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Crohn's Disease – Epidemiology, Clinical Presentation and Treatment Possibilities

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ABSTRACT

Introduction. Crohn's disease is a chronic, relapsing–remitting inflammatory disorder of the gastrointestinal tract. Once concentrated primarily in high-income regions, Crohn's disease has now become a global condition. Advances in understanding immune and stromal cell populations, their interactions, and the cytokine and chemokine networks that drive pathogenesis and rapid technological progress have greatly broadened therapeutic options. Currently treatment strategies aim not only to induce and maintain deep, durable remission, but also to prevent complications and slow or stop the progressive nature of the disease.

Aim. The aim of this review is to summarize current evidence of epidemiology, pathophysiology, diagnosis, and treatment options in Crohn's disease.

Material and methods. This research involves a review of literature found in PubMed, Google Scholar, electronic databases, and books using key words combinations such as "Crohn's disease", "symptoms", "epidemiology", "and", "treatment", "clinical trial", "risk factors", "pathogenesis", "surgery".

Conclusions. Despite advancements in Crohn's disease treatment, recurrence rate is still at high levels resulting in the need for surgical management for the majority of patients diagnosed with Crohn's disease. Further studies are still necessary to confirm efficacy and potential of existing treatment options and to search for new substances, which might be effective in Crohn's disease management.

Keywords: Crohn's disease, inflammatory bowel disease, inflammation, treatment, surgery

1. Introduction

Crohn's disease (CD), one of the major forms of inflammatory bowel disease (IBD), is a chronic, relapsing–remitting inflammatory disorder of the gastrointestinal tract that can progressively lead to bowel damage, complications, and disability [1]. Although any part of the gut may be affected, the terminal ileum and colon are most involved, with inflammation that is typically segmental, asymmetrical, and transmural. Common presenting symptoms include diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue. Patients with Crohn's disease are at increased risk of cancer, osteoporosis, anemia, nutritional deficiencies, depression, infection, and thrombotic events [2]. Most individuals initially present an inflammatory disease pattern, but over time about half develop strictures, fistulas, or abscesses, many of which eventually require surgical intervention [3].

Once concentrated primarily in high-income regions, Crohn's disease has now become a global condition, driven in part by rising incidence rates in both adults and children in middle-income countries [4]. Advances in understanding immune and stromal cell populations, their interactions, and the cytokine and chemokine networks that drive pathogenesis and rapid technological progress have greatly broadened therapeutic options. Parallel to this therapeutic expansion, new non-invasive tools for diagnosis and disease monitoring are quickly emerging [5].

Currently treatment strategies aim not only to induce and maintain deep, durable remission, but also to prevent complications and slow or stop the progressive nature of the disease.

2. Research materials and methods

This research involves a review of literature published between 1989-2025. Research was carried out using PubMed, Google Scholar, electronic databases, and books. The search strategy utilized key words combinations such as "Crohn's disease", "symptoms", "epidemiology", "and", "treatment", "clinical trial", "risk factors", "pathogenesis", "surgery". The research included full-text articles written in English, including original research, clinical trials, systematic reviews, meta-analysis and practice guidelines.

3. Research results

3.1. Epidemiology

IBD affects more than 2 million Europeans with an incidence rate of 10.5 to 46.14 per 100 000 in Europe, while Crohn's disease incidence rate ranges from 4.1 to 22.78 per 100 000 in Europe [6, 7]. The incidence rate of IBD varies by geographical region. Studies showed that the incidence of Crohn's disease was twice as high in western Europe compared with eastern Europe [8]. However, population-based data revealed that incidence of CD grew rapidly in

eastern Europe, while remaining on similar level in western Europe [9]. Prevalence is rising both in western and eastern Europe, because incidence exceeds mortality associated with IBD [10]. Sex differences are not significant, which suggests that CD affects equally men and women [11].

3.2. Risk factors

Crohn's disease (CD) arises from the interaction between environmental exposures and genetic susceptibility.

Environmental factors:

Smoking is the strongest modifiable risk factor in Western populations, doubling CD risk especially in women and contributing to earlier onset, greater need for immunosuppression, higher surgical rates, and postoperative recurrence [12]. Ethnic differences exist, and in Japan passive smoke exposure also increases risk [13]. Diet-related gut dysbiosis is another key contributor: shifts from high-fibre, low-fat diets to processed foods and additives reduce microbial diversity and may promote CD [14]. Although dietary effects on the microbiota are largely transient, adherence to a Mediterranean diet has been linked to lower CD risk [15]. Childhood antibiotic exposure [16], oral contraceptives [17] and NSAIDs [18] also increase risk. Protective factors include breastfeeding (evidence is inconsistent) and statin use [19].

Given substantial geographic differences in environmental exposures, especially diet, smoking, antibiotic use, and urbanization preventive strategies must be population specific. Modifying smoking behaviors, limiting unnecessary antibiotics, supporting breastfeeding, and providing evidence-based dietary guidance may help reduce CD incidence and improve long-term outcomes.

Genetic factors:

Genetic advances have identified more than 200 loci associated with CD, although most exert only small individual effects [20,21]. A few genes, especially NOD2, ATG16L1, and IL23R, account for a larger share of inherited risk and implicate pathways such as bacterial recognition, autophagy, and IL-23 signaling [20-23]. These variants differ across populations: NOD2 and ATG16L1 risks are prominent in White populations [24] but largely absent in Asians, where TNFSF15 is a major risk gene [25]. Rare IL-10 receptor mutations cause severe, early-onset forms with strong Mendelian inheritance [26].

Overall, genetic factors explain only about 13% of CD heritability [27], indicating that environmental and epigenetic influences are substantial. Genetics may predict disease location such as ileal versus colonic CD, but does not fully explain disease behavior or complications, which seem to reflect disease progression rather than inherited traits [28].

In sum, CD develops from a complex, population-specific interplay between modifiable environmental exposures, diet-microbiome interactions, and diverse genetic risk architecture.

3.3. Pathogenesis and molecular mechanisms

The pathogenesis of Crohn's disease involves an excessive, uncontrolled immune response to bacterial antigens in the intestinal lumen. Numerous immune cells infiltrate the tissues of patients, including T lymphocytes (CD4, CD8), B lymphocytes, monocytes, and NK cells. Susceptibility to the disease is influenced by disorders of innate defense mechanisms, such as reduced mucus production (Muc2 mutations) and altered interaction with bacteria resulting from FