunistic taxa. At the population level, urbanisation and Westernisation (changes in diet, environment, pollution and microbial exposures) have been correlated with rising IBD incidence[30]. These lines of evidence support a model in which antibiotic exposure, infections and urban lifestyles jointly alter the microbiome and immune programming, increasing susceptibility to Crohn's disease.

3. Clinical Presentation and Classification

The primary and most frequent manifestations of Crohn's disease involve the gastrointestinal tract. The most common symptoms of CD include diarrhea, abdominal pain and weight loss[31]. In many cases, diarrhea may be persistent and intermittent, sometimes accompanied by abdominal cramping. In most cases, they occur in young patients and include abdominal pain in the right iliac fossa, chronic diarrhea, weight loss, anorexia and fatigue[32]. Rectal bleeding is less frequent than in ulcerative colitis. Stools frequently contain microscopic blood (eg, positive guaiac or immunochemical test); however, some patients with CD with predominantly colonic involvement may have grossly bloody stools[33]. When the small intestine (e.g., terminal ileum) is affected, malabsorption may cause steatorrhea, nutrient deficiencies (e.g., iron, vitamin B12), and protein loss, contributing to systemic signs of malnutrition.

Crohn's disease commonly extends beyond the gut: many patients experience extraintestinal symptoms that may occur in the eyes, joints, and skin[34]. Articular involvement may manifest as peripheral or axial arthritis, while dermatologic lesions - such as erythema nodosum or pyoderma gangrenosum - are among the more frequent skin manifestations. Ophthalmologic complications (e.g., uveitis, episcleritis) are also encountered, as well as hepatobiliary disorders including stones, cholangitis or steatosis. In some patients, these extraintestinal signs may precede the intestinal symptoms or even be the first clue that motivates further diagnostics[31].

The clinical course and complications of Crohn's disease are heavily influenced by its pathoanatomic behaviour. Traditionally, three main phenotypes are recognized:

1. Inflammatory (non-stricturing, non-penetrating) - characterised by mucosal and transmural inflammation without significant structural complications.
2. Stricturing - marked by progressive bowel wall thickening and fibrosis, leading to luminal narrowing, obstructive symptoms, and possible intermittent sub-occlusion.
3. Penetrating/fistulizing - inflammation leads to sinus tract formation, abscess or fistula formation, typically to perianal skin, other bowel loops or adjacent organs.

These categories reflect disease behaviour and inform prognosis and therapeutic decisions. Transmural inflammation often results in sinuses and fistulas, associated with sinus tracts that may give rise to fistulas and phlegmon formation[33]. Some patients initially present in a silent or mild form, only to develop strictures or fistulas years later.

To systematise the heterogeneity of Crohn's disease, the Montreal Classification is widely used; it considers three main domains: age at onset, disease location, and disease behaviour/phenotype. Under this scheme, patients are categorised based on when the disease first appeared (e.g., A1: ≤16 years; A2: 17-40; A3: >40), the anatomical distribution (e.g., L1 - ileal, L2 - colonic, L3 - ileocolonic, L4 - upper GI), and the behaviour (B1 - non-stricturing/non-penetrating, B2 - stricturing, B3 - penetrating)[35]. This classification is clinically valuable because it correlates with prognosis, risk of complications and helps guide therapeutic strategies (e.g., choice of biologics, monitoring, surgery).

Due to its transmural and segmental nature, Crohn's disease carries a substantial risk of complications: fistulas, abscesses, strictures, intestinal obstruction, malabsorption, nutritional deficiencies[31]. Perianal disease (fistulas, fissures, abscesses) is common and significantly impairs quality of life. Strictures of small or large intestine may lead to recurrent obstruction - patients may present with cramp-like abdominal pain, bloating, nausea and vomiting. Also, patients with Crohn's disease are at risk for early small bowel and colorectal cancer[36].

4. Diagnostics

The diagnostic process in Crohn's disease relies on the integration of clinical features, biomarkers, endoscopic findings, histopathology and cross-sectional imaging. There is no single diagnostic tool for IBD[37], necessitating a multimodal approach. Clinical suspicion based on diarrhea, abdominal pain, weight loss and systemic symptoms prompts further testing. Current guidelines emphasise that accurate diagnosis requires a combination of clinical, endoscopic, radiologic and histologic criteria[38]. Because Crohn's disease can affect any region from mouth to anus, and often involves the small bowel, the diagnostic process is individualized and sequential, progressing from non-invasive assessment to direct visualization and imaging.

