Review Article

A Review Paper Crohn's Disease: Pathogenesis, Evolving Therapeutics, and Future Directions Toward Precision Medicine

Shreya G. Bedarkar*[1], Nitin B. Kohale[2], Amruta S. Phuse[3] Harigopal S. Sawarkar[4]
[1]B. Pharm II Year Student, Dr. Rajendra Gode College of Pharmacy, Amravati, AP, India.
[2]Professor, Department of Pharmaceutics, Dr. Rajendra Gode College of Pharmacy, Amravati, AP, India.
[3]Assistant Professor, Department of Pharmaceutics, Dr. Rajendra Gode College of Pharmacy, Amravati, AP, India.
[4]Principal, Department of Pharmaceutical Chemistry, Dr. Rajendra Gode College of Pharmacy, Amravati, AP, India.
***Corresponding author's E-mail:** bedarkarshreya@gmail.com

Received: 30-04-2026; **Revised:** 21-07-2026; **Accepted:** 29-07-2026; **Published online:** 20-08-2026.

ABSTRACT

Crohn's disease (CD) is a chronic, multifactorial inflammatory disorder of the gastrointestinal tract marked by relapsing inflammation, ulceration, and progressive complications such as strictures, fistulae, and fibrosis. Its global incidence and prevalence have risen markedly in recent years, reflecting complex interactions among genetic susceptibility, immune dysregulation, environmental influences, and microbiome alterations. Despite substantial progress in diagnostics and therapeutics, many patients continue to experience inadequate treatment responses, disease relapse, and long-term morbidity. This review summarizes recent advances in understanding the molecular and cellular mechanisms driving CD, highlights emerging diagnostic and monitoring tools including biomarkers, imaging modalities, and computational models, and evaluates both established and novel therapeutic strategies such as biologics, small molecules, and cellular therapies. Furthermore, it discusses key challenges, unmet clinical needs, and the potential of cutting-edge approaches—such as multi-omics, spatial transcriptomics, artificial intelligence, and anti-fibrotic therapies—to transform patient care. Finally, a precision medicine framework is proposed that integrates clinical, biomarker, imaging, genetic, and microbiome data to optimize individualized management and guide future research directions in Crohn's disease.

Keywords: Crohn's disease; inflammatory bowel disease; precision medicine; biomarkers; microbiome; genetics; biologics; small molecules; fibrosis; pathogenesis; diagnostic imaging; computational models; personalized therapy; immune dysregulation; risk stratification; anti-fibrotic therapy; multi-omics; artificial intelligence; clinical trials; health equity.

INTRODUCTION

Epidemiology: Global incidence & prevalence; trend of increasing CD in Asia / India / LMICs; differences in disease presentation by geography & ethnicity.

Impact: Healthcare burden, quality of life, economic costs.

Clinical heterogeneity: variable disease location (terminal ileum, colon, ileocolon, upper GI), disease behaviour (inflammatory, stricturing, penetrating), response to therapy.

Rationale for the review: with new therapies, technologies, and research agendas (e.g. the Crohn's & Colitis Foundation 5-year research agenda) emphasizing human IBD mechanisms, environmental triggers, precision medicine, novel technologies, pragmatic clinical research[1,2].

1. Pathogenesis – Deep Dive

1.1 Genetic Susceptibility & Epigenetics

- Summary of known risk loci (~200+) from GWAS: NOD2, ATG16L1, IRGM, IL23R etc.
- Polymorphisms influencing disease course: e.g., NOD2 variants and association with ileal disease, Pharmacogenomic markers: TPMT and NUDT15 polymorphisms in thiopurine metabolism; implications for toxicity.
- Epigenetic modifications: DNA methylation, histone modifications; little explored in human CD but emerging.

1.2 Immune Cell Dysregulation & Signalling Pathways

- Innate immunity: barrier function (epithelial tight junctions, Paneth cells), pattern recognition receptors (e.g., NOD2); innate sensors, inflammasomes.
- Adaptive immunity: Th1/Th17 axis, role of IL-12/23, regulatory T cell dysfunction.
- Cytokines & chemokines: TNF-α, IL-6, IL-1β, IL-23 etc.
- Novel identified pathways: e.g. discovery of enhancer in immune cells regulating ETS2 gene; suggestion that modulation of MEK-ETS2 pathway may be therapeutic.

