



Regulatory Mechanisms and Pathological Significance of Crohn's Disease Focused on Recent Advancements: A Narrative Review

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Received 17 May, 2026

Revised 20 June, 2026

Accepted 20 June, 2026

Published 22 June, 2026

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<https://doi.org/10.59493/advpbl/2026.1.3>

Abstract

Crohn's disease is a multifactorial inflammatory bowel disease that involves genetic susceptibility, dysregulated immune responses, and environmental triggers. This study was a narrative review of the regulatory mechanisms and pathological significance of Crohn's disease. Scientific databases were searched, including: PUBMED, Embase, Google Scholar, Web of Science, and Scopus. The studies considered were original research articles, meta-analyses, randomized controlled trials, and systematic reviews published between 2020 and 2026. A total of 118 articles were screened for eligibility (except those articles used during the 'Introduction section'). A total of 98 articles were eligible, while 20 were ineligible. The articles reviewed provided information on the fundamental pathophysiology of Crohn's disease and its regulatory mechanisms; genetic and molecular drivers; immune regulation and dysregulation; the microbiome and environmental factors; and emerging therapeutic targets and mechanisms. The fundamental pathophysiology and regulatory mechanisms identified include: intestinal barrier dysfunction, defective bacterial clearance, transmural inflammation and granuloma formation, fibrosis and stricture formation, and mesenteric fat hypertrophy. Other parameters highlighted were the microbiome and environmental factors, including dysbiosis of the gut microbiota, smoking, dietary factors, and vitamin D deficiency. Others were medications, psychological and environmental stress, infections, urbanization, pollution, and exposomes. New findings include: exposome-diet epigenome and E-cigarettes. Emerging therapeutic targets and mechanisms were emphasized: anti-TNF/IL-12/IL-23 inhibitors, adhesion molecule inhibitors, restoring barrier formation, and mesentery-based surgery. Despite Crohn's disease being studied extensively, and many pathophysiological and regulatory mechanisms elucidated, there has not been a radical cure for the ailment. This necessitated research and a consequent development of new treatment approaches.

Keywords: Crohn's disease, dysbiosis, genetic factors, pathological significance. regulatory mechanisms

Introduction

Crohn's disease (CD) is a multifactorial inflammatory bowel disease (IBD) that involves genetic susceptibility, dysregulated immune responses, and environmental triggers [1]. CD causes transmural inflammation due to abnormal helper T-cell activity and cytokine signaling, which lead to noncaseating granuloma formation and progressive tissue injury in any segment of the gastrointestinal tract, but it mostly affects the terminal ileum and proximal colon [2]. Some of the symptoms of CD are abdominal pain, chronic diarrhea, weight loss, fatigue, arthropathy, and skin lesions [3]. Diagnosis of CD is done by endoscopy, histopathology, X-ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Ultrasound;

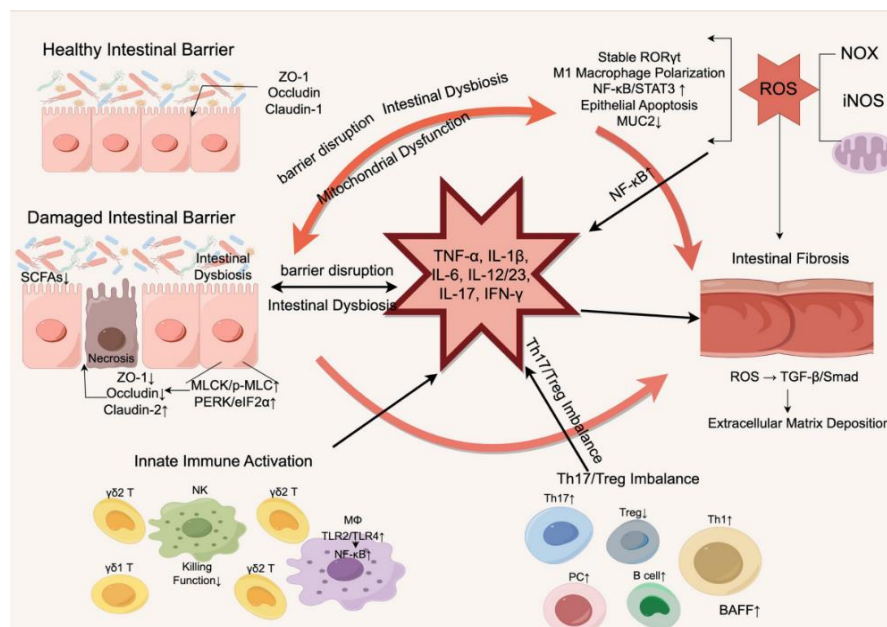
ileocolonoscopy and histology are the diagnostic gold standard [4]. Management of CD includes anti-inflammatory drugs, immunomodulators, biologic therapies, and surgery [5]. Current treatment rationale for patients with CD focuses on endoscopic healing and alteration of disease progression [6]. The use of early effective advanced therapies and the development of therapies that target alternative novel pathways with improved safety profiles have resulted in a new era of healing in CD management [7]. In CD, the physiology and functioning of the epithelial barrier are inhibited due to the correlation of various factors, such as the environment, genetics, and intestinal microbiota [8]. The symptoms of CD are very troublesome and cause significant reductions in quality of life, sometimes

occurring with paralyzing permanent damage to the digestive tract, requiring enteral or parenteral nutrition throughout life [9]. Medical biology and the analysis of metalloproteinases have also proved helpful in diagnosing changes occurring as a result of CD [10]. CD can affect individuals of all ages, from children to the elderly, leading to significant morbidity and diminished quality of life [11]. CD is marked by periods of exacerbation and remission and can lead to complications such as strictures, fistulas, and abscesses, and with rising prevalence globally, understanding and managing CD is necessary for improvement of patient outcomes [12]. The development of CD is characterized by a breakdown of homeostatic immune-bacterial communication, due to failure of mucosal defense mechanisms at various stages and a consequent compromise in the integrity of the epithelial barrier, leading to accelerated influx of intraluminal antigens and intact microorganisms within the immunologically rich lamina propria [13].

Overview of the regulatory mechanisms and pathophysiology of Crohn's disease

CD is a complex and multifactorial disease that is influenced by a combination of genetic and environmental factors. Some important factors involved in the development of the illness are nucleotide-binding oligomerization domain-2, smoking, and vitamin D [14]. Activation of the immune system and consequent inflammation depend on the working balance between effector T cells (Th1, Th17, and Th9 subsets), Th cell lineages, and regulatory T cells, which are present in the intestinal mucosa, and these have also been shown to be dysregulated in CD patients [15]. MicroRNAs (miRNAs) play an important role in regulating gene expression in CD, and there is significant intestinal tissue-specific variability, and identified major alterations in the miRNA-mRNA interactome, which might be involved in CD [16]. As CD progresses, fibrosis and

narrowing of the intestine occur, leading to severe complications such as intestinal obstruction, and with the progressive intestinal inflammation, cytokines and growth factors, including transforming growth factor (TGF- β), stimulate intestinal myofibroblasts, contributing to fibrosis of the intestine, smooth muscle hypertrophy, and mesenteric fat hypertrophy [17]. Another contributory factor in CD is autophagy, which is the primary intracellular degradation mechanism, in which damaged organelles and self-cytoplasmic proteins are transported to the lysosome for degradation [18]. The regulatory T cells (Tregs), characterized by the transcription factor Forkhead box P3 (FoxP3) expression, are crucial for maintaining immune homeostasis through Programmed Cell Death Protein 1/Programmed Death-Ligand 1 (PD-1/PD-L1) interaction, IL-10 release, and granzyme B (GrB) production [19]. CD is associated with myofibroblast activation, and transcription factors such as Charged Multivesicular Body Protein 1A (CHMP1A), T-Box Transcription Factor 3 (TBX3), and Ring Finger Protein 168 (RNF168) were identified as regulators of fibrotic complications [20]. Genetic and transcriptional analyses have revealed main genes and gene variants, as well as their protein products, and an additional layer of epigenetic regulation, contributing to disease severity, complications, and response to medical therapy, and this led to the development of novel diagnostic, prognostic, and therapeutic strategies for the management of CD [21]. Other factors that were implicated in the pathogenesis of CD are related to immune dysregulation, and they include macrophage polarization (M1 vs M2) and Th17 activation, dysbiosis, as a result of reduced alpha and beta diversity and overgrowth of harmful taxa, and environmental factors, including air and water pollutants, maternal smoking, and antibiotic exposure during pregnancy and infancy [22]. These are shown in Figure 1 below [23].



Source: Link.Springer.com [23].

Figure 1: Multi-layer pathophysiology of Crohn's Disease [23]

Rationale for this narrative review

Review of this kind is urgently needed at this time due to several factors, including expanding therapeutic capabilities in which the approval of next-generation medications, such as advanced IL-23 inhibitors, selective JAK inhibitors, and S1P modulators, has expanded treatment options beyond traditional anti-TNFs. This review helps clinicians contextualize these mechanisms within the immune cascade. Current management has shifted from merely controlling symptoms to achieving transmural, endoscopic, and histological healing. The review evaluated modern biomarkers that make this objective monitoring possible. Furthermore, researchers have unveiled deep complexities regarding the interaction between genetic susceptibility, microbial dysbiosis, and the intestinal mucosal immune system. Therefore, there is a pressing need to integrate these findings into a unified pathogenic framework. With the incidence of CD rising in newly industrialized countries, assessing recent pathogenetic insights is crucial for adapting global diagnostic and management protocols.

Methodology

This study is a narrative review in which some scientific databases, including PUBMED, Embase, Google Scholar, Web of Science, and Scopus, were searched. A total of 118 articles were screened, and 98 were found to be eligible.

Search terms/keywords

The keywords used during the literature search include: "Crohn's disease" OR "Crohn disease" OR "CD" OR "Inflammatory Bowel Disease*" OR "IBD" "Pathogenesis" OR "Pathophysiology" OR "Immunology" OR "Immunopathogenesis" OR "Immune dysregulation" OR "Inflammatory cascade*" OR "Molecular mechanisms" OR "Cellular pathways" OR "Autophagy" OR "Microbiome" OR "Cytokines" OR "Th1" OR "Th17" OR "Intestinal permeability" OR "Recent advance*" OR "New insights" OR "Emerging" OR "Novel" OR "Treatments" OR "Biologics" OR "Therapeutics" OR "Genomics" OR "Translational research" OR "2024" OR "2025" OR "2026".

Inclusion criteria

The studies considered were original research articles, meta-analyses, randomized controlled trials, and systematic reviews. Observational studies and case reports that worked on Crohn's disease, particularly pathophysiology and regulatory mechanisms, were also eligible. Articles reviewed gave information about Crohn's disease: Fundamental Pathophysiology & Regulatory Mechanisms, Genetic and Molecular Drivers, Immune Regulation & Dysregulation, Microbiome and Environmental Factors, and Emerging Therapeutic Targets and Mechanisms. Only those articles written in the English language were considered to be eligible.