Laboratory tests support initial evaluation by quantifying inflammatory activity, detecting anemia and assessing nutritional status. In clinical practice, CRP and FCP are frequently used by primary care clinicians to differentiate between IBD and irritable bowel syndrome (IBS) and by IBD clinicians to evaluate symptoms and monitor response to therapy[39]. Additional laboratory abnormalities include microcytic or normocytic anemia and hypoalbuminemia in advanced or complicated disease. Although laboratory markers support the diagnostic process, they lack specificity and must be interpreted alongside endoscopic and imaging findings.

Endoscopy remains the most definitive diagnostic tool and is used to evaluate disease location, severity, and mucosal pattern. The European Crohn's and Colitis Organisation underscores that for suspected CD, ileocolonoscopy and biopsies from the terminal ileum as well as each colonic segment to look for microscopic evidence of CD are first line procedures to establish the diagnosis[40]. Classic endoscopic features include discontinuous ("skip") lesions, aphthous and linear ulcers and segmental inflammation. The presence of cobblestoning, reflecting intersecting ulcers and edematous mucosa, is another hallmark Endoscopy also enables biopsy collection, essential for histologic confirmation.

Histopathologic evaluation provides important support for the diagnosis and can differentiate Crohn's disease from ulcerative colitis or infectious etiologies. The presence of epithelioid non-caseating granulomas on histology has been described as the hallmark of CD[41]. However, granulomas are present in only a minority of biopsies, and their absence does not exclude the diagnosis. Crohn's disease typically shows focal crypt architectural distortion, patchy and transmural inflammation[42], distinguishing Crohn's disease from the continuous mucosal disease of ulcerative colitis (2012). Also, fibrosis, neural hyperplasia and smooth muscle hypertrophy are common in stricturing disease.

Cross-sectional imaging is indispensable, especially for assessing small bowel involvement and extramural complications such as fistulas, abscesses and strictures. Magnetic resonance enterography (MRE) is recommended as a modality with the highest accuracy for CD lesions[43]. Intestinal ultrasound has a good accuracy in the diagnosis of Crohn's disease, as well as in the assessment of disease activity, extent, and evaluating disease-related complications, namely strictures, fistulae, and abscesses[44]. Computed tomography (CT), although associated with radiation, remains essential in the emergency setting because CT is useful to detect abscesses, fistulas and obstruction.

While conventional biomarkers remain clinically dominant, advances in molecular diagnostics offer new opportunities for precision medicine. Novel biomarkers include cytokines, genetic markers and microbial signatures. Microbiome-based diagnostics are particularly promising. Genetic markers, although not diagnostic by themselves, may refine risk stratification. For instance, the discovery that IL23R variants represent a major IBD susceptibility gene[10] supports the integration of genomic data into future diagnostic models.

Identifying Crohn's disease often requires distinguishing it from ulcerative colitis (UC), infectious colitides and functional disorders. Infectious etiologies may closely resemble Crohn's disease both clinically and radiologically. Infectious colitis can mimic IBD clinically and radiologically. Functional bowel disorders also complicate the diagnostic picture, as IBS symptoms overlap with mild IBD. Comprehensive, sequential evaluation is therefore essential to avoid misclassification.

5. Treatment

Management of Crohn's disease increasingly follows a structured treat-to-target (T2T) approach, replacing traditional symptom-driven strategies. Clinical remission and endoscopic healing are the primary treatment targets in Crohn's disease. This shift reflects evidence linking mucosal healing with reduced hospitalizations, surgeries and long-term disability. Because of the poor correlation between clinical symptoms and disease activity, symptom monitoring alone is insufficient[45]. Biomarkers (CRP, fecal calprotectin), endoscopy and imaging form the basis of tight disease control, allowing early treatment adjustment when targets are not met.

Therapy in Crohn's disease is divided into induction - aimed at rapidly suppressing active inflammation - and maintenance, focused on sustaining remission. The goals of induction therapy are rapid control of inflammation, whereas maintenance therapy focuses on sustaining remission and preventing complications. Induction uses fast-acting agents such as corticosteroids, enteral nutrition or biologics. Maintenance relies on immunomodulators or biologics to prevent relapse. Anti-TNF therapy is recommended for induction and maintenance of remission in moderate-to-severe Crohn's disease Importantly, steroids should not be used for maintenance therapy due to toxicity and lack of long-term efficacy. Together, induction and maintenance strategies form a continuous, target-driven therapeutic pathway.