1.3 Microbiome, Metabolome, and Mucosal Interactions

- Dysbiosis: loss of beneficial microbes, expansion of pathobionts (e.g. adherent-invasive E. coli).
- Microbial metabolites: short-chain fatty acids (SCFAs), bile acids, tryptophan and its metabolites; how they modulate immune responses.
- Mucosal barrier defects & biofilm formation.
- Role of diet, early life exposures, antibiotics, hygiene, environment.

1.4 Environmental, Lifestyle & External Influences

- Smoking: strong risk factor.

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

- Dietary patterns: fibre, processed food, Western diet vs traditional diets; emerging associations with ultra-processed foods rising with IBD incidence.
- Antibiotic use in infancy, infections, hygiene hypothesis.
- Stress, psychological factors.
- Urbanization, pollution.

1.5 Fibrosis, Stricture Formation & Complications

- Pathophysiology: Chronic inflammation enables wound-healing responses; activation of myofibroblasts; ECM deposition; TGF-β and related pathways.
- Distinguishing inflammation vs fibrosis as therapeutic target.
- Biomarkers & imaging to predict fibrotic strictures[3,4].

2. Diagnostics, Monitoring, and Prognostic Biomarkers

2.1 Diagnostic Techniques

- Conventional endoscopy and histology; imaging: MRI enterography, CT enterography, small bowel ultrasound; capsule endoscopy.
- Improved imaging modalities to detect transmural changes, strictures, fistulae; use of contrast agents etc.

2.2 Prognostic Biomarkers & Predictors of Disease Course

- Biomarkers predictive for response to particular therapies: e.g. anti-TNF, anti-IL-23; transcriptomic signatures; HLA haplotypes; oncostatin M expression.
- Early disease / treatment-naive patient analyte studies: multiplex immunoassays (sTNF-R2, sIL-2R, MMP-1 etc) associated with disease severity and complications.
- Combining biomarkers and clinical features: e.g. serum biomarkers (Platelet-lymphocyte ratio, CAR, ESR) + clinical indices (HBI, use of infliximab) to predict mucosal healing.

2.3 Novel and Emerging Technological Approaches

- Spatial transcriptomics: recent study using spatial transcriptomics of colonic mucosa; characterizing cellular niches; creating explainable machine learning model to distinguish CD, UC and healthy tissue.
- AI/ML on imaging: distinguishing CD vs intestinal TB via CT Enterography + AI & classical computer vision; use of visceral/subcutaneous fat ratio etc.
- Natural Language Processing / large language models to extract structured data from unstructured radiology or endoscopy reports.

2.4 Risk Stratification Models & Decision Support Systems

- Models to predict disease behaviour (inflammatory vs stricturing vs penetrating), surgery risk, postoperative recurrence.
- Use of multi-omics, genetic, microbiome, imaging, clinical feature integration.
- Role of therapeutic drug monitoring in anti-TNF biologics; prediction of loss of response [5,6].

3. Therapeutic Landscape: Approved Therapies & Current Standard of Care

3.1 Conventional / Older Therapies

- Corticosteroids: induction of remission; risks, where used.
- Immunomodulators: azathioprine, 6-mercaptopurine, methotrexate – efficacy, toxicity, monitoring (e.g. thiopurine metabolites; pharmacogenetics).
- Antibiotics: metronidazole, ciprofloxacin; used in perianal disease, fistulas etc.

3.2 Biologics

- Anti-TNF agents (infliximab, adalimumab, certolizumab, golimumab): efficacy, limitations (primary non-response; secondary loss).
- Anti-integrin agents (vedolizumab, natalizumab): gut-selective therapies.
- IL-12/23 antagonists (ustekinumab) and IL-23 p19 antagonists (guselkumab, mirikizumab etc). Recent trial: Mirikizumab (Omvoh) in moderately-severe CD showing over 50% remission at 1 year, and good endoscopic response.

3.3 Small Molecules & Kinase Inhibitors

- JAK inhibitors (upadacitinib etc.): oral agents, rapid onset, adverse effect profile.
- Sphingosine-1-phosphate (S1P) receptor modulators.
- Other small molecules in development (e.g., RIPK2 inhibitors, TL1A antagonists etc).