Exclusion criteria

Studies not focusing on Crohn's disease, its pathophysiology, and regulatory mechanisms.

Search strategy

The search terms were categorized into three groups: group 1 is under Crohn's Disease, using MeSH Terms such as "Crohn Disease" OR "Inflammatory Bowel Diseases", "Crohn's Disease" OR "Crohns Disease" OR "Regional Enteritis" OR "Granulomatous Enteritis". Group 2 involve the Regulatory Mechanisms & Pathology using keywords like "pathogenesis" OR "pathological significance" OR "regulatory mechanisms" OR "immune regulation" OR "mucosal immunity" OR "intestinal barrier" OR dysbiosis OR "genetic susceptibility." Group 3 considered Recent Advancements and used "recent advancements" OR "recent developments" OR "emerging therapies" OR "molecular pathways" OR "targeted therapy" OR "biological agents" OR 2020 OR 2021 OR 2022 OR 2023 OR 2024 OR 2025 OR 2026.

Screening of articles

A total of 118 articles were screened from the databases. Sections of the articles considered during the screening were the titles, abstracts, and the main text, which were considered only when information in the title and abstract was not adequate to make immediate decisions. At the end of the screening process, 98 articles were included in the study, while 20 articles were excluded.

Data extraction

Data from eligible articles were collected and analyzed by two reviewers (D.I.O and H.O.A), recorded, and discussed in detail by all four authors. The data were extracted using a pre-specified form. The column headings of the form included serial number, Name of first author/year, Title, Study characteristics, intervention/dosages/frequencies. Extracted data included study design, participant demographics, Crohn's disease pathophysiology, regulatory mechanisms, and intervention details. Discrepancies were resolved by consensus.

Data analysis/synthesis

Data were synthesized in order to highlight pathophysiology and regulatory mechanisms, the interventions, and the outcomes. As such, polygenic risk factors, specifically mutations in susceptibility genes such as NOD2, epithelial barrier dysfunction, immune dysregulation, and microbial dysbiosis, transmural inflammation, and fibrostenotic & fistulizing phenotypes; targeted biologics, and patient-derived organoids were highlighted.

Results

The findings of this review included the various factors that play major roles in the pathophysiology and regulation of CD. These were grouped into the fundamental pathophysiology, genetic and molecular drivers, immune regulation and dysregulation, microbiome and environmental factors, and exposomes and new findings, as shown in Table 1. Emerging therapeutic targets and mechanisms were also highlighted in Table 2. These results were discussed in detail in the discussion section, and all the findings were adequately referenced.

Table 1: Summary of the major Crohn's disease regulatory mechanisms and their components

S/n	Major regulatory mechanisms	Components
1	Fundamental pathophysiology and regulatory mechanisms	Intestinal barrier dysfunction, defective bacterial clearance, transmural inflammation, granuloma formation, fibrosis and stricture formation, and mesenteric fat hypertrophy.
2	Genetic and molecular drivers	Several susceptibility loci, nucleotide binding oligomerization domain 2 (NOD2), interactome and signaling, autophagy defects, endoplasmic reticulum stress, and unfolded protein response.
3	Immune regulation and dysregulation	Th1 and IL23/Th17, innate immune hyperactivity, dysregulation of T regulatory cell activity, innate lymphoid cells, and leucocyte migration and adhesion.
4	Microbiome and environmental factors	Dysbiosis of gut microbiota, smoking, dietary factors, vitamin D deficiency, medications, psychological and environmental stress, microbiome and infections, urbanization, and pollution.
5	Exposomes and new findings	Exposome-diet epigenome and E-cigarettes.

Table 2: Emerging therapeutic targets and mechanisms highlighted in the study

S/n	Emerging therapeutic targets and mechanisms	Example of therapeutic agents
1	Anti-Tumor Necrosis Factor α (A-TNF- α)	Adalimumab, Infliximab, Certolizumab, Golimumab
2	TNF- α /IL-12/IL-23 axis inhibitors	Ustekinumab, Risankizumab, Guselkumab, Mirikizumab
3	Adhesion molecule inhibitors	Vedolizumab, Natalizumab, Etrolizumab
4	Restoring barrier formation	Anti-TNF- α Agents: Drugs like Infliximab and Adalimumab JAK Inhibitors like Upadacitinib
5	Mesentery-based surgery approaches	Extended Mesenteric Excision Mesenteric Exclusion (Kono-S Anastomosis) Combined Extensive Resection & Antimesenteric Anastomosis

Discussion

Fundamental Pathophysiology & Mechanisms

Intestinal Barrier Dysfunction: Many studies have reported intestinal barrier dysfunction as a contributory factor to CD. Some of the elements that constitute the intestinal barrier include enzymes, bile acids, the water layer, epithelial layer, and enterocyte layer. The intestinal barrier acts as an interface between the luminal contents of food, commensal and pathogenic bacteria, and the gastrointestinal tract. The role of barrier dysfunction is of significant research interest in the development and targeted treatment of chronic inflammatory gastrointestinal conditions, such as IBDs. This stems from the fact that intestinal barrier dysfunction, such as increased barrier permeability, leads to IBD, like CD [24]. This is because increased intestinal permeability enables bacterial toxins, antigens, and other harmful substances to cross the epithelial barrier, exacerbating inflammation and contributing to systemic complications [25, 26, 27].

Defective Bacterial Clearance: In CD, multiple factors, including intestinal dysbiosis and possibly damaged epithelial barrier due to ulceration and inflammatory conditions, caused significantly higher influx of translocating and potentially invading bacteria [28]. These bacterial invaders have access to the bloodstream due to an impaired host-microbe gut interaction and bacterial overgrowth and dysbiosis, coupled

with increased intestinal barrier permeability, and altered inflammatory responses, and these in turn favor a sustained inflammatory response in CD patients [29]. The breakdown of homeostatic immune-bacterial communication, which took place at the intestinal mucosa due to failure of mucosal defense mechanisms at various stages, led to inadequate clearance of these invading microorganisms and prevented the timely and complete resolution of acute inflammatory responses [30].

Transmural Inflammation and Granuloma Formation:

This was also implicated in CD evolution, which was mediated by a complex alteration of the inflammatory response, characterized by alterations of the innate immunity of the intestinal mucosa barrier together with a remodeling of the extracellular matrix through the expression of metalloproteins and increased adhesion molecules expression [31]. Transmural inflammation observed in CD was driven by aberrant helper T-cell activity and cytokine signaling and led to noncaseating granuloma formation and progressive tissue injury, which affected the gastrointestinal tract, especially the terminal ileum and proximal colon [32,33].

Fibrosis and Stricture Formation: In some CD patients, chronic inflammation led to re-modelling of the extracellular matrix and fibrosis, which, in combination with expansion of smooth muscle layers, left the bowel segment narrowed and stiff and resulted in strictures [34]. Over the past few decades, remarkable progress has been made in the field of mechanisms

of fibrosis in CD, including the feature of fibrosis progressing independently of inflammation, the role of microbiome and mesenteric fat-influencing fibrosis, and reversibility of fibrosis; but up to 70% of CD patients still eventually undergo surgery mainly due to fibrostenotic strictures [35]. Fibrosis occurred due to prolonged inflammation and abnormal wound healing, involving complex interactions between immune cells, mesenchymal cells, cytokines, and the gut microbiota, and the main fibrogenic mechanisms included the activation of fibroblasts and myofibroblasts, cytokine signaling, and disrupted turnover of the extracellular matrix [36]. Currently, antifibrotic therapy has not been discovered, but some progress has been made in an attempt to quantify stricture morphology for clinical practice and trials; however, determination of the degree of fibrosis within a stricture is still difficult, requiring more research [37].

Mesenteric Fat Hypertrophy: Mammalian fat tissue is not solely a reservoir for excess nutrients but also an active and dynamic organ involved in the development of metabolic syndromes and the regulation of immunity and inflammation [38]. The profile of mesenteric adipose tissue (MAT) secretome had a significant role in the pathogenesis of CD, especially that of creeping fat (CrF), and this suggested a modification of the adaptive immune response, and a more pro-angiogenic and pro-fibrotic profile [39, 40]. Mesenteric fat hypertrophy was significantly associated with stricture behavior, blood platelets, C-reactive protein, fecal calprotectin, and bowel wall thickness; it was correlated with intestinal stenosis and disease activity in patients with CD [41]. Fibrofatty proliferation of mesenteric fat was a common finding on magnetic resonance enterography (MRE) in CD patients, and it is independently associated with increased risk of hospitalizations and surgery [42].

Genetic and Molecular Drivers of Crohn's disease

Genetic Susceptibility Loci: Inverse variance weighted (IVW) analysis identified 56 protein quantitative trait loci (pQTL) genes significantly associated with CD risk, with six genes including: Human Leukocyte Antigen class I heavy chain A (HLA-A), Macrophage Stimulating 1 (MST1), and Cadherin 5 (CDH5), passing false discovery rate (FDR) correction, and sharing causal variants with CD, suggesting that HLA-A represents a genetically validated immune susceptibility marker in CD [43]. Meta-analysis, including Genome-wide association studies (GWASs) have identified a number of genetic risk loci associated with CD, such as Interleukin-12 Receptor Subunit Beta-2 (IL-12RB2), Interferon Regulatory Factors 1/Solute Carrier Family 22 Member 5 (IRF1/SLC22A5), Signal Transducer and Activator of Transcription 3 (STAT3), a Chromosomal Location at 6p21.31, and IL-12 family and type I interferon signaling pathways, some of which conferred susceptibility to the diseases [44, 45].

Nucleotide-binding oligomerization domain 2 (NOD2)

Interactome and Signaling: NOD2 is the first susceptibility gene to be discovered for CD, and because of its impact in clinical practice, more research followed its discovery, leading to the finding that these genetic variants increased the risk of developing the disease, and can aid in tailoring diagnosis and treatment [46]. Mutations and single-nucleotide polymorphisms of NOD2 created a genetic predisposition for autoimmune CD, and polymorphisms in NOD2 were the strongest known genetic risk factors in the development of CD, in which three common NOD2 variants (R702W, G908R, and 3020insC) were linked to the development of the disease [47, 48]. NOD2

primarily acted as a cytoplasmic pattern recognition receptor (PRR) that recognized muramyl dipeptide (MDP), the basic unit of bacterial cell wall; thus, NOD2 played a major role in the sensing of pathogens, and also had a wide range of immunomodulatory effects, and it was involved in the pathogenesis of several inflammatory diseases, including CD [49].