5.1 Conventional Therapies

Corticosteroids remain an important component of induction therapy in moderate to severe Crohn's disease due to their potent anti-inflammatory effects. Their mechanism relies on broad suppression of pro-inflammatory pathways, inhibition of cytokine transcription, and reduction of immune cell trafficking. Short-term efficacy has been consistently demonstrated; randomized trials established that corticosteroids were found to be significantly more effective than placebo at inducing remission in Crohn's disease[46]**.** However, despite their rapid onset of action, corticosteroids do not promote mucosal healing or alter long-term disease progression. This is why current international guidelines recommend restricting their use to induction phases only. Steroids carry substantial toxicity, especially with prolonged exposure. Adverse effects include metabolic disturbances, infections, osteoporosis, psychiatric symptoms and skin changes. Because of this, a key goal in modern management is achieving steroid-free remission using immunomodulators or biologic therapy.

Immunomodulatory thiopurines - azathioprine (AZA) and 6-mercaptopurine (6-MP) - as well as methotrexate (MTX) represent cornerstone therapies for maintenance of remission in Crohn's disease. Their onset of action is slow, but they are effective for long-term disease control and for reducing steroid dependence. A Cochrane review concluded that Azathioprine and 6-mercaptopurine are more effective than placebo for maintenance of remission in Crohn's disease[47]. Mechanistically, thiopurines inhibit lymphocyte proliferation via purine synthesis pathways. Azathioprine is frequently combined with anti-TNF therapy to improve durability of response and reduce immunogenicity. Methotrexate is an alternative for patients intolerant of thiopurines or with contraindications. MTX's immunomodulatory effects are mediated through inhibition of dihydrofolate reductase and altered cytokine signaling. All immunomodulators require careful monitoring due to potential hematologic, hepatic and infectious complications. Thiopurines can cause leukopenia or pancreatitis, whereas MTX may induce hepatotoxicity or pulmonary toxicity. Therefore, therapy is individualized based on TPMT activity, tolerance, disease phenotype and long-term treatment goals.

5.2 Biologic and Targeted Therapies

The anti-TNF agents such as Infliximab and Adalimumab remain foundational in the management of moderate-to-severe Crohn's disease. Anti-TNF therapies achieved higher clinical remission rates than placebo, with infliximab yielding the most favorable results[48]. In randomized clinical trials, these agents have demonstrated efficacy both for induction and maintenance of remission: the level of evidence supporting the use of infliximab and adalimumab for the induction and maintenance of remission is stronger than that for certolizumab pegol[49]. In many patients, anti-TNF therapy also reduces the need for steroids and lowers rates of hospitalizations and surgery over the long term, supporting its position as first-line biological therapy in appropriately selected patients.

Targeting the IL-12/23 axis with Ustekinumab offers an alternative mechanism of immune modulation in CD. Ustekinumab binds the p40 subunit shared by interleukins 12 and 23, thereby inhibiting Th1 and Th17 mediated inflammatory pathways. For patients with prior anti-TNF failure or intolerance, ustekinumab often constitutes a valuable second-line biologic.

Gut-selective anti-integrin therapy with Vedolizumab offers a different safety and pharmacologic profile. Vedolizumab acts by blocking the α4β7 integrin, preventing leukocyte trafficking to the intestinal mucosa, which results in a mostly gut-specific immunosuppressive effect. The selectivity reduces systemic immunosuppression; as one review notes, vedolizumab's gut-selective mechanism … results in a lower risk of systemic infections[50]. It maintains remission in moderate-to-severe CD, especially in patients who failed or did not tolerate anti-TNF or immunomodulator therapy.

Recently, small-molecule drugs have expanded the therapeutic toolkit for CD. Among them, oral Upadacitinib, Tofacitinib and Filgotinib - all inhibitors of Janus kinases (JAK) - have shown promising results. According to a 2024 review: Small molecule Janus kinase (JAK) inhibitors have revolutionized the

management of … Crohn's disease … through their low immunogenicity, safety, and consistent pharmacologic response[51]. These agents offer rapid onset of action and can achieve clinical remission and maintenance in patients who are refractory or intolerant to biologics. Given their oral administration and favorable pharmacokinetics, JAK inhibitors represent a valuable option - although long-term safety data and individualized risk/benefit assessment remain necessary

5.3 Nutritional Therapy

Exclusive enteral nutrition (EEN) is widely recognized as a first-line nutritional intervention, particularly in pediatric patients with active CD. As noted in a recent review, EEN with polymeric diets satisfies the need to revert the acute inflammation in most pediatric CD patients[52]. In many cases, EEN has comparable efficacy to steroid therapy while avoiding the negative impact of corticosteroids on growth - an important consideration in pediatric populations. However, long-term adherence and palatability issues limit the practical use of EEN, especially over extended treatment periods or in older patients.