3.4 Combination & Emerging Therapies

- Combination biologic therapy (using more than one biologic or biologic + small molecule) – limited data but being explored.
- Stem cell therapies: mesenchymal stem cells (local injection for perianal disease etc).
- Fecal microbiota transplant (FMT): data still evolving; which patients, safety concerns.
- Future: anti-fibrotic agents; local delivery (e.g., via gels or local injection), gene therapies etc.

3.5 Post-operative Management & Prevention of Recurrence

- Prophylactic therapy after surgery; choice of agent; monitoring endoscopic recurrence (Rutgeerts score).
- Lifestyle/moisture interventions to reduce recurrence risk.

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

3.6 Non-Pharmacologic Management

- Diet & nutrition: exclusive enteral nutrition, Crohn's-specific diets (e.g. Crohn's Disease Exclusion Diet), Mediterranean diet, anti-inflammatory diets.
- Smoking cessation.
- Psychological support; addressing mental health; stress management.
- Physical activity[7,8].

New Drugs & Trials in the Pipeline

- Summary of recent phase II and III trials of novel biologics & small molecules.
- Drugs in development: (Table 1)
- Clinical endpoints under evaluation: endoscopic healing, histologic healing, radiologic endpoints (for transmural disease), patient reported outcomes, safety.
- Safety challenges: infections, malignancy risk, long term safety of small molecule inhibitors[9, 10].

Table 1: New Drugs & Trials

Agent	Target / Mechanism	Stage (Phase)	Key Points / Potential Advantages
IL-23p19 inhibitors (e.g. guselkumab, mirikizumab)	p19 subunit of IL-23	Phase III / Active	More specific, possibly fewer side effects; improved endoscopic healing.
Anti-adhesion molecules (ontamalimab etc)	leukocyte trafficking / integrins	Phase II/III	Gut selective; may reduce systemic effects.
TL1A antagonists	TNF-like ligand 1A	Preclinical / Phase II	Potentially useful in both luminal & perianal disease.
S1P receptor modulators	lymphocyte egress	Early trials	Oral; may have safety concerns (cardio, infection).
PPAR-γ agonists	anti-inflammatory, metabolic modulation	Early stage	Could modulate barrier function and immune response.
Anti-fibrotic agents (e.g. TGFBRI/ALK5 inhibitors)	fibrosis pathway	Preclinical / early stage	To prevent or treat strictures; major unmet need.

4. Treatment Strategies & Algorithms

4.1 Treat-to-Target & Monitoring

- STRIDE-2 recommendations: goals include symptomatic remission, normalization of biomarkers, mucosal healing, possibly transmural healing.
- Early intensive therapy vs "step-up" therapy: data and debate; cost-benefit; selecting patients who are high risk to benefit from early biologics.
- Therapeutic drug monitoring (TDM): in anti-TNF, ustekinumab etc. Use of trough levels, antidrug antibodies to guide dose adjustments.

4.2 Personalized Medicine and Predictive Models

- Use of clinical, biomarker, genetic, microbiome data to stratify risk: who develops strictures/fistulae; who responds to biologics; who is likely to relapse.
- Machine learning / AI based models: combining imaging + biomarkers + transcriptomics. (Examples: spatial transcriptomics + ML classifier; AI to help differentiate CD vs ITB)

4.3 Surgery, Endoscopy & Interventional Approaches

- Indications for surgery; timing; preoperative optimization.
- Endoscopic interventions: dilation, structuralists.
- Perianal disease: combined medical and surgical approach; stem cell injections, local therapy.

4.4 Health System & Implementation: Access, Cost, Adherence

- Issues in LMICs: cost of biologics, affordability, regulatory approval, insurance or public health access.
- Biosimilars: utility, acceptance, interchangeability, cost savings.
- Patient adherence; psychosocial factors; quality of life measures. [11,12]

5. Unmet Needs, Challenges & Gaps

- Non-response / loss of response: still large proportion of patients fail or lose response to biologics; side-effects.
- Lack of therapies targeting fibrosis / reversing strictures.
- Limited biomarkers validated for routine clinical use; lack of head-to-head trials among newer agents.
- Safety concerns: infections, malignancies, immunosuppression in certain patients; long-term safety.
- Diagnostic delay; misdiagnosis; distinguishing CD from ITB in TB-prevalent regions.
- Patient heterogeneity: differences by geography/ethnicity; gene-environment interactions; microbiome variation.