Autophagy Defects in Crohn's disease: In CD, significant abnormalities in autophagy were observed, as evident in the expression of three main autophagy-related genes, including Beclin 1 (BECN1) (macroautophagy), Phosphatase and tensin homolog-induced kinase 1 (PINK1) (mitophagy), and Lysosome-associated membrane protein 2 (LAMP2) (chaperone-mediated autophagy), in tissue samples from patients with CD [50]. Dysregulation of autophagy components influenced inflammatory responses [51, 52, 53]. A significant reduction in the autophagosomal marker, light chain 3 beta II (Lc3b-II), in patients with active inflammation and stenosis may play a pivotal role in CD by failing to eliminate detrimental molecules and pathogenic bacteria, thereby promoting fibrosis [54, 55]. Autophagy was essential for gut homeostasis and the regulation of immune responses, and when autophagy was impaired, dysbiosis occurred, which individually contributed to CD, and their combined impact intensified inflammation [56, 57]. Increased gut serotonin (5-HT) inhibited autophagy and led to enhanced colitis susceptibility [58]. Dysregulation of autophagy in CD was revealed by the identification of several susceptibility genes, such as NOD2 and ULK1 [59].

Endoplasmic Reticulum (ER) Stress & unfolded protein response (UPR):

In a recent study, CD was marked by an abnormal immune response and excessive pro-inflammatory cytokines, which led to impaired protein processing and endoplasmic reticulum (ER) stress, that was caused by the accumulation of misfolded proteins, which triggered the unfolded protein response (UPR) through Inositol-requiring enzyme 1/X-box binding protein 1 (IRE1/Xbp-1), Protein kinase R-like ER kinase/eukaryotic initiation factor 2 α (PERK/eIF2 α), and Activating transcription factor 6 (ATF6) pathways, and these were linked to intestinal inflammation [60]. During the development of IBD, the stress on the endoplasmic reticulum and the beginning of the unfolded protein response were very important; some chemicals, including 4-methylumbelliferone 8-carbaldehyde (4 μ 8C), small molecule agonists of X-box binding protein 1, and Integrated Stress Response Inhibitor (ISRIB), worked on the inositol-requiring enzyme 1, turned on transcription factor 6, and activated protein kinase RNA-like endoplasmic reticulum kinase pathways, which helped to ease the symptoms of the disease [61, 62]. The complex networking and dynamic microenvironment in the intestine demanded highly functional cells, ultimately burdening the endoplasmic reticulum, and leading to endoplasmic reticulum stress, which contributed to the pathogenesis of CD [63, 64].

Immune Regulation & Dysregulation in Crohn's disease (Th1) and IL-23/Th17 pathways:

Pro-inflammatory cytokines IL-17 and IL-23 were implicated in the pathogenesis of CD. IL-23, a member of the IL-12 family of cytokines, enhanced and affected the expansion of pathogenic T helper type 17 (Th17) cells through various mechanisms, which include maintenance of Th17 signature genes, upregulation of effector genes or suppression of repressive factors, inducing a cascade of pro-inflammatory molecules like TNF, IFN γ , IL-22, lymphotoxin, IL-1 β and lipopolysaccharide (LPS) and

mediating signaling synergistically with TNF to drive expression of inflammatory genes [65]. Targeting IL-12/23 was effective for the treatment of both moderate-to-severe CD, and ustekinumab (an IL-12/23p40 antagonist) was effective for such indication [66]. Studies indicated that an imbalance between T helper 17 (Th17) and regulatory T (Treg) cells contributed significantly to the development of CD, while intestinal Tregs suppress inflammation and were critical for maintaining tissue homeostasis [67]. Th17 cell differentiation was regulated by intestinal bacteria and cytokines, and Th17 cells regulated the intestinal mucosal immune microenvironment by secreting cytokines, such as IL-17, IL-21, and IL-26 [68, 69, 70, 71].

Innate Immune Hyperactivity: CD evolution was mediated by a complex alteration of the inflammatory response, which was characterized by alterations of the innate immunity of the intestinal mucosa barrier, together with a remodeling of the extracellular matrix through the expression of metalloproteins, and increased adhesion molecules expression, such as Mucosal Vascular Addressin Cell Adhesion Molecule-1 (MAcCAM-1) [31]. CD was triggered through the activation of excessive innate and adaptive immune responses against luminal antigens, and identification of mechanisms underlying the amplification of the immune steps in the diseased tissue, facilitated the development of several immune-related biotherapeutic compounds that largely improved the management of CD [72, 73]. Alterations in the innate and adaptive immune systems were involved in the pathogenesis of CD due to hyperactive antigen-presenting cells, intestinal barrier disruption, and increased autophagy activity [74, 75].

Dysregulated T Regulatory Cell (Treg) Activity: The function of T regulatory (Treg) cells was to maintain immune homeostasis by secreting anti-inflammatory cytokines like IL-10 and Transforming Growth Factor-beta (TGF- β) [76]. This Treg cell function was impaired, or their number was reduced in CD, leading to an imbalance in the immune system, and thereby worsening intestinal inflammation [76, 77]. Tregs were strongly influenced by cellular stress, the Unfolded Protein Response (UPR), microbial dysbiosis, and reduced short-chain fatty acids (SCFAs), and these modified their stability, metabolic programming, and function [64, 78, 79]. Effector CD4⁺ T cells and regulatory CD4⁺ T cells (Treg) were central players in maintaining the balance between tolerance and inflammation [80, 81, 82, 83]. Phenotypic and functional characterization of Treg cells over the last decade was used to optimize the procedures for in vitro expansion of these cells for developing therapeutic interventional strategies [84]. Several types of cells were differentially expressed between stricture and non-stricture CD; Treg cells accounted for a larger proportion and were significantly increased in stenotic tissues of stricture CD [85, 86].

Innate Lymphoid Cells (ILCs): Innate lymphoid cells (ILCs) were noted to be a large family of cells of the immune system that performed various functions in immune defense, inflammation, and tissue remodeling. They are a distinct form of lymphocytes different from T and B cells, and ILCs provide host defense against the source of infection and initiate the repair and remodeling processes to restore and maintain host body homeostasis [87, 88]. In the blood of patients with CD, ILCs were activated, and circulating signaling lymphocytic activation molecule Family-1 (SLAMF1) + ILC2 were increased in patients with less active disease, introducing SLAMF1 + ILC2 as an interesting therapeutic target [89].

Leucocyte Migration & Adhesion: The soluble forms of cell adhesion molecules (CAMs), particularly soluble intercellular adhesion molecule-1 (sICAM-1) and Endothelial-selectin (E-selectin), reflected the extent of endothelial injury and served as potential biomarkers of disease activity, supporting a role of endothelial injury in disease pathogenesis [90]. IBD was characterized by the accumulation of immune cells, myeloid cells, and lymphocytes in the inflamed intestine, and blockade of leukocyte migration to the intestine controlled the disease and alleviated symptoms [91]. Peripheral monocytes from active CD patients retained functional responsiveness to granulocyte-macrophage colony-stimulating factor (GM-CSF) activation, and displayed preserved migratory, adhesive, metabolic, and differential cytokine production, which reflected disease-specific regulation [92, 93]. Several observational studies showed that circulating leukocytes were strongly associated with IBD and that there was a causal relationship which existed between circulating leukocytes and the risk of IBD [94].

Microbiome and Environmental Factors

Dysbiosis of Gut Microbiota: One of the major factors that leads to CD is the alterations of gut microbiota and the immune system, in which there were changes in alpha and beta diversity in interaction networks, and increases in Proteobacteria abundance when the disease becomes severe [95]. The main pathogenic mechanisms of dysbiosis include: impaired intestinal mucosal barrier function, inflammation activation, immune dysregulation, and metabolic abnormalities, all of which involve dysfunctions in the gut-brain axis, gut-liver axis, and others, and cause broader effects [96]. Due to the symbiotic relationship between the intestinal microbiome and the host, any alteration in the gut microbiota would result in various diseases, including CD, and anti-tumor necrosis factor (TNF) drugs are currently used for the treatment of CD [97, 98]. In patients with controlled CD, there were compositional microbiota differences, including decreased genera of *Streptococcus* and *Actinobacillus*, increased *Oribacterium* and *Prevotella* disease, increased epithelial integrity, decreased intraepithelial lymphocytes, and increased peripheral CD4⁺ T cells compared to controls [99]. In a study aimed to characterize the fecal virome in children with CD, trans-kingdom correlations were disrupted, particularly between *Torque teno* viruses and beneficial bacteria, such as *Blautia* [100]. Dysbiosis was influenced by diet, lifestyle rhythms, hygiene conditions, drugs, and the inflammatory state of IBD patients [101]. Patients with CD showed reduced commensal microbial diversity, increased numbers of pathogenic Enterobacteriaceae and Proteobacteriaceae, reduced numbers of *Faecalibacterium prausnitzii*, and these were associated with an increased risk of recurrence [102, 103, 104]. Dysbiosis induced pore formation in the intestinal epithelium, and intestinal pathogens, antigens, and toxins translocate via the impaired gut barrier into extra-intestinal sites [105, 106].

Environmental Triggers (The "Exposome") in Crohn's disease

Smoking: Smoking had negative effects on CD progression, post-surgical recurrence, post-surgical complications after intestinal resection, on its influence on the reservoir, and on the modification of the natural evolution of CD towards fistulizing and stenosing forms, all of which make a proper approach to the problem imperative [107]. A hospital-based cohort study conducted from the National Health Interview Survey Database

of Taiwan showed that smoking does not affect CD occurrence, but it was related to more aggressive behavior, which resulted in a higher surgical rate [108, 109]. Smoking had more issues with CD than other IBDs [110, 111, 112].

Dietary Factors: Conflicting results have been reported on dietary factors in inflammatory bowel diseases, in which lower intakes of vitamin C, dietary fiber, calcium, vegetables, decanoic acid, milk, dairy foods, other processed foods, and β -carotene were identified as risk factors [113, 114, 115, 116]. A 3-month observational study, which was conducted at the University of Calgary in Calgary, Alberta, Canada, between 2016 and 2018, in 66 outpatients with CD in clinical remission, reported that daily intake of leafy green vegetables was associated with fecal calprotectin, and increasing omega-3 was associated with C-reactive protein [117]. Data linking dietary factors to CD prevention and treatment were inconsistent, with the highest quality evidence for CD treatment being exclusive enteral nutrition [118].

Vitamin D Deficiency: CD patients exhibited vitamin D deficiency, which increased disease activity, impaired mucosal healing, and exhibited a higher risk of complications, including infections and osteoporosis [119, 120]. In determining the prevalence of vitamin D deficiency in adults with CD in Birmingham, UK, vitamin D deficiency was found in 53.3% of participants; an indication that patients with CD were at high risk of vitamin D deficiency [121]. Low serum levels of vitamin D have been associated with CD, but Limketkai *et al.* [122] suggested that low vitamin D does not contribute to the development of CD; instead, CD leads to low vitamin D.

Medications: Studies have found associations between oral antibiotic use and CD in children and showed a link between antibiotics and CD, in which people who had taken metronidazole were five times more likely to develop CD [123]. Nonsteroidal anti-inflammatory drugs (NSAIDs), including common over-the-counter medications like aspirin, ibuprofen, and naproxen, and also prescription drugs such as celecoxib, diclofenac, and indomethacin, increased the risk of CD [124]. Oral contraceptives, specifically combination birth control pills such as estrogen-containing birth control, led to a higher risk of CD by 24% [125].

Psychological and Environmental Stress: Stress exacerbated symptoms of CD, as evident in patients with CD in the flare-up phase who were subjected to a considerable increase in stress level due to a deficit in social support [126]. Four novel factors were discovered to be associated with CD, including prenatal smoke exposure, having a bed partner, allergies, and cow's milk hypersensitivity, which were important for both understanding disease etiology and future prevention strategies to decrease the development of CD in genetically susceptible persons [127]. Diet and psychological stress were recognized contributors to IBD, and those with higher perceived stress showed greater symptom burden, softer stool consistency, more frequent comfort food consumption (CFC), and stronger emotional reliance on certain foods [128].

The "Exposome" Concept and New Findings

Exposome-Diet-Epigenome Axis: Epigenetics, acting by DNA methylation, post-translational histone modifications, or by non-coding RNAs, explained how the exposome influenced the gene expression to contribute to intestinal inflammation [129]. Recent studies in genomics and metabolomics unveiled the intricate relationship between microbial influencers and host epigenetics, in which the dynamics of gut microbiota and

its metabolites were intricately aligned with DNA methylation, histone methylation, lactylation, glycosylation, and non-coding RNAs, which were vital players in epigenetics [130, 131].

E-cigarettes: Tobacco smoke and heat-not-burn tobacco (HNBT) were established risk factors of CD postoperative recurrence, and e-cigarettes were associated with increased endoscopic recurrence of CD compared to nonsmoking [132]. Traditional cigarette use adversely impacted disease outcomes in CD, but on multivariable analysis, current e-cigarette use was not associated with a higher risk of the study outcome, and no difference was observed separately among those who were current or former e-cigarette users [133]. Histologic and transcriptome analyses revealed that chronic nicotine-free e-cigarette use increased inflammation and reduced expression of tight junction (TJ) markers, caused barrier disruption, downregulation of TJ protein, and enhanced inflammation in response to infection, highlighting the harmful effects of the non-nicotine component of e-cigarettes on the gut barrier [134].

Emerging Therapeutic Targets and Mechanisms

Anti-TNF/IL-12/IL-23 Inhibitors Targeting interleukin-23 (IL-23) is an important therapeutic strategy for CD. Analysis showed that targeting IL-23 was superior to placebo for inducing clinical remission in biologic-naïve and biologic-experienced patients, and it was associated with a decreased risk of serious adverse events in induction and maintenance trials compared to placebo [135]. IL-23p19 inhibitors—such as risankizumab, mirikizumab, and guselkumab—have promising results in patients with moderate-to-severe CD [136, 137].

Adhesion Molecule Inhibition: Biologic treatments used in CD include tumor necrosis factor alpha inhibitors (anti-TNF α) such as infliximab, adhesion molecule inhibitors, and IL-12 and IL-23 inhibitors, which target the underlying immunopathogenesis seen in CD, primarily by decreasing pro-inflammatory cytokines [138, 139]. Anti-TNF- α agents have emerged as the first-line therapy for moderate to severe IBDs, and anti-integrin antibodies have also become important for the treatment, and vedolizumab is often used in cases of anti-TNF- α failure and intolerance to other treatments [140].

Restoring Barrier Function: The intestinal barrier, maintained by various types of columnar epithelial cells, played a crucial role in regulating the interactions between the intestinal contents (such as the intestinal microbiota), the immune system, and other components [141]; and dysfunction of the intestinal mucosa was a significant pathophysiological mechanism and clinical manifestation of CD [141]. Immune-mediated approaches did not address additional pathogenic mechanisms of CD, such as impairment of the epithelial barrier and gut microbial ecology; thus, innovative strategies, such as intestinal epithelial barrier restoration, were required to bring the field closer to a definitive cure [142, 143]. Pharmacologic activation of HNF4 α / γ with plant-derived, non-toxic, translationally ready agonists [N-trans caffeoyltyramine (NCT) and N-trans feruloyltyramine (NFT)] restored barrier function, establishing the first barrier-healing therapy for CD [144, 145].

Mesentery-Based Surgery: Increasing evidence suggested that CD was a primary mesenteropathy and that resection of the mesentery, or its exclusion from an anastomosis, altered disease progression [146]. Postoperative anastomotic recurrence of CD was challenging and led to symptom recurrence and further surgery; however, the role of mesentery in the postoperative recurrence remained controversial [147, 148]. The structures of the mesentery, including adipose tissue, nerves, and lymphatics, played important roles in the pathogenesis and disease

progression of CD, and preliminary evidence from studies revealed that applying the principle of mesocolic excision to CD surgery reduced the risk of postoperative recurrence [149, 150]. In patients undergoing surgery for CD, inclusion of the mesentery was associated with similar short-term outcomes and improved long-term outcomes compared with those seen when the mesentery was retained [151].

Conclusion

Despite the fact that CD has been studied extensively, and many pathophysiological and regulatory mechanisms have been elucidated, there has not been any medication that provides a complete cure for the ailment. This necessitated more research, leading to the emergence of new therapeutic targets, including mesentery-based surgery.

Conflict of interest

There is no conflict of interest in this study.

Author contribution

D.I.O and H.O.A collected and analyzed data. D.I.O wrote the first draft of the manuscript. D.I.O, H.O.A, O.C.O, and O.M reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Declaration

This study did not receive any funding.

Acknowledgement

We want to show appreciation to some of my colleagues for their support while this study was going on. They include: Dr. Chukwuka Benjamin Uzodimma and Dr. Orji Harrison Uchechukwu. My thanks also go to Dr. Okonkwo Fabian Chukwujekwu and Mr. Mbachu Henry Chukwuemeka for their financial support.

Ethical compliance

Not applicable

References

1. Dolinger M, Torres J, Vermeire S. Crohn's disease, 2024. *The Lancet*, 403 (10432): 1177-1191. [https://doi.org/10.1016/S0140-6736\(23\)02586-2](https://doi.org/10.1016/S0140-6736(23)02586-2)
2. Michael WW, Joel VW, 2020. Chapter 46 - Inflammatory Bowel Disease. *The Autoimmune Diseases* (Sixth Edition). Academic Press, p 871-894. <https://doi.org/10.1016/B978-0-12-812102-3.00046-4>
3. da Silva Júnior RT, Apolonio JS, de Souza NJO, da Costa BT, Malheiro LH, Silva LM, de Carvalho LS, da Silva Santos C, de Melo FF. 2023. Crohn's disease and clinical management today: How does it work? *World Journal of Methodology*, 13 (5): 399–413. <https://doi.org/10.5662/wjm.v13.i5.399>
4. Cicero G & Mazziotti S, 2021. Crohn's disease at radiological imaging: focus on techniques and intestinal tract. *Intestinal Research*, 19 (4): 365–378. <https://doi.org/10.5217/ir.2020.00097>
5. Cushing K, Higgins PDR, 2021. Management of Crohn Disease: A Review. *JAMA*, 325 (1): 69-80. <https://doi.org/10.1001/jama.2020.18936>
6. D'Amico F, Massironi S, Allocca M, Danese S, 2023. Advancing transmural remission as a treatment target in Crohn's disease: The future of tight-control strategy? *United European Gastroenterology Journal*, 11 (10): 948-950. <https://doi.org/10.1002/ueg2.12495>
7. Girgis P, Lnu T, Ahmad A, Daniel M, Kamel M, Gambill JI, Shahzadi A, Khan U, Zara A, Sharma V, 2024. Advancements in Targeted Therapies for the Management of Crohn's Disease: A Comprehensive Review. *Cureus*, 16 (6): e61751. <https://doi.org/10.7759/cureus.61751>
8. Pasternak G, Chrzanowski G, Aebisher D, Myśliwiec A, Dynarowicz K, Bartusik-Aebisher D, Sosna B, Cleslar G, Kawczyk-krupka A, Filip R, 2023. Crohn's Disease: Basic Characteristics of the Disease, Diagnostic Methods, the Role of Biomarkers, and Analysis of Metalloproteinases: A Review. *Life*, 13 (10): 2062. <https://doi.org/10.3390/life13102062>
9. Bargas A, Palmela C, Glória L, 2025. Enteral Nutrition in Crohn's Disease: A Comprehensive Review of Its Role in Induction and Maintenance of Remission and Perioperative Management in Adult Patients. *Nutrients*, 17 (9): 1481. <https://doi.org/10.3390/nu17091481>
10. Chrzanowski G, Pasternak G, Aebisher D, Dynarowicz K, Myśliwiec A, Aebisher DB, Sosna B, Cleslar G, Kawczyk-krupka A, Filip R, 2023. An Analysis of the Content of Metalloproteinases in the Intestinal Wall of Patients with Crohn's Disease. *Life (Basel)*, 13 (10): 2013. <https://doi.org/10.3390/life13102013>
11. Karabulut A*, Kaya M, 2023. Crohn's disease from past to present: Research trends and global outcomes with scientometric analysis during 1980 to 2022. *Medicine*, 102 (35): e34817. <https://doi.org/10.1097/MD.00000000000034817>
12. Thompson JM, 2024. Crohn's Disease: An Overview of Pathogenesis, Diagnosis, and Management. *Acute Chronic Dis. Short Communication*, 8(3): 231. doi: 10.35248/ACDR.24.8.231
13. Giorgos B. & Cominelli F, 2021. Exploring the Early Phase of Crohn's Disease. *Clinical Gastroenterology and Hepatology*, 19 (12): 2469-2480. Accessed 3 March 2026.
14. Fan YH, Wang MW, Gao YN, Li WM, Jiao Y, 2025. Genetic and environmental factors influencing Crohn's disease. *World Journal of Gastrointestinal Surgery*, 17 (3): 98526. <https://doi.org/10.4240/wjgs.v17.i3.98526>
15. Chandwaskar R, Dalal R, Gupta S, Sharma A, Parashar D, Kashyap VK, Sohal JS, Tripathi SK, 2024. Dysregulation of T cell response in the pathogenesis of inflammatory bowel disease. *Scandinavian Journal of Immunology*, 100: e13412. <https://doi.org/10.1111/sji.13412>
16. Cervera-Seco L, Baldán-Martín M, Fernández-Tomé S, Moreno LO, Lozano JJ, Aransay AM, Chaparro M, Gisbert JP, Marigorta UM, 2025. Characterization of the Regulatory Landscape in Crohn's Disease Reveals microRNA-Associated Alterations that Shape Anti-TNF Response, Inflammatory Bowel Diseases, 31 (7): 980-1993. <https://doi.org/10.1093/ibd/izaf029>
17. Hayashi Y and Nakase H, 2022. The Molecular Mechanisms of Intestinal Inflammation and Fibrosis in Crohn's Disease. *Frontiers in Physiology*, 13: 845078. <https://doi.org/10.3389/fphys>
18. Yuan Z, Ye J, Liu B, Zhang L, 2024. Unraveling the role of autophagy regulation in Crohn's disease: from genetic mechanisms to potential therapeutics. *Biotechnology Advances*, (2): 14. <https://doi.org/10.1007/s44307-024-00021-z>