The Crohn's Disease Exclusion Diet (CDED) has emerged as the most evidence-supported elimination diet for CD. It was developed to reduce exposure to dietary components that are potentially pro-inflammatory, mediated by negative effects on the gut microbiota, immune response, and the intestinal barrier[53]. Additional clinical data confirm that CDED has been shown to induce remission in pediatric and adult patients with CD[54]. By contrast, evidence for the low-FODMAP diet (LFD) in CD remains limited. Current data are insufficient to show effects on inflammation or remission maintenance. A 2025 pilot study likewise concludes that LFD offers short-term relief of gastrointestinal symptoms[55] but may also reduce beneficial microbial taxa.

5.4 Surgical Treatment

Surgical intervention in CD is generally reserved for patients with complications that are refractory to medical therapy or when medical therapy fails to control disease. The most common indication for surgery is obstruction from stricturing disease, followed by abscesses and fistulae[56]. In addition, emergent surgical indications may include perforation or massive hemorrhage, while chronic complications such as non-resolving fistulae or abscesses may prompt elective surgery. Thus, surgery remains a critical option in the management of complicated CD, when structural complications (stenosis, fistulizing disease, abscess, perforation) occur or when disease fails to respond to pharmacologic therapy.

The surgical management of CD encompasses a variety of procedures, depending on the type and location of complications. For symptomatic fibrotic strictures (especially when not responsive to endoscopic dilation) - segmental resection of the diseased bowel segment or strictureplasty may be indicated. In more aggressive disease patterns - e.g. with abscesses, phlegmons, fistulae or perforation - bowel resection is generally preferred. In case of abscess formation or phlegmon, initial surgical management may involve drainage of abscess, often combined with resection or creation of a stoma if needed. For perianal or enteric fistulae, surgical drainage, seton placement, or resection may be used - depending on fistula complexity, location and associated sepsis. Overall, several surgical options are possible in medically refractory or complex Crohn's disease.

5.5 Future and Experimental Terapies

Recent advances highlight the gut microbiome as a key target for novel CD therapies, aiming to correct dysbiosis and restore intestinal homeostasis. As reviewed recently: therapies that directly target the dysbiotic microbiome for effective outcomes are emerging in IBD, including CD[57]. One such approach is Fecal Microbiota Transplantation (FMT). In a 2025 prospective trial in paediatric CD, oral FMT capsules combined with partial enteral nutrition (PEN) significantly decreased inflammatory markers and endoscopic disease activity by week 10. The authors conclude that FMT restores gut microbiota diversity and may be an effective therapy for children with active CD[58]. Meta-analyses and systematic reviews give a more cautious assessment: while some studies report increased remission or symptomatic improvement, a 2025 randomized controlled trial found that FMT was not effective at inducing clinical or endoscopic remission in adults with Crohn's disease. Thus, although FMT and other microbiome-modulating strategies (e.g. next-generation probiotics, prebiotics, microbial engineering) are promising, their utility in CD remains investigational, and larger controlled trials are still needed.

Another frontier in CD therapy involves cell-based and potentially gene-modulating approaches. Recent reviews on IBD experimental therapies list, among emerging strategies, mesenchymal stem cells (MSCs) and modulation of gut proteins including those regulating barrier function or autophagy, as plausible future

directions. Such therapies aim to leverage the regenerative and immunomodulatory capacities of MSCs or to correct underlying molecular dysfunctions (e.g. autophagy, epithelial barrier integrity) that contribute to chronic inflammation. Although clinical data remain limited, the conceptual framework supports that therapies beyond conventional immunosuppression targeting tissue repair, barrier function, or gene regulation may become part of future personalized treatment algorithms.

Given the heterogeneity of CD in terms of clinical presentation, course, and response to therapy, personalized treatment - guided by biomarkers, microbiome analysis, and phenotypic stratification - is increasingly considered a goal for future research. The gut microbiome itself may serve not only as therapeutic target, but also as potential biomarker for diagnosing, prognosing, and predicting therapy outcomes in IBD[57]. Computational approaches - for example in silico modeling of individual microbiomes to predict metabolic output and dietary needs - have been proposed as a tool to guide personalized nutritional or microbiome-targeted interventions in CD. In the future, such integration of microbiome profiling and possibly genotypic or transcriptomic data may allow to tailor therapy (immunologic, microbial, dietary or regenerative) to the individual patient's disease phenotype, underlying pathomechanism, and risk profile.

6. Prognosis and Quality of Life

Crohn's disease (CD) is a chronic, relapsing and remitting inflammatory bowel disease[1]. The risk of relapse is modulated by several factors: smoking (which increases recurrence and surgical risk), disease location and phenotype, treatment adherence, and early inflammatory burden. For example, studies report that patients with Crohn's disease who smoke have a 2.5-fold increased risk of surgical recurrence and a twofold risk of clinical recurrence compared to non-smokers[59]. Additional patient-related factors such as young age at diagnosis or penetrating disease phenotype are likewise associated with more aggressive disease trajectories and shorter remission intervals. Health-related quality of life is substantially impaired in CD: Patients with Crohn's disease consistently report lower quality of life compared with the general population and that symptom burden includes severe fatigue. Psychological comorbidity (depression, anxiety) is prevalent and correlates with higher healthcare use and worse outcomes. Long-term structural complications are frequent: population-based analyses report that nearly half of CD patients required a surgical resection within 10 years of diagnosis[60]. Nutritional deficiencies (iron, B12, folate, vitamin D) and other extraintestinal consequences are common.

7. Conclusions and Future Research Directions

Crohn's disease (CD) is a chronic, immune-mediated condition arising from the interaction of genetic susceptibility, environmental triggers, dysbiosis of the intestinal microbiome, and dysregulated mucosal immunity. Its heterogeneous clinical presentation and relapsing-remitting course necessitate a multidimensional diagnostic approach that integrates clinical evaluation, endoscopy, imaging, and biomarker assessment. Therapeutically, the management of CD has evolved from symptom-oriented strategies toward targeted modulation of immune pathways, with biologics, small-molecule inhibitors, and nutritional interventions now forming the backbone of contemporary care. Despite these advances, CD remains a condition marked by cumulative bowel damage, highlighting the importance of timely diagnosis, aggressive control of inflammation, and individualized treatment strategies.

Future research in CD is increasingly centered on mechanistic insights that may redefine therapeutic paradigms. Advances in microbiome science have revealed profound alterations in the composition and function of gut microbial ecosystems, positioning microbiome-directed therapies - including fecal microbiota transplantation, next-generation probiotics, and microbial metabolite supplementation - as promising investigational modalities. Parallel progress in mucosal immunology supports the development of highly specific immune interventions, such as cytokine-targeted antibodies, autophagy-modulating therapies, and cell-based approaches including mesenchymal stem cell transplantation. Precision medicine also represents a rapidly expanding frontier: the integration of pharmacogenomics and biomarker-driven stratification may allow clinicians to predict therapeutic response, identify high-risk phenotypes earlier, and tailor treatment with unmatched accuracy. As the understanding of CD pathobiology deepens, these research directions are anticipated to converge into personalized, mechanism-based care.

The final and critical consideration is the impact of early diagnosis and treatment optimization on long-term outcomes. Delayed recognition of CD allows inflammation to progress unchecked, increasing the likelihood of stricturing and penetrating complications, irreversible bowel damage, and surgical intervention. Early implementation of effective therapies - particularly biologics within a treat-to-target framework - has

been shown to improve remission rates, reduce hospitalization, and modify disease trajectory. Equally important is continuous monitoring and timely adjustment of treatment strategies to maintain mucosal healing and prevent relapse. As evidence accumulates, it becomes increasingly clear that early, proactive management represents one of the most powerful tools available to clinicians, reinforcing the need for improved diagnostic pathways, accessible specialized care, and personalized therapeutic planning.

