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## A Comprehensive Review and Update on Crohn's Disease

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### ABSTRACT

In the United States, it is currently estimated that about 1.5 million people suffer from Inflammatory Bowel Disease, causing considerable suffering, mortality and economic loss every year. Yet the cause of IBD is unknown, and until we understand more, prevention or cure will not be possible. There is a lot of variation in the incidence and prevalence of Crohn's Disease based on geographic region, environment, immigrant population, and ethnic groups. The annual incidence of Crohn's Diseases in North America is reported to be 3.1–20.2 per 100,000 with a prevalence of 201 per 100,000 population. Based on the epidemiological, genetic and immunological data, Crohn's Disease is considered to be a heterogeneous disorder with multifactorial etiology in which genetics and environment interact to manifest the disease. Several genes have been studied so far with respect to Crohn's Disease, but thus far the strong and replicated associations have been identified with NOD2, IL23R and ATG16L1 genes. The risk factors implicated with Crohn's Disease include smoking, low fiber- high carbohydrate diet, altered [microbiome](#) and medications such as non-steroidal anti-inflammatory drugs.

**KEY WORDS:** Crohn's Disease, Ulcerative colitis, Claudins

### INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal (GI) tract from mouth to anus, though it most commonly involves the terminal ileum and proximal colon. Characterized by transmural inflammation, Crohn's disease differs from ulcerative colitis (UC), the other major form of IBD, which is limited to the colonic mucosa. The disease presents a variable clinical course with periods of remission and exacerbation, making its management complex and patient-specific.

### EPIDEMIOLOGY

The global incidence and prevalence of Crohn's disease have been rising steadily, particularly in industrialized countries, with emerging increases in newly industrializing nations. In North America and Western Europe, prevalence rates are estimated at 200–300 cases per 100,000 population. Environmental shifts, including Westernized diets, antibiotic exposure, and urbanization, are implicated in this trend.

### ETIOLOGY

Crohn's disease is multifactorial in origin, involving a complex interplay between:

**Genetics:** Over 200 genetic loci have been associated with IBD, with NOD2, ATG16L1, and IL23R being notably implicated in Crohn's disease.

**Immune dysregulation:** A dysregulated immune response to gut microbiota plays a central role. Innate and adaptive immune responses are aberrantly activated, contributing to chronic intestinal inflammation.

**Microbiome alterations:** Dysbiosis, or an imbalance in gut microbial composition, is commonly observed in CD patients and may exacerbate inflammation.

**Environmental factors:** Smoking, NSAID use, diet high in processed foods, stress, and early-life antibiotic exposure increase disease risk or severity.

## **PATHOPHYSIOLOGY**

Crohn's disease is a **chronic, relapsing-remitting inflammatory condition** of the gastrointestinal tract. It can affect any part of the GI tract (most commonly the terminal ileum and colon) and involves **transmural (full-thickness) inflammation**.

### **1. Genetic Predisposition**

**NOD2** mutations (seen in ~15–20% of CD patients):

- Impair recognition of bacterial peptidoglycans.
- Result in defective innate immune activation and defective autophagy.

**ATG16L1, IRGM:**

- Disrupt autophagy and bacterial clearance in intestinal epithelial cells and Paneth cells.

**IL23R, STAT3:**

- Promote dysregulated adaptive immune responses (particularly Th17-mediated).

**Key effect:** A genetically primed immune system has impaired microbial sensing and overactive inflammation.

### **2. Intestinal Barrier Dysfunction**

**Epithelial barrier:**

Disruption of tight junction proteins (e.g., occludin, claudins) increases permeability.

- **Mucus layer:**

Thinner and deficient in protective mucins (especially MUC2), allowing closer contact between luminal microbes and epithelium.

- **Paneth cell defects:**

Reduced secretion of defensins and antimicrobial peptides in the ileum.

- **Key effect:** Increased intestinal permeability allows bacterial antigens to penetrate the mucosa.

### **3. Dysbiosis (Altered Gut Microbiota)**

↓ Commensals: *Faecalibacterium prausnitzii*, *Bifidobacterium*.

↑ Pathobionts: Adherent-invasive *Escherichia coli* (AIEC), *Clostridium difficile*.

**Key effect:** Imbalance in microbiota composition promotes immune activation and chronic inflammation.

### **4. Innate Immune Activation**

**Pattern recognition receptors (PRRs)** such as TLRs and NOD2 detect microbial products.

In Crohn's Disease:

- Inadequate bacterial clearance.
- Macrophages and dendritic cells become chronically activated.
- Secrete excessive pro-inflammatory cytokines: **TNF- $\alpha$ , IL-1 $\beta$ , IL-6**.

**Key effect:** Persistent innate immune stimulation drives inflammation.

### **5. Adaptive Immune Dysregulation**

CD is characterized by **exaggerated Th1 and Th17 responses**:

- **Th1 response:**

↑ IFN- $\gamma$  → activates macrophages, promotes tissue damage.

- **Th17 response:**

↑ IL-17, IL-22, and IL-23 → recruits neutrophils and further damages mucosa.

- **Tregs (regulatory T cells):**

Often functionally impaired → reduced control of inflammation.

**Key effect:** A shift from immune tolerance to immune aggression against self-antigens and gut flora.

## 6. Cytokine Storm and Tissue Injury

Major cytokines involved:

- **TNF- $\alpha$ :** Central mediator, promotes granuloma formation, apoptosis resistance, and matrix degradation.
- **IL-12, IL-23:** Promote Th1/Th17 polarization.
- **IL-6:** Sustains chronic inflammation and resistance to apoptosis in T cells.

**Key effect:** Persistent cytokine signaling leads to transmural inflammation and tissue remodeling.

## 7. Chronic Inflammation and Complications

Chronic activation results in:

- **Granuloma formation:** Non-caseating, found in ~30–50% of patients.
- **Fibrosis and stricturing:** From fibroblast activation and collagen deposition.
- **Fistulas and abscesses:** From deep tissue ulceration and transmural penetration.
- **Strictures:** From repeated cycles of injury and healing.

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## DIAGNOSIS

Diagnosis is based on a combination of clinical evaluation, laboratory tests, endoscopic and histologic examination, and imaging:

- **Endoscopy:** Reveals skip lesions, aphthous ulcers, and cobblestone mucosa.
- **Biopsy:** May show non-caseating granulomas.
- **Imaging:** MRI enterography and CT are useful in assessing transmural involvement and complications.

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## MANAGEMENT

Management focuses on achieving and maintaining remission, improving quality of life, and preventing complications. Therapeutic approaches include:

- **Medications:** Aminosalicylates, corticosteroids, immunomodulators (azathioprine, methotrexate), and biologics (anti-TNF agents, anti-integrins, IL-12/23 inhibitors).
- **Novel therapies:** Janus kinase (JAK) inhibitors and microbiome-targeted therapies are under investigation.
- **Surgery:** Reserved for complications like strictures, perforation, or refractory disease; not curative.

### Prognosis and Monitoring

Crohn's disease has a relapsing-remitting course, and many patients require multiple surgeries over their lifetime. Advances in treat-to-target strategies, involving tight disease control using biomarkers like fecal calprotectin and imaging, have improved outcomes.

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## NON-PHARMACOLOGICAL

Non-pharmacological strategies are increasingly recognized as critical components of comprehensive Crohn's disease (CD) management. These approaches aim to reduce disease burden, prolong remission, enhance quality of life, and address both physical and psychological aspects of living with a chronic illness. While they do not replace medication in moderate to severe disease, they are essential in optimizing outcomes.

### 1. Nutritional and Dietary Interventions

#### a. Exclusive Enteral Nutrition (EEN)

Particularly effective in **pediatric** Crohn's disease.

- Involves exclusive consumption of a nutritionally complete liquid formula for 6–8 weeks.
- Shown to induce remission comparable to corticosteroids, with added benefits of mucosal healing and growth promotion.
- Less commonly used in adults due to poor adherence.

**b. Partial Enteral Nutrition (PEN)**

- Combines enteral formulas with some regular food.
- May help maintain remission, though less effective than EEN for induction.

**c. Specific Diets**

- **Crohn's Disease Exclusion Diet (CDED):** A structured, whole-food diet that excludes pro-inflammatory and processed foods; has shown promise in both children and adults.
- **Specific Carbohydrate Diet (SCD) and Low FODMAP Diet:** May reduce symptoms like bloating or diarrhea, though evidence for disease control is limited.
- **Anti-inflammatory diets:** Emphasize whole, unprocessed foods, omega-3 fatty acids, and fiber (when tolerated).

**d. Nutritional Support**

- Monitoring for deficiencies (iron, B12, vitamin D, zinc) is critical.
- Supplementation may be required due to malabsorption or dietary restrictions.

**2. Lifestyle Modifications****a. Smoking Cessation**

- Smoking is a well-established risk factor for disease onset and exacerbation.
- Quitting smoking significantly reduces the risk of flares, surgery, and complications.

**b. Exercise**

- Regular moderate exercise improves overall well-being, fatigue, bone health, and mood.
- May have mild anti-inflammatory effects and support immune regulation.

**c. Stress Management**

- Chronic stress can exacerbate symptoms and increase relapse risk.
- Mind-body interventions such as **mindfulness-based stress reduction (MBSR)**, **yoga**, **breathing exercises**, and **meditation** can reduce anxiety and improve quality of life.

**3. Psychosocial Support****a. Cognitive Behavioral Therapy (CBT)**

- Beneficial for patients experiencing depression, anxiety, or difficulty coping with a chronic disease.
- May improve adherence and reduce perceived disease activity.

**b. Support Groups and Counseling**

- Peer support can reduce feelings of isolation and improve coping strategies.
- Family counseling may help in pediatric cases and in families dealing with stress due to a child's chronic illness.

**4. Patient Education and Self-Management**

- Empowering patients through education about disease mechanisms, symptom tracking, and treatment options can improve outcomes.
- Use of mobile health apps and digital platforms for monitoring symptoms and adherence is growing.
- "Treat-to-target" strategies may include patient self-monitoring of fecal calprotectin or symptom scoring tools.

**5. Complementary and Alternative Medicine (CAM)**

- **Probiotics:** Limited evidence for Crohn's, more effective in ulcerative colitis.
- **Acupuncture:** Some reports of symptomatic improvement, though evidence is weak.
- **Herbal therapies** (e.g., turmeric/curcumin): Mild anti-inflammatory properties, but should be used cautiously and under medical supervision.

**6. Surgical and Mechanical Non-Drug Interventions**

While technically medical, some non-drug interventions include:

- **Nutritional stoma care and stricture dilation techniques.**
- **Bowel-sparing procedures** that aim to preserve function in patients needing surgery.

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## CONCLUSION

Non-pharmacological management of Crohn's disease plays a vital role in supporting medical treatment, enhancing quality of life, and potentially improving long-term outcomes. While these interventions cannot replace pharmacologic therapy in moderate to severe disease, they offer meaningful benefits across physical, psychological, and social dimensions of care. Nutritional strategies, particularly exclusive enteral nutrition and individualized dietary modifications, can help induce and maintain remission, especially in pediatric populations. Lifestyle adjustments—such as smoking cessation, regular physical activity, and stress reduction—can reduce disease activity and the risk of complications. Psychological support, through cognitive behavioral therapy, counseling, and peer engagement, addresses the emotional burden of chronic illness and fosters resilience.

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