19. Patra S, Chaudhary S, Samal SC, Ayyanar P, Padhi S, Nayak HK, 2025. FoxP3-positive T regulatory cells and their effector mechanisms in Crohn's disease: an immunohistochemical and image morphometric analysis on endoscopic mucosal biopsies. *European Journal of Gastroenterology & Hepatology*, 37 (7): 799-809. <https://doi.org/10.1097/MEG.0000000000002971>
20. Kong L, Pokatayev V, Lefkovich A, Carter GT, Creasey EA, Krishna C, Subramanian S, Kochar B, Ashenberg O, Lau H, Ananthakrishnan AN, Graham DB, Deguine J, Xavier RJ, 2023. The landscape of immune dysregulation in Crohn's disease was revealed through single-cell transcriptomic profiling in the ileum and colon. *Immunity*, 56 (2): 444-458.e5. <https://doi.org/10.1016/j.immuni.2023.01.002>
21. Longman RS, 2024. Multiomics Resolves Regulatory Mechanisms in a Diverse Cohort of Crohn's Disease, *Journal of Crohn's and Colitis*, 18 (12): 1937–1938. <https://doi.org/10.1093/ecco-jcc/jjae154>
22. Calvez V, Puca P, Di Vincenzo F, Del Gaudio A, Bartocci B, Murgiano M, Iaccarino J, Parand E, Napolitano D, Scaldaferrì F, 2025. Novel Insights into the Pathogenesis of Inflammatory Bowel Diseases. *Biomedicines*, 13 (2): 305. <https://doi.org/10.3390/biomedicines13020305>
23. Yang, X., Guo, H. & Zou, M, 2026. Inflammatory bowel diseases: pathological mechanisms and therapeutic perspectives. *Molecular Biomedicine*, 7 (2). <https://doi.org/10.1186/s43556-025-00395-z>
24. Dunleavy KA, Raffals LE, Camilleri M, 2023. Intestinal Barrier Dysfunction in Inflammatory Bowel Disease: Underpinning Pathogenesis and Therapeutics. *Digestive Diseases and Sciences*, 68 (12): 4306-4320. <https://doi.org/10.1007/s10620-023-08122-w>
25. Selvakumar B, Samsudin R, 2025. Intestinal Barrier Dysfunction in Inflammatory Bowel Disease: Pathophysiology to Precision Therapeutics. *Inflammatory Bowel Diseases*, 31 (12): 3450–3464. <https://doi.org/10.1093/ibd/izaf225>
26. Nakai D, Miyake M, 2024. Intestinal Membrane Function in Inflammatory Bowel Disease. *Pharmaceutics*, 16 (1): 29. <https://doi.org/10.3390/pharmaceutics16010029>
27. Zhao Z, Liu X, Zhang R, Ke R, Zhang S, Chen Y, 2025. Intestinal Barrier in Inflammatory Bowel Disease: Mechanisms and Treatment. *Journal of Translational Gastroenterology*, 3 (2): 62-73. <https://doi.org/10.14218/JTG.2024.00038>
28. Ghate A, Uhlig H, 2023. Defective microbial sensing and clearance in perianal Crohn's disease: a role for complement factor B. *Gut*, 72 (11): 2010-2012. <https://doi.org/10.1136/gutjnl-2023-329801>
29. Linares R, Francés R, Gutiérrez A, Juanola O, 2021. Bacterial Translocation as Inflammatory Driver in Crohn's Disease. *Frontiers in Cell and Developmental Biology*, 9: 703310. <https://doi.org/10.3389/fcell.2021.703310>
30. Bamiás G, Cominelli F, 2021. Exploring the Early Phase of Crohn's Disease. *Clinical Gastroenterology and Hepatology*, 19 (12): 2469-2480. <https://doi.org/10.1016/j.cgh.2020.09.023>
31. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, Efrati C, Franceschilli M, Guida AM, Ingallinella S, Montagnese F, Sensi B, Siragusa L, & Sica GS, 2020. Pathophysiology of Crohn's disease inflammation and recurrence. *Biology Direct*, 15 (1): 23. <https://doi.org/10.1186/s13062-020-00280-5>
32. Tian C, Ranasinghe IR, Hsu R, 2025. Crohn's Disease. [Updated 2025 Dec 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK436021/> (Accessed 5 March 2026).
33. Amarnath S, Deeb L, Philipose J, Zheng X, Gumaste VA, 2021. Comprehensive Review of Infectious Granulomatous Diseases of the Gastrointestinal Tract. *Gastroenterology Research and Practice*, 8167149. <https://doi.org/10.1155/2021/8167149>
34. Alfredsson J, Wick MJ, 2020. Mechanism of fibrosis and stricture formation in Crohn's disease. *Scandinavian Journal of Immunology*, 92 (6): e12990. <https://doi.org/10.1111/sji.12990>
35. Yoo JH, Holubar S, Rieder F, 2020. Fibrostenotic strictures in Crohn's disease. *Intestinal Research*, 18 (4): 379-401. <https://doi.org/10.5217/ir.2019.09148>
36. Fousekis FS, Mpakogiannis K, Mastorogianni IN, Lianos GD, Christodoulou DK, Katsanos KH, 2025. Intestinal Fibrosis in Crohn's Disease: Pathophysiology, Diagnosis, and New Therapeutic Targets. *Journal of Clinical Medicine*, 14 (12): 4060. <https://doi.org/10.3390/jcm14124060>
37. Rieder F, Mukherjee PK, Massey WJ, Wang Y, Fiocchi C, 2024. Fibrosis in IBD: from pathogenesis to therapeutic targets. *Gut*, 73 (5): 854-866. <https://doi.org/10.1136/gutjnl-2023-329963>
38. Wang Q, Li H, Huan Y, Zhou T, Zhang J, Fang R, Sun Y, Lan A, Xu W, 2025. Adipose tissue: an inflammatory organ that cannot be ignored in periodontal disease related to obesity. *Frontiers in Immunology*, 16: 1698207. <https://doi.org/10.3389/fimmu.2025.1698207>
39. Martín-Reyes F, Kentaoui-Bousellam I, Ruiz-Malagón AJ, López-Gómez C, Herraiz-Vilela M, Herraiz-Vilela M, Alcaín-Martínez G, Camargo-Camero R, Martos-VanDussen JV, Camacho-Martel L, Gutiérrez-Martínez F, Arranz-Salas I, Ortega-Jimenez MV, Escamilla-Sánchez A, Daza-González JJ, Sanchiz-Cardenas E, Rivas-Becerra J, García-Fuentes E, Rodríguez-Pacheco F, & Rodríguez-Díaz C, 2025. Mesenteric adipose tissue in Crohn's disease alters the immune response of the ileal mucosa and increases angiogenesis and fibrosis. *Scientific Reports*, 15: 22591. <https://doi.org/10.1038/s41598-025-07147-7>
40. Coffey J, Bai L, Wu F, 2024. Catching up with Creeping Fat: Unravelling the Mysteries of the Mesentery in Crohn's Disease. *Gastroenterology*, 168: 454-456. Accessed 5 March 2026.
41. Li LZ, Zhang YY, Cui XF, Ma JJ, Wang D, Zhang HJ, 2020. *Chinese Journal of Internal Medicine*, 59 (9): 711-715. <https://doi.org/10.3760/cma.j.cn112138-20191213-00816>
42. Koifman E, Cohen IS, Lopez-Alonso R, Hur DB, Ilivitzki A & Waterman M, 2025. Mesenteric fat proliferation on magnetic resonance enterography is a predictor of long-term disease complications in Crohn's disease. *BMC Gastroenterology*, 25: 593. <https://doi.org/10.1186/s12876-025-04085-6>
43. Li Z, 2026. Genetically Validated Immune Susceptibility Markers for Crohn's Disease: A Multi-Omics Mendelian