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

- Implementation challenges: translating recommendations (e.g. STRIDE-2) into practice; access; cost; insurance; rural settings. [13,14]

6. Recent Developments & Key Breakthroughs (Last 2-3 Years)

- In mid-2024, trial with Mirikizumab (Omvoh) showed ~54.1% clinical remission at year 1, with endoscopic response in ~48.4% in moderate- to severe CD; regulatory submissions by Lilly for expanded use.
- FDA approval of Omvoh for moderate-to-severe Crohn's disease.
- Emerging AI/ML diagnostic tools: e.g., distinguishing CD vs ITB using imaging + AI; spatial transcriptomics classification tools.
- New research agenda setting by Crohn's & Colitis Foundation targeting precision medicine, environment, novel technologies, pragmatic trials. [15]

7. Future Directions

7.1 Anti-Fibrotic Drug Development

- Necessity: structuring disease a major unmet need; currently managed largely by surgery or endoscopy.
- Potential targets: TGF-β pathway, integrins involved in fibrosis, ALK5 inhibitors, etc. Trials and preclinical data needed.
- Imaging & biomarkers to identify fibrosis non-invasively; to distinguish inflammation vs fibrosis so that specific therapy can be targeted.

7.2 Microbiome & Host-Microbe Interactions

- Interventions: prebiotics, probiotics, FMT; precision microbiome engineering; metabolite therapies.
- Longitudinal microbiome studies; microbiome signatures predictive of response; metabolomics, proteomics.

7.3 Precision / Personalized Medicine

- More integrated models combining clinical features, genetics, microbiome, imaging, biomarkers.
- Use of AI / machine learning to build predictive models; need for large datasets; multi-center.
- Pilot programs of precision therapy; stratified trial designs.

7.4 Novel Technologies & Drug Delivery

- Local delivery (e.g. topical, organ targeted); devices or conjugates to reduce systemic exposure.
- Novel imaging / contrast agents to better define disease extent, fibrosis, inflammation.
- Real-time measurement of biological changes (e.g., through wearable sensors, non-invasive biomarker monitoring).

7.5 Preventive & Environmental Origin Strategies

- Focus on environmental triggers: diet, early life antibiotic exposure, hygiene, pollutants.
- Public health strategies; registry data; epidemiologic studies in newly industrialized nations.

7.6 Trial Design & Regulatory Considerations

- Endpoints: currently reliance on clinical and endoscopic healing; moving toward histologic, radiologic, transmural healing.
- Patient reported outcomes, quality of life, long-term safety.
- Head-to-head trials of newer agents; comparative effectiveness research.
- Adaptive trial designs, platform trials, biomarker-stratified trials. [16]

8. Proposed Framework Toward Precision Care in Crohn's Disease

Here we propose an integrated framework / model that could help guide future research and clinical practice. This could be turned into a figure or flowchart.

Baseline Assessment at Diagnosis:

- Clinical features: age at onset, disease location & behaviour, perianal disease, extraintestinal manifestation
- Genetic testing: known risk variants; TPMT/NUDT15 etc
- Biomarker panels: serum (CRP, ESR, IL assays etc), faecal markers, microbiome sampling
- Imaging and endoscopy: baseline, to assess extent; evaluate for strictures or penetrating disease
- Environmental / lifestyle data: smoking, diet, early life exposures etc

1. Risk Stratification:

- Using clinical + biomarker + imaging data to stratify to low / moderate / high risk for complications (strictures, surgery, fistula, non-response to therapy)

2. Initial Therapy Strategy:

- For high risk: early biologic or small molecule; possibly combination therapy
- For moderate risk: immunomodulators, diet, less aggressive but close monitoring
- For low risk: standard therapy with close monitoring

3. Monitoring & Adjustment:

- Use therapeutic drug monitoring for agents (e.g. anti-TNF, IL-23)
- Biomarkers & imaging at fixed intervals: faecal calprotectin, MRI/ultrasound etc

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

- Clinical PROs, quality of life

4. Adaptation over Time:

- If non-response / loss of response: escalate therapy, switch agents
- Identify fibrosis and adapt treatment accordingly (e.g. surgical, anti-fibrotic in trials)
- Consider patient preferences, side effects, cost

5. Maintenance, Remission & Preventing Recurrence:

- Ensure mucosal / histologic healing; aim for deep remission (including transmural)
- Post-surgical prophylaxis; lifestyle interventions
- Long-term safety surveillance