REFERENCES

1. Cockburn E. al. (2023). *Crohn's disease: An update. Clinical Medicine*, 23(6), 549–557. https://www.sciencedirect.com/science/article/pii/S1470211824000253
2. Cushing K. & Higgins P. D. R. (2021). *Management of Crohn disease: A review. JAMA*, *325*(1), 69–80. https://pmc.ncbi.nlm.nih.gov/articles/PMC9183209/
3. Anaya P. & Pérez C. (2023). *An updated review of Crohn's disease. International Journal of Medical Sciences and Clinical Research*, 3 (8):1592-94. https://ijmscr.ijpbms.com/index.php/ijmscrs/article/view/987
4. Mukim M. et al. (2022). *Crohn's disease: A review on epidemiology, diagnosis and therapeutic management. Indian Drugs,* 59(9), 16–28. https://www.indiandrugsonline.org/issuesarticle-details?id=MTM0Nw==
5. Janssen L. M. et al. (2023). *A systematic review on long-term efficacy outcome measures in Crohn's disease patients. Journal of Crohn's and Colitis, 17(9), 1528–1536. https://doi.org/10.1093/ecco-jcc/jjad037*
6. Jostins L. et al. (2012). *Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature*, *491*(7422), 119–124. https://www.nature.com/articles/nature11582
7. Liu, J. Z., et al. (2015). *Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nature Genetics*, *47*(9), 979–986. https://www.nature.com/articles/ng.3359
8. Ogura Y. et al. (2001). *A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. The New England Journal of Medicine*, *345*(15), 1085–1090. https://pubmed.ncbi.nlm.nih.gov/11385577/
9. Cadwell K. et al. (2008). *A key role for autophagy and the autophagy gene ATG16L1 in mouse and human intestinal Paneth cells. Nature*, *456*(7219), 259–263. https://pubmed.ncbi.nlm.nih.gov/18849966/
10. Duerr R. H. et al. (2006). *A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science*, *314*(5804), 1461–1463. https://www.science.org/doi/10.1126/science.1135245
11. Xie H. et al. (2025). *Gut microbiota dysbiosis in inflammatory bowel disease: Interaction with intestinal barriers and microbiota-targeted treatment options. Frontiers in Cellular and Infection Microbiology*, 15, Article 1608025. https://www.frontiersin.org/articles/10.3389/fcimb.2025.1608025
12. Frank D. N. et al. (2007). *Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proceedings of the National Academy of Sciences of the United States of America*, 104(34), 13780–13785. https://www.pnas.org/doi/10.1073/pnas.0706625104
13. Darfeuille-Michaud A. et al. (2004). *High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. Gastroenterology*, 127(2), 412–421. https://www.gastrojournal.org/article/S0016-5085(04)00771-1/fulltext
14. Canani R. B. et al. (2011). *Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. Journal of Pediatric Gastroenterology and Nutrition*, 53(Suppl 2).
15. Beutler B. (2000). *Tlr4: Central component of the sole mammalian LPS sensor. Current Opinion in Immunology*, *12*(1), 20–26. https://doi.org/10.1016/S0952-7915(99)00046-1
16. Alexander C. & Rietschel E. T. (2001). *Bacterial lipopolysaccharides and innate immunity. Journal of Endotoxin Research*, 7(3), 167–202. https://journals.sagepub.com/doi/10.1177/09680519010070030101
17. Katsanos K. A. & Papadakis K. A. (2016). *Inflammatory bowel disease: Updates on molecular targets for biologics. Gut and Liver*, 11(5), 597–612. https://www.gutnliver.org/journal/view.html?doi=10.5009/gnl16308
18. Sartor R. B. (2008). *Microbial influences in inflammatory bowel diseases. Gastroenterology*, 134(2), 577–594. https://www.gastrojournal.org/article/S0016-5085%2807%2902157-9/fulltext
19. Levine B. et al. (2011). *Autophagy in immunity and inflammation. Nature*, 469(7330), 323–335. https://www.nature.com/articles/nature09782
20. Zhong-Xing M. et al. (2025). *Autophagy in inflammatory bowel disease: Immunization, etiology, and therapeutic potential. Frontiers in Immunology*, 16, Article 1543040. https://www.frontiersin.org/articles/10.3389/fimmu.2025.1543040/full
21. Kuballa P. et al. (2008). *Impaired autophagy of an intracellular pathogen induced by a Crohn's disease–associated ATG16L1 variant. PLoS ONE*, 3(10), e3391. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0003391
22. Luissint A.-C. et al. (2016). *Inflammation and the intestinal barrier: Leukocyte–epithelial cell interactions, cell junction remodeling, and mucosal repair. Gastroenterology*, 151(4), 616–632. https://www.gastrojournal.org/article/S0016-5085(16)34785-0/fulltext