- Randomization Analysis. *JGH Open*, 10 (1): e70332. <https://doi.org/10.1002/jgh3.70332>
44. González-Serna D, Ochoa E, López-Isac E, Julià A, Degenhardt F, Ortego-Centeno N, Radstake TRDJ, Franke A, Marsal S, Mayes MD, Martín J, Márquez A & Scleroderma GC, 2020. Scleroderma Genetic Consortium A cross-disease meta-GWAS identifies four new susceptibility loci shared between systemic sclerosis and Crohn's disease. *Scientific Reports*, 10: 1862. <https://doi.org/10.1038/s41598-020-58741-w>
 45. Kugathasan S, Fiocchi C, 2025. Towards IBD Prediction and Prevention: The Contribution of Genetics and Genomics. *Inflammatory Bowel Diseases*, 31 (Supplement_2): S3–S13. <https://doi.org/10.1093/ibd/izaf206>
 46. Kayali S, Fantasia S, Gaiani F, Cavallaro LG, de'Angelis GL, Laghi L, 2025. NOD2 and Crohn's Disease Clinical Practice: From Epidemiology to Diagnosis and Therapy, Rewired. *Inflammatory Bowel Diseases*, 31 (2): 552–562. <https://doi.org/10.1093/ibd/izae075>
 47. Dixon CL, Wu A, and Fairn GD, 2023. Multifaceted roles and regulation of nucleotide-binding oligomerization domain-containing proteins. *Frontiers in Immunology*, 14: 1242659. <https://doi.org/10.3389/fimmu.2023.1242659>
 48. Ashton JJ, Seaby EG, Beattie RM, Ennis S, 2023. NOD2 in Crohn's Disease—Unfinished Business. *Journal of Crohn's and Colitis*, 17 (3): 450–458. <https://doi.org/10.1093/ecco-jcc/jjac124>
 49. Wang Y, Mi Z, Liu H, Zhang F, 2024. NOD2 in signaling, immunity, and mycobacterial infection. *Authorea, Immunity, Inflammation and Disease*, Preprint 6 April 2024; <https://doi.org/10.22541/au.171239819.95495747/v1>
 50. Bichalska-Lach M, Waniczek D, Kowalczyk P, Śnietura M, Kryj M, Bednarczyk M, 2026. Autophagy Dysregulation in Crohn's Disease and Colorectal Cancer—An Analysis of *BECN1*, *PINK1*, and *LAMP2* Gene Expression. *Current Issues in Molecular Biology*, 48 (1): 31. <https://doi.org/10.3390/cimb48010031>
 51. Lin R, Xu Z, Zhi M, 2026. Canonical pathways and selective mechanisms of autophagy in inflammatory bowel disease. *Advanced Biotechnology (Singapore)*, 4 (1): 4. <https://doi.org/10.1007/s44307-026-00094-y>
 52. Múnera-Rodríguez AM, Leiva-Castro C, Reina-Pérez I, Benítez-Márquez JM, Palomares F, López-Enríquez S, 2026. The Role of Autophagy in Inflammatory Diseases: Challenges and Therapeutic Potential, *Inflammatory Bowel Diseases*, 32 (3): 562–571. <https://doi.org/10.1093/ibd/izaf279>
 53. Creoli M, Buono P, Cenni S, Casertano M, Vitale A, Maglio M, 2026. Pharmacological Modulation of Autophagy Corrects Cellular Defects in Pediatric Crohn's Disease. *Molecular and Cellular Biology*, 46 (2): 270–280. <https://doi.org/10.1080/10985549.2025.2583173>
 54. Schirone D, Paolo MC, Vecchio D, Nocella CD, Amico A, Urgesi R, Pallotta L, Fanello G, Villotti G, Graziani MG, Peruzzi M, De Falco E, Carnevale R, Sciarretta S, Frati G & Pagnini C, 2024. Stenosing Crohn's disease patients display gut autophagy/oxidative stress imbalance. *Scientific Reports*, 14: 27312. <https://doi.org/10.1038/s41598-024-79308-z>
 55. Miao Z-X, Meng H, Wang J, Hou X-T, Cheng W-W, Liu B-H, Zhang Q, Yuan S., 2025. Autophagy in inflammatory bowel disease: immunization, etiology, and therapeutic potential. *Frontiers in Immunology*, 16: 1543040. <https://doi.org/10.3389/fimmu.2025.1543040>
 56. Subramanian AJA, Kumarasamy V, Begum MY, Sekar M, Subramaniyan V, Wong LS, Sekar M, 2024. Exploring the Connections: Autophagy, Gut Microbiota, and Inflammatory Bowel Disease Pathogenesis. *Journal of Inflammation Research*, 17: 10453–10470. <https://doi.org/10.2147/JIR.S483958>
 57. Okai N, Watanabe T, Minaga K, Kamata K, Honjo H, Kudo M, 2022. Alterations of autophagic and innate immune responses by the Crohn's disease-associated *ATG16L1* mutation. *World Journal of Gastroenterology*, 28 (26): 3063–3070. <https://doi.org/10.3748/wjg.v28.i26.3063>
 58. Haq S, Wang H, Grondin J, Banskota S, Marshall JK, Khan II, 2021. Disruption of autophagy by increased 5-HT alters gut microbiota and enhances susceptibility to experimental colitis and Crohn's disease. *Science Advances*, 7: 6442. <https://doi.org/10.1126/sciadv.abi6442>
 59. Alula KM, Theiss AL, 2023. Autophagy in Crohn's Disease: Converging on Dysfunctional Innate Immunity. *Cells*, 12 (13): 1779. <https://doi.org/10.3390/cells12131779>
 60. Rodrigues BL, Pascoal LB, Genaro LM, Warrak LSCA, Rodrigues BAG, Coope A, Camargo MG, Oliveira PDP, Ayrizono MDS, Leal RF, 2025. In Vitro Inhibition of Endoplasmic Reticulum Stress: A Promising Therapeutic Strategy for Patients with Crohn's Disease. *Cells*, 14 (4): 270. <https://doi.org/10.3390/cells14040270>
 61. Zheng T, Huang KY, Tang XD, Wang FY, Lv L, 2025. Endoplasmic reticulum stress in gut inflammation: Implications for ulcerative colitis and Crohn's disease. *World Journal of Gastroenterology*, 31 (13): 104671. <https://doi.org/10.3748/wjg.v31.i13.104671>
 62. Ziyu L, Zahra Z, Tao H, Yingying H, Lushan P, Dan W, Zhou Z, Ousmane D, Wang J, 2024. Identification of endoplasmic reticulum stress-associated genes and subtypes for predicting risk signature and depicting immune features in inflammatory bowel disease, *Heliyon*, 10 (17): e37053. <https://doi.org/10.1016/j.heliyon.2024.e37053>
 63. Eugene SP, Reddy VS, and Trinath J, 2020. Endoplasmic Reticulum Stress and Intestinal Inflammation: A Perilous Union. *Frontiers in Immunology*, 11: 543022. <https://doi.org/10.3389/fimmu.2020.543022>
 64. Alula KM, Nguyen TT, & de Zoeten EF, 2026. Regulation of intestinal regulatory T cells via stress response pathways in inflammatory bowel disease. *Autoimmunity*, 59 (1). <https://doi.org/10.1080/08916934.2025.2602715>
 65. Schmitt H, Neurath MF, Atreya R, 2021. Role of the IL23/IL17 Pathway in Crohn's Disease. *Frontiers in Immunology*, 12: 622934. <https://doi.org/10.3389/fimmu.2021.622934>
 66. Vuyyuru SK, Shackelton LM, Hanzel CM, Vipul J & Brian GF, 2023. Targeting IL-23 for IBD: Rationale and Progress to Date. *Drug*, 83: 873–891. <https://doi.org/10.1007/s40265-023-01882-9>
 67. Ji-Hyun P, Min Hyeok L, Chan-Su P*, 2024. Inflammatory bowel disease pathogenesis mediated by Th17 cells: cytokines, microbiota, and therapies. *Journal of Biomedical and Translational Research*, 25 (2): 15–32. <https://doi.org/10.12729/jbtr.2024.25.2.15>

68. Chen L, Ruan G, Cheng Y, Yi A, Chen D and Wei Y, 2023. The role of Th17 cells in inflammatory bowel disease and the research progress. *Frontiers in Immunology*, 13: 1055914. <https://doi.org/10.3389/fimmu.2022.1055914>
69. Pastras P, Aggeletopoulou I, Papantoniou K, Triantos C, 2025. Targeting the IL-23 Receptor Gene: A Promising Approach in Inflammatory Bowel Disease Treatment. *International Journal of Molecular Sciences*, 26 (10): 4775. <https://doi.org/10.3390/ijms26104775>
70. Hu Y, Yang Y, Li Y, Zhang Q, Zhang W, Jia J, 2025. Th17/Treg imbalance in inflammatory bowel disease: immunological mechanisms and microbiota-driven regulation. *Frontiers in Immunology*, 16: 1651063. <https://doi.org/10.3389/fimmu.2025.1651063>
71. Gavin WS, Arthur K, 2022. Interleukin-23 in the Pathogenesis of Inflammatory Bowel Disease and Implications for Therapeutic Intervention, *Journal of Crohn's and Colitis*, 16 (Supplement_2): ii3–ii19. <https://doi.org/10.1093/ecco-jcc/jjac034>
72. Monteleone G, Calisi C, Salvatori S, and Marafini I, 2025.vFundamental and emerging insights into innate and adaptive immunity in inflammatory bowel diseases. *Frontiers in Immunology*, 16: 165530. <https://doi.org/10.3389/fimmu.2025.1665530>
73. Yue N, Hu P, Tian C, Kong C, Zhao H, Zhang Y, 2024. Dissecting Innate and Adaptive Immunity in Inflammatory Bowel Disease: Immune Compartmentalization, Microbiota Crosstalk, and Emerging Therapies. *Journal of Inflammation Research*, 17: 9987-10014. <https://doi.org/10.2147/JIR.S492079>
74. Darmadi D1*, Riska HR, 2021. Immunological Aspect in Inflammatory Bowel Disease. *Open Access Macedonian Journal of Medical Sciences*, 9 (F): 708-711. <https://doi.org/10.3889/oamjms.2021.7733>
75. Mousa RS, Invernizzi P, and Mousa HS, 2024. Innate immune cells in the pathogenesis of inflammatory bowel disease -from microbial metabolites to immune modulation. *Frontiers in Gastroenterology*, 3: 1452430. <https://doi.org/10.3389/fgstr.2024.1452430>
76. Yuyuan H, Yuhang Y, Yan L, Qiang Z, Wei Z, Jinxi W*, Han Z, Wang J, 2025. Th17/Treg imbalance in inflammatory bowel disease: immunological mechanisms and microbiota-driven regulation. *Frontiers in Immunology*, 16: 1651063. <https://doi.org/10.3389/fimmu.2025.1651063>
77. Sznurkowska KT, 2025. Regulatory Cells in Inflammatory Bowel Disease—Are They Major Players? *International Journal of Molecular Sciences*, 26 (24): 11944. <https://doi.org/10.3390/ijms262411944>
78. Chaelin L, Ye WP, Min HP, Yong JL, Inmoo R, 2025. Regulatory T cells and their role in inflammatory bowel disease: molecular targets, therapeutic strategies and translational advances. *Biochemical Pharmacology*, 239: 117087. <https://doi.org/10.1016/j.bcp.2025.117087>
79. Clough JN, Omer OS, Tasker S, Lord GM, Irving PM, 2020. Regulatory T-cell therapy in Crohn's disease: challenges and advances. *Recent advances in basic science, Gut*, 69: 942-952. Accessed March 2026.
80. Jiménez JM, Contreras-Riquelme JS, Vidal PM, Prado C, Bastías M, Meneses C, Martín AJM, Perez-Acle T & Pacheco R, 2024. Identification of master regulator genes controlling pathogenic CD4+ T cell fate in inflammatory bowel disease through transcriptional network analysis. *Scientific Reports*, 14: 10553. <https://doi.org/10.1038/s41598-024-61158-4>
81. Jacobse J, Li J, Rings EHHM, Samsom JN and Goettel JA, 2021. Intestinal Regulatory T Cells as Specialized Tissue-Restricted Immune Cells in Intestinal Immune Homeostasis and Disease. *Frontiers in Immunology*, 12: 716499. <https://doi.org/10.3389/fimmu.2021.716499>
82. Laukova M. and Glatman ZA, 2023. Regulatory T cells as a therapeutic approach for inflammatory bowel disease. *European Journal of Immunology*, 53: 2250007. <https://doi.org/10.1002/eji.202250007>
83. Jalalvand M, Enayati S, Akhtari M, Madreseh E, Jamshidi A, Farhadi E, Mahmoudi M, Amirzargar A, 2023. Blood regulatory T cells in inflammatory bowel disease: a systematic review and meta-analysis. *International Immunopharmacology*, 117: 109824. <https://doi.org/10.1016/j.intimp.2023.109824>
84. Negi S, Saini S, Tandel N, Sahu K, Mishra RPN, Tyagi RZ, 2021. Translating Treg Therapy for Inflammatory Bowel Disease in Humanized Mice. *Cells*, 10 (8): 1847. <https://doi.org/10.3390/cells10081847>
85. Wang L, Wang S, Lin J, Jiajia L, Mingyuan W, Jiang Y, Sun J, Tang N, Jiao C, Ma J, Zhao X, & Zhang H, 2025. Treg and intestinal myofibroblast-derived Amphiregulin induced by TGF- β mediates intestinal fibrosis in Crohn's disease. *Journal of Translational Medicine*, 23 (1): 452. <https://doi.org/10.1186/s12967-025-06413-6>
86. Zhang S, Zhong R, Tang S, Chen L, Zhang H, 2024. Metabolic regulation of the Th17/Treg balance in inflammatory bowel disease. *Pharmacological Research*, 203: 107184. <https://doi.org/10.1016/j.phrs.2024.107184>
87. Wu Y, Shen J, 2020. Innate Lymphoid Cells in Crohn's Disease. *Frontiers in Immunology*, 11: 554880. <https://doi.org/10.3389/fimmu.2020.554880>
88. Yao X, Ma K, Zhu Y, Cao S, 2025. Innate Lymphoid Cells in Inflammatory Bowel Disease. *Cells*, 14 (11): 825. <https://doi.org/10.3390/cells14110825>
89. Mazzurana L, Bonfiglio F, Forkel M, D'Amato M, Halfvarson J, Mjösberg J, 2021. Crohn's Disease Is Associated with Activation of Circulating Innate Lymphoid Cells. *Inflammatory Bowel Diseases*, 27 (7): 1128–1138. <https://doi.org/10.1093/ibd/izaa316>
90. Przeczek K, Cibor D, Zwolińska-Wcisło M and Owczarek D, 2025. Circulating cell adhesion molecules as biomarkers in inflammatory bowel disease: a systematic review and meta-analysis. *Frontiers in Immunology*, 16: 1680317. <https://doi.org/10.3389/fimmu.2025.1680317>
91. Veny M, Fernández-Clotet A, Panés J, 2020. Controlling leukocyte trafficking in IBD. *Pharmacological Research*, 159: 105050. <https://doi.org/10.1016/j.phrs.2020.105050>
92. Winkel PP, Bergmann-Ewert W, Reiner J, Huth A, Kleimeier D, Casalegno Garduño R, Wrobel IM, Domanska G, Däbritz J, Wirthgen E, 2025. Peripheral monocytes from Crohn's disease patients retain functional responsiveness to GM-CSF during active disease. *Frontiers in Immunology*, 16:1663713. <https://doi.org/10.3389/fimmu.2025.1663713>
93. Mitselou A, Grammeniatas V, Varouktsi A, Papadatos SS, Klaroudas A, Katsanos K, Galani V, 2021. Immunohistochemical Study of Adhesion Molecules in Irritable Bowel Syndrome: A Comparison to Inflammatory