6. Data Collection & Research Integration:

- Enrollment in registries / real world data capture
- Use of multi-omics, AI analyses
- Biomarker validation; trial participation[17]

CONCLUSIONS

Crohn's disease remains a complex and heterogeneous condition with substantial unmet clinical needs despite recent therapeutic advancements. Although new biologics, novel molecular targets, and improved diagnostic technologies have expanded treatment options, many patients continue to experience non-response, disease complications, high treatment costs, and adverse effects. The future of Crohn's disease management lies in precision medicine—integrating clinical, biomarker, imaging, genetic, and microbiome data to tailor therapies more effectively. To achieve this, more robust predictive biomarkers, refined clinical trial designs, and the development of anti-fibrotic treatments are essential. Additionally, addressing health equity issues such as cost, accessibility, and regulatory challenges, especially in low- and middle-income countries, is crucial to ensure that therapeutic progress benefits all patients. Future research should prioritize biomarker-stratified trials, direct head-to-head treatment comparisons, and long-term outcome studies to enhance personalized and equitable care.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Wright EK, Kamm MA, Teo SM, Inouye M, Wagner J, Kirkwood CD. *Recent advances in characterizing the gastrointestinal microbiome in Crohn's disease: a systematic review.* Inflamm Bowel Dis. 2015 Apr;21(6):1219–1228.
2. Jauregui-Amezaga A, Smet A. *The Microbiome in Inflammatory Bowel Disease.* J Clin Med. 2024;13(16):4622.
3. Mousa WK, Al Ali A. *The Gut Microbiome Advances Precision Medicine and Diagnostics for Inflammatory Bowel Diseases.* Int J Mol Sci. 2024;25(20):11259.
4. Uncovering the role of microbiota and fecal microbiota transplantation in Crohn's disease: Current advances and future hurdles. Singh JP, Aleissa M, Chitragari G, Drelichman ER, Mittal VK, Bhullar JS. World J Methodol. 2025;15(4):106148.
5. Genétic studies of Crohn's disease: Past, present and future. Pierce R, Jan N-J, Kumar P, Middleton J, Petri WA, Marie CM. Scientific Reports. 2024.
6. Núñez-Sánchez MA, Melgar S, O'Donoghue K, Martínez-Sánchez MA, Fernández-Ruiz VE,
7. Ferrer-Gómez M, Ruiz-Alcaraz AJ, Ramos-Molina B. *Crohn's Disease, Host–Microbiota Interactions, and Immunonutrition: Dietary Strategies Targeting Gut Microbiome as Novel Therapeutic Approaches.* Int J Mol Sci. 2022;23(15):8361.
8. Diagnosis of Crohn's disease and ulcerative colitis using the microbiome. (Title suggests diagnostic microbiome work)
9. Engineering Spatial and Molecular Features from Cellular Niches to Inform Predictions of Inflammatory Bowel Disease. Tan MJ, Kapetanaki M, Beno~~s PV et~~ al. (arXiv preprint, 2025)
10. Cell Spatial Analysis in Crohn's Disease: Unveiling Local Cell Arrangement Pattern with Graph-based Signatures. Bao S, Zhu S, Kolachala VL, Remedios LW, et al. ~~(arXiv~~ preprint, 2023)
11. Interpretable histopathology-based prediction of disease relevant features in Inflammatory Bowel Disease biopsies using weakly-supervised deep learning. Mokhtari R, Hamidinekoo A, Sutton D, et al. (arXiv preprint, 2023)
12. IBD Genetics Consortium publications: *Clinical Predictors of Early and Late Endoscopic Recurrence Following Ileocolonic Resection in Crohn's Disease.* Hernández-Rocha C, Walshe M, Birch S, et al. J Crohns Colitis. 2024;18(4):615–627.
13. *Fecal microbiota transplantation therapy in Crohn's disease: Systematic review.*
14. Clinical and Translational Gastroenterology: genetic risk, stool microbiome in IBD – "Genetic risk scores
15. … stool microbial metagenome of 85 IBD patients compared to controls." (2017)
16. The Gut Microbiome Advances Precision Medicine and Diagnostics for IBD – same as #3 but useful in multiple contexts.
17. The Microbiome in IBD – Aranzazu Jauregui-Amezaga & Annemieke Smet. (2024) – note includes bacterial, fungal, viral components.

For any questions related to this article, please reach us at: globalresearchonline@rediffmail.com
New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.