23. Tokiyoshi A. et al. (2004). *The role of Paneth cells and their antimicrobial peptides in innate host defense. Trends in Microbiology*, 12(9), 394–398. https://www.cell.com/trends/microbiology/abstract/S0966-842X(04)00139-8
24. Michielan A. & D'Incà R. (2015). *Intestinal permeability in inflammatory bowel disease: Pathogenesis, clinical evaluation, and therapy of leaky gut. Mediators of Inflammation*, 2015, Article 628157. https://pmc.ncbi.nlm.nih.gov/articles/PMC4637104/
25. Wehkamp, J. et al. (2005). *Reduced Paneth cell α-defensins in ileal Crohn's disease. Proceedings of the National Academy of Sciences of the United States of America*, 102(50), 18129–18134. https://www.pnas.org/doi/10.1073/pnas.0505256102
26. Manski A. et al. (2023). *Diet and nutrition in inflammatory bowel disease: A review of the literature. Nutrients*, 15(19), Article 4176. https://pmc.ncbi.nlm.nih.gov/articles/PMC10782214/
27. Adolph T. E. et al. (2022). *Food fuelling inflammatory bowel diseases: Preclinical and clinical evidence. Gut*, 71(12), 2574–2586. https://gut.bmj.com/content/71/12/2574
28. Karczewski, J. et al. (2014). *The effect of cigarette smoking on the clinical course of inflammatory bowel disease. Przegląd Gastroenterologiczny*, 9(3), 153–158. https://pmc.ncbi.nlm.nih.gov/articles/PMC4110362/
29. Andes M-Ch. et al. (2021). *Early-life exposure to antibiotics and risk of Crohn's disease: A nationwide cohort study. Alimentary Pharmacology & Therapeutics*, 53(8), 939–948. https://pmc.ncbi.nlm.nih.gov/articles/PMC8889299/
30. Hracs L. et al. (2025). *Global evolution of inflammatory bowel disease across countries and its relation to urbanisation and Westernisation. Nature*, 629, 123–132. https://www.nature.com/articles/s41586-025-08940-0
31. Łodyga M. et al. (2021). *Guidelines for the management of patients with Crohn's disease: Recommendations of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology. Przegląd Gastroenterologiczny*, 16(4), 257–296. https://www.termedia.pl/Guidelines-for-the-management-of-patients-with-Crohn-s-disease-Recommendations-of-the-Polish-Society-of-Gastroenterology-and-the-Polish-National-Consultant-in-Gastroenterology,41,45649,1,1.html
32. Teixeira da Silva Júnior, R. et al. (2023). *Crohn's disease and clinical management today: How it does? World Journal of Methodology*, 13(4), 236–251. https://pmc.ncbi.nlm.nih.gov/articles/PMC10789097/
33. Peppercorn M. A. & Kane S. V. (2020). *Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults.* In *UpToDate*. Wolters Kluwer. https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohn-disease-in-adults
34. AMBOSS. (2024). *Crohn disease.* AMBOSS Medical Knowledge Platform.
35. Satsangi J. et al. (2006). *The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut*, 55(6), 749–753. https://pmc.ncbi.nlm.nih.gov/articles/PMC1856208/
36. Baumgart D. C., & Sandborn W. J. (2012). *Crohn's disease. The Lancet*, 380(9853), 1590–1605. https://www.thelancet.com/article/S0140-6736(12)60026-9/fulltext
37. Yang H. et al. (2024). *Diagnostic procedures for inflammatory bowel disease: Laboratory, endoscopy, pathology, imaging, and beyond. Diagnostics*, 14(5), Article 1047. https://pmc.ncbi.nlm.nih.gov/articles/PMC11241288/
38. Panés J. et al. (2016). *Advances in the use of endoscopy, radiology, and biomarkers to monitor inflammatory bowel diseases. Gastroenterology*, 150(2), 415–429. https://www.gastrojournal.org/article/S0016-5085(16)35227-1/fulltext
39. Pouillon L. et al. (2023). *Biomarkers in inflammatory bowel disease: A practical guide. Therapeutic Advances in Gastroenterology*, 16, 1–20. https://pmc.ncbi.nlm.nih.gov/articles/PMC11085009/
40. Van Assche G. et al. (2010). *The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. Journal of Crohn's and Colitis*, 4(1), 7–27. https://www.getaid.org/wp-content/uploads/2013/07/https__www.ecco-ibd.eu_images_6_Publication_6_3_ECCO-Guidelines_2010_CD_guidelines_definitions_diagnosis.pdf
41. Saade M. C. et al. (2022). *Significance of granulomas in the outcomes of Crohn's disease patients. Journal of Clinical Medicine*, 11(18), Article 5408. https://pmc.ncbi.nlm.nih.gov/articles/PMC9399581/
42. Marini M. et al. (2003). *TNF-α neutralization ameliorates the severity of murine Crohn's-like ileitis by abrogation of intestinal epithelial cell apoptosis. Proceedings of the National Academy of Sciences of the United States of America*, 100(14), 8366–8371. https://www.pnas.org/doi/10.1073/pnas.1432897100
43. Ohtsuka K. et al. (2016). *Magnetic resonance enterography for the evaluation of the deep small intestine in Crohn's disease. Intestinal Research*, 14(2), 148–155. https://www.researchgate.net/publication/302876384_Magnetic_resonance_enterography_for_the_evaluation_of_the_deep_small_intestine_in_Crohn's_disease
44. Frias-Gomes C. et al. (2021). *Intestinal ultrasound in inflammatory bowel disease: A valuable and increasingly important tool. GE Portuguese Journal of Gastroenterology*, 28(2), 104–113. https://pmc.ncbi.nlm.nih.gov/articles/PMC9275009/
45. Kemp K. et al. (2024). *Crohn's disease management: Translating STRIDE-II for UK clinical practice. Therapeutic Advances in Gastroenterology*, 17, 1–15.
46. Benchimol E. I. et al. (2008). *Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews*, 2008(2), CD006792. https://pmc.ncbi.nlm.nih.gov/articles/PMC6718222/