- Bowel Diseases. *Advanced Biomedical Research*, 10: 21. https://doi.org/10.4103/abr.abr_2_20
94. Tian L, Yang X, Zheng Y, and Peng C, 2024. The association between circulating leukocytes and inflammatory bowel disease: a two-sample Mendelian randomization study. *Frontiers in Medicine*, 11: 1399658. doi: 10.3389/fmed.2024.1399658
 95. Buffet-Bataillon S, Durão G, Le Huërou-Luron I, Rué O, Le Cunff Y, Cattoir V, Bouguen G, 2025. Gut microbiota dysfunction in Crohn's disease. *Frontiers in Cellular and Infection Microbiology*, 15: 1540352. <https://doi.org/10.3389/fcimb.2025.1540352>
 96. Shen Y, Fan N, Ma SX, Cheng X, Yang X, Wang G, 2025. Gut Microbiota Dysbiosis: Pathogenesis, Diseases, Prevention, and Therapy. *MedComm* (2020), 6 (5): e70168. <https://doi.org/10.1002/mco.270168>
 97. Alshehri D, Saadah O, Mosli M, Edris S, Alhindi R, Bahieldin A, 2021. Dysbiosis of gut microbiota in inflammatory bowel disease: Current therapies and potential for microbiota-modulating therapeutic approaches. *Bosnian Journal of Basic Medical Sciences*, 21 (3): 270-283. <https://doi.org/10.17305/bjbms2020.5016>
 98. Turcanu L, 2026. Gut Microbiota Alterations and Dysbiosis Patterns in Pediatric Inflammatory Bowel Disease: Clinical Correlations and Therapeutic Impact. *Journal of Clinical Medicine*, 15 (4): 1589. <https://doi.org/10.3390/jcm15041589>
 99. Pierce R, Jan NJ, Kumar P, Middleton J, Petri WA, & Marie C, 2024. Persistent dysbiosis of duodenal microbiota in patients with controlled pediatric Crohn's disease after resolution of inflammation. *Scientific Reports*, 14: 12668. <https://doi.org/10.1038/s41598-024-63299-y>
 100. Ge T, Zhao T, Ruan Y, Ye L, Xiao Y, Xiao F, Li Y, Li X, Wang R, Hu H, Lu C, Sun H, Zhang C, Yu G, Zhang T, 2026. Dysbiosis of fecal virome in pediatric Crohn's disease and its dynamic changes during infliximab therapy. *mSystems*, e01489-25. Published online March 9, 2026. Accessed April 20 2026. <https://doi.org/10.1128/msystems01489-25>
 101. Zhang H, Xiang J, Feng J, Zhang M, Xi Q, 2025. Gut Microbiome Dysbiosis and Inflammatory Bowel Disease Complement Each Other. *Digestive Diseases*, 43 (3): 345–357. <https://doi.org/10.1159/000544771>
 102. Rupa T, Geetika MA, Savitesh K, Poonam K, 2024. Gut microbiota disparities between active Crohn's disease and healthy controls: A global systematic review. *Clinical Epidemiology and Global Health*, 25: 101497. <https://doi.org/10.1016/j.cegh.2023.101497>
 103. Sharma J, Banerjee T, Naithani M, Kumar N, Kumar SS, Basu S, 2023. Gut Microbiome and Crohn's Disease: An Enigmatic Crosstalk [Internet]. *Crohn's Disease - The Current State of the Art*. IntechOpen, 2023; Accessed 5 March 2026. <https://doi.org/10.5772/intechopen.110768>
 104. Xie H, Yu S, Tang M, Xun Y, Shen Q and Wu G, 2025. Gut microbiota dysbiosis in inflammatory bowel disease: interaction with intestinal barriers and microbiota-targeted treatment options. *Frontiers in Cellular and Infection Microbiology*, 15: 1608025. <https://doi.org/10.3389/fcimb.2025.1608025>
 105. Caparrós E, Wiest R, Scharl M, Rogler G, Casbas AG, Yilmaz B, Wawrzyniak M, Francés R, 2021. Dysbiotic microbiota interactions in Crohn's disease. *Gut Microbes*, 13 (1): 1949096. <https://doi.org/10.1080/19490976.2021.1949096>
 106. Pisani A, Rausch P, Bang C, Ellul S, Tabone T, Marantidis CC, 2022. Dysbiosis in the Gut Microbiota in Patients with Inflammatory Bowel Disease during Remission. *Microbiology Spectrum*, 10: e00616-22. <https://doi.org/10.1128/spectrum.00616-22>
 107. Mínguez A., Nos P, 2024. Association of Smoking and Crohn's Disease: An Update. *Journal of Cellular Immunology*, 6 (3): 140-147. <https://doi.org/10.33696/immunology.6.200>
 108. Chen B, Weng M, Chang C, Huang L, & Wei S, 2022. Effect of smoking on the development and outcomes of inflammatory bowel disease in Taiwan: a hospital-based cohort study. *Scientific Reports*, p. 12: 7665. <https://doi.org/10.1038/s41598-022-11860-y>
 109. Jones DP, Tom GR, George DS, David G, Marcus RM, Robyn EW, 2020. Exploring the Effects of Cigarette Smoking on Inflammatory Bowel Disease Using Mendelian Randomization. *Crohn's & Colitis*, 360, 2 (1): otaa018, <https://doi.org/10.1093/crocol/otaa018>
 110. Alzahrani BA, Aljuhani JA, Badri ZA, Alshamrani RM, Algaows FS, and Ahmed ME, 2024. The effect of smoking on inflammatory bowel disease outcomes. *Frontiers in Gastroenterology*, 3: 1395269. <https://doi.org/10.3389/fgstr.2024.1395269>
 111. Nicolaides S, Vasudevan A, Long T, van Langenberg D, 2021. The impact of tobacco smoking on treatment choice and efficacy in inflammatory bowel disease. *Intestinal Research*, 19 (2): 158-170. <https://doi.org/10.5217/ir.2020.00008>
 112. Papoutsopoulou S, Satsangi J, Campbell BJ, Probert CS, 2020. Review article: impact of cigarette smoking on intestinal inflammation—direct and indirect mechanisms. *Alimentary Pharmacology & Therapeutics*, 51: 1268–1285. <https://doi.org/10.1111/apt.15774>
 113. Hu J, Chen W, Zhu R, Yang F, Xu J, Xiang B, Li Y, Wang W, Zhu L, Chen G, & Zhi M, 2025. Dietary risk factors in Crohn's disease and ulcerative colitis: a cohort study with paired healthy relatives as controls. *European Journal of Nutrition*, 64 (3): 123. <https://doi.org/10.1007/s00394-025-03598-w>
 114. Christensen C, Knudsen A, Arnesen EK, Hatlebakk JG, Sletten IS, Fadnes LT, 2024. Diet, Food, and Nutritional Exposures and Inflammatory Bowel Disease or Progression of Disease: An Umbrella Review. *Advances in Nutrition*, 15 (5): 100219. <https://doi.org/10.1016/j.advnut.2024.100219>
 115. Mallon K, McBride C, O'Morain C, Doherty GA, Burns R, 2025. Dietary risk factors for inflammatory bowel disease: A systematic review and meta-analysis. *Clinical Nutrition Open Science*, 63: 12-29. <https://doi.org/10.1016/j.nutos.2025.07.001>
 116. Papadimitriou K, Deligiannidou G-E, Voulgaridou G, Giaginis C, Papadopoulou SK, 2025. Nutritional Habits in Crohn's Disease Onset and Management. *Nutrients*, 17 (3): 559. <https://doi.org/10.3390/nu17030559>
 117. Naqvi SA, Taylor LM, Panaccione R, Ghosh S, Barkema HW, Hotte N, Shommu N, Kaur S, Reimer RA, Madsen KL & Raman M, 2021. Dietary patterns, food groups, and nutrients in Crohn's disease: associations with gut and

- systemic inflammation. *Scientific Reports*, 11: 1674. <https://doi.org/10.1038/s41598-020-80924-8>
118. Halmos EP, Godny L, Vanderstappen J, Sarbagili-Shabat C, Svolos V, 2024. Role of diet in prevention versus treatment of Crohn's disease and ulcerative colitis. *Frontline Gastroenterology*, 15: 247-257. <https://doi.org/10.1136/flgastro-2023-102417>
 119. Dell'Anna G, Fanizzi F, Zilli A, Furfaro F, Solitano V, Parigi TL, Ciliberto A, Fanizza J, Mandarino FV, D'Amico F, 2025. The Role of Vitamin D in Inflammatory Bowel Diseases: From Deficiency to Targeted Therapeutics and Precise Nutrition Strategies. *Nutrients*, 17 (13): 2167. <https://doi.org/10.3390/nu17132167>
 120. Calabro' A, Iannelli F, Pellicano S, Pirillo A, Pungitore M, Rosselli C, Paone C, 2023. Low Levels of Vitamin D and Crohn's Disease. Which Connection? A Review. *Journal of Nutritional Medicine and Diet Care*, 9: 063. <https://doi.org/10.23937/2572-3278/1510063>
 121. Fletcher J, Brown M, Hewison M, Swift A, Cooper SC, 2023. Prevalence of vitamin D deficiency and modifiable risk factors in patients with Crohn's disease: A prospective observational study. *Journal of Advanced Nursing*, 79 (1): 205-214. <https://doi.org/10.1111/jan.15476>
 122. Limketkai BN, Manish BS, Rodriguez B, Veerappan GR, Betteridge JD, Ramos MA, Hutfless SM, Brant SR, 2020. Levels of Vitamin D Are Low After Crohn's Disease Is Established but Not Before. *Clinical Gastroenterology and Hepatology*, 18 (8): 1769-1776. <https://doi.org/10.1016/j.cgh.2019.09.034>
 123. Mak JWY, Yang S, Stanley A, Lin X, Morrison M, Ching JYI, Niu J, Wilson-O'Brien AL, Feng R, Tang W, Hamilton AL, Or L, Trakman GL, Lin WYY, Sung JJY, Chen MH, Mao Y, Kamm MA, Ng SC, 2022. Childhood antibiotics as a risk factor for Crohn's disease: The ENIGMA International Cohort Study. *JGH Open*, 6 (6): 369-377. <https://doi.org/10.1002/jgh3.12755>
 124. Cohen-Mekelburg S, Van T, Wallace B, Berinstein J, Yu X, Lewis J, Hou J, Dominitz JA, Waljee AK, 2022. The Association Between Nonsteroidal Anti-Inflammatory Drug Use and Inflammatory Bowel Disease Exacerbations: A True Association or Residual Bias? *The American Journal of Gastroenterology*, 117 (11): 1851-1857. <https://doi.org/10.14309/ajg.0000000000001932>
 125. Pasvol TJ, Bloom S, Segal AW, Rait G, Horsfall L, 2022. Use of contraceptives and risk of inflammatory bowel disease: a nested case-control study. *Alimentary Pharmacology & Therapeutics*, 55: 318-326. <https://doi.org/10.1111/apt.16647>
 126. de Dios-Duarte MJ, Arias A, Barrón A, 2024. Impact of Psychosocial Factors on the Activity of Crohn's Disease: A Cross-Sectional Analysis of Social Support, Stress, and Flare-Up Incidence. *Journal of Clinical Medicine*, 13 (11): 3086. <https://doi.org/10.3390/jcm13113086>
 127. van der Sloot KWJ, Weersma RK, Alizadeh BZ, Dijkstra G, 2020. Identification of Environmental Risk Factors Associated with the Development of Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 14 (12): 1662-1671. <https://doi.org/10.1093/ecco-jcc/ijaa114>
 128. Usta D, Acampora M, Pereira AC, Savarese M, De Rocchis MS, Avedano L, 2026. Psychological stress and eating behaviors as interacting influences on patient-reported disease activity in Italian patients with inflammatory bowel disease. *Scientific Reports*, 16: 322. <https://doi.org/10.1038/s41598-025-29573-3>
 129. Vieujean S, Caron B, Haghnejad V, Jouzeau J, Netter P, Heba A, Ndiaye NC, Moulin D, Barreto G, Peyrin-Biroulet L, 2022. Impact of the Exposome on the Epigenome in Inflammatory Bowel Disease Patients and Animal Models. *International Journal of Molecular Sciences*, 23 (14): 7611. <https://doi.org/10.3390/ijms23147611>
 130. Guo X, Li J, Xu J, Zhang L, Huang C, Nie Y, Zhou Y, 2025. Gut microbiota and epigenetic inheritance: implications for the development of IBD. *Gut Microbes*, 17 (1): 2490207. <https://doi.org/10.1080/19490976.2025.2490207>
 131. Marangoni K, Dorneles G, da Silva DM, Pinto LP, Rossoni C, Fernandes SA, 2023. Diet as an epigenetic factor in inflammatory bowel disease. *World Journal of Gastroenterology*, 29 (41): 5618-5629. <https://doi.org/10.3748/wjg.v29.i41.5618>
 132. Parigi TL, Nardone OM, Lisa M, Massimino L, Gabbiadini R, Innocenti T, Bertani L, Gaudio AD, Florez P, Bertin L, Barberio B, Hupé M, Lopetuso L, Allocca M, D'Amico F, Furfaro F, Zilli A, Fiorino G, Ungaro F, Castiglione F, Savarino E, Dragoni G, Scaldaferri F, Armuzzi A, Peyrin-Biroulet L, Jairath V, Pizarro TT, Danese S, 2025. The Impact of E-Cigarettes and Heat-Not-Burn Tobacco on Postoperative Recurrence of Crohn's Disease: A Multicenter International Study. *The American Journal of Gastroenterology*, Published online October 24. Accessed 20 April 2026. doi:10.14309/ajg0000000000003810
 133. Sheehan GT, Twardus SW, Cagan A, Ananthakrishnan AN, 2023. E-cigarette Use and Disease Outcomes in Inflammatory Bowel Diseases: A Case-Control Study. *Digestive Diseases and Sciences*, 68 (1): 208-213. <https://doi.org/10.1007/s10620-022-07539-z>
 134. Sharma A, Lee J, Fonseca AG, Moshensky A, Kothari T, Sayed IB, Ibeawuchi S, Pranadinata RF, Ear J, Sahoo D, Crotty-Alexander LE, Ghosh P, Das S, 2021. E-cigarettes compromise the gut barrier and trigger inflammation. *iScience*, 24 (2): 102035. <https://doi.org/10.1016/j.isci.2021.102035>
 135. Vuyyuru SK, Solitano V, Hogan M, MacDonald JK, Zayadi A, Parker CE, Sands BE, Panaccione R, Narula N, Feagan BG, Singh S, Jairath V, Ma C, 2023. Efficacy and Safety of IL-12/23 and IL-23 Inhibitors for Crohn's Disease: Systematic Review and Meta-Analysis. *Digestive Diseases and Sciences*, 68 (9): 3702-3713. <https://doi.org/10.1007/s10620-023-08014-z>
 136. Costa C, Noor NM, Estevinho MM, 2026. Beyond tumor necrosis factor and interleukin-12/23: The rise of interleukin-23 inhibitors in inflammatory bowel disease management. *Current Opinion in Pharmacology*, 86: 102583. <https://doi.org/10.1016/j.coph.2025.102583>
 137. Gao B, Shentu H, Sha S, Wang D, Chen X, Huang Z, Dong N, Lai H, Xu J, Zhou X, 2023. Efficacy of IL-23 inhibitors and IL-12/23 inhibitors in the induction treatment of Crohn's disease: A meta-analysis based on randomized controlled trials. *Central European Journal of Immunology*, 48 (4): 301-310. <https://doi.org/10.5114/ceji.2023.134257>
 138. Mikail M, 2023. Treatment is on target in Crohn's disease with biologic agents. *Royal College of Surgeons in Ireland*

- Student Medical Journal. 11(1): 52-58. Accessed 20 April 2026. <https://hdl.handle.net/10779/rcsi.23921289.v1>.
139. Laffusa A, Burti C, Viganò C, Poggi F, Grieco L, Occhipinti V, Greco S, Orlando S, 2025. Inflammatory Bowel Disease: Understanding Therapeutic Effects of Distinct Molecular Inhibitors as the Key to Current and Future Advanced Therapeutic Strategies. *Biomedicines*, 13 (11): 2667. <https://doi.org/10.3390/biomedicines13112667>
 140. Jia-Chen X, Xiao-Ting H, Yu-Wei Z, Shuo Y, 2025. Biological agents as attractive targets for inflammatory bowel disease therapeutics. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1871 (3): 167648. <https://doi.org/10.1016/j.bbadis.2024.167648>
 141. Kong C, Yang M, Yue N, Zhang Y, Tian C, Wei D, hi R, Yao J, Wang L, Li D, 2024. Restore Intestinal Barrier Integrity: An Approach for Inflammatory Bowel Disease Therapy. *Journal of Inflammation Research*, 17: 5389-5413. <https://doi.org/10.2147/JIR.S470520>
 142. Noviello D, Amoroso C, Vecchi M, Facciotti F, Caprioli F, 2025. Curing inflammatory bowel diseases: breaking the barriers of current therapies– emerging strategies for a definitive treatment. *Current Opinion in Immunology*, 95: 102593. <https://doi.org/10.1016/j.coi.2025.102593>
 143. da Costa FHB, Araújo GAC, Sales TMAL, Paula SM, de Freitas CMA, Havt A, Soares PMG, Souza MHLP, 2025. Restoration of colonic barrier function by tofacitinib in experimental colitis: anti-inflammatory effects and decreased expression of claudins-2 and claudin-15. *Intestinal Research*, 23 (4): 502-511. <https://doi.org/10.5217/ir.2024.00186>
 144. Halder D, Ghazi A, Wang Y, Hou JK, Verzi M, Khurana S, 2025. Pharmacologic activation of HNF4 α / γ Restores Epithelial Barrier Function in Crohn's disease. Preprint. *Biloxi*, 10 (27): 684895. <https://doi.org/10.1101/2025.10.27.684895>
 145. King MR, Kemp RA, and Gadeock S, 2025. Type I interferons in inflammatory bowel diseases: balancing barrier integrity, repair, and inflammation in the intestinal epithelium. *Frontiers in Medicine*, 12: 1713424. <https://doi.org/10.3389/fmed.2025.1713424>
 146. Coffey JC, Devine ML, 2024. The Surgical Management of the Mesentery in Crohn's Disease. *Clinics in Colon and Rectal Surgery*, 38 (2): 113-121. <https://doi.org/10.1055/s-0044-1786197>
 147. Duan M, Coffey JC, Li Y, 2024. Mesenteric-based surgery for Crohn's disease: evidence and perspectives, *Surgery*, 176 (1): 51-59. <https://doi.org/10.1016/j.surg.2024.02.025>
 148. Maatouk M, Khalifa MB, Essid N, Mabrouk A, Nouria M, Boudokhane M, Moussa MB, 2025. Mesenteric inclusion in Crohn's disease surgery: Promising breakthrough or tempest in a teapot? An updated meta-analysis. *Surgery Open Science*, 28: 89-97. <https://doi.org/10.1016/j.sopen.2025.10.010>
 149. Li Y, Mohan H, Lan N, Wu X, Zhou W, Gong J, Shen B, Stocchi L, Coffey JC, Zhu W, 2020. Mesenteric excision surgery or conservative limited resection in Crohn's disease: study protocol for an international, multicenter, randomized controlled trial. *Trials*, 21: 210. <https://doi.org/10.1186/s13063-020-4105-x>
 150. Turri G, Carvello M, Ben DN, Spinelli A, 2022. Intriguing Role of the Mesentery in Ileocolic Crohn's Disease. *Clinics in Colon and Rectal Surgery*, 35 (4): 321-327. <https://doi.org/10.1055/s-0042-1743590>
 151. Zhu Y, Qian W, Huang L, Xu Y, Guo Z, Cao L, Gong J, Coffey JC, Shen B, Li Y, Zhu W, 2021. Role of Extended Mesenteric Excision in Postoperative Recurrence of Crohn's Colitis: A Single-Center Study. *Clinical and Translational Gastroenterology*, (10): e00407. <https://doi.org/10.14309/ctg.00000000000000407>