47. Prefontaine E. et al. (2009). *Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews*, 2009(1), CD000067. https://pubmed.ncbi.nlm.nih.gov/19160175/
48. Zaidi S. F. et al. (2025). *A comprehensive review of the role of biologics and small-molecule therapies in the long-term management of Crohn's disease. Cureus*, 17(1), e367814. https://assets.cureus.com/uploads/review_article/pdf/367814/20251022-197145-xhdh51.pdf
49. Telli P. et al. (2024). *Treatment of Crohn's disease: Induction of remission, maintenance, and management of remission period - A comprehensive review. Journal of Enterocolitis*, 14(1), 1–18. https://jenterocolitis.org/storage/upload/pdfs/1745495943-en.pdf
50. Babczyńska M. et al. (2025). *Comparative effectiveness of risankizumab versus other biologics in Crohn's disease: Long-term and quality-of-life outcomes after inadequate response to prior therapy. Journal of Clinical Medicine*, 14(4), Article 998.
51. Fansiwala K. et al. (2024). *Small molecules, big results: How JAK inhibitors have transformed the treatment of patients with inflammatory bowel disease. Digestive Diseases and Sciences*, 69(4), 1087–1098. https://link.springer.com/article/10.1007/s10620-024-08792-0
52. Brindicci V. F. et al. (2025). *Enteral nutrition in pediatric Crohn's disease: New perspectives. Nutrients*, 17(19), Article 3124. https://www.mdpi.com/2072-6643/17/19/3124
53. Sigall Boneh R. et al. (2024). *The Crohn's disease exclusion diet: A comprehensive review of evidence, implementation strategies, practical guidance, and future directions. Nutrients*, 16(2), Article 243. https://pubmed.ncbi.nlm.nih.gov/37978895/
54. Fliss-Isakov N. et al. (2023). *Crohn's disease exclusion diet for the treatment of Crohn's disease: Real-world experience from a tertiary center. Nutrients*, 15(7), Article 1684. https://pmc.ncbi.nlm.nih.gov/articles/PMC10455757/
55. Castillo A. et al. (2025). *Effects of a low FODMAP diet on gut microbiota in inflammatory bowel disease: A systematic review. The American Journal of Gastroenterology*, 120(Suppl 1), S2154. https://journals.lww.com/ajg/Fulltext/2025/10002/S2154_Effects_of_a_Low_FODMAP_Diet_on_Gut.2154.aspx
56. Toh J. W. et al. (2016). *Indications and surgical options for small bowel, large bowel and perianal Crohn's disease. World Journal of Gastroenterology*, 22(40), 8892–8904. https://www.wjgnet.com/1007-9327/full/v22/i40/8892.htm
57. Wang X. et al. (2024). *The emerging role of the gut microbiota and its application in inflammatory bowel disease. Biomedicine & Pharmacotherapy*, 173, Article 116065. https://www.sciencedirect.com/science/article/pii/S0753332224011867
58. Zou B. et al. (2025). *Fecal microbiota transplantation restores gut microbiota diversity in children with active Crohn's disease: A prospective trial. Journal of Translational Medicine*, 23, Article 112. https://link.springer.com/article/10.1186/s12967-024-05832-1
59. Reese G. E. et al. (2008). *The effect of smoking after surgery for Crohn's disease: A meta-analysis of observational studies. International Journal of Colorectal Disease*, 23(12), 1213–1221. https://pubmed.ncbi.nlm.nih.gov/18762954/
60. Ma C. et al. (2017). *Surgical rates for Crohn's disease are decreasing: A population-based time trend analysis and validation study. The American Journal of Gastroenterology*, 112(12), 1840–1848. https://pmc.ncbi.nlm.nih.gov/articles/PMC5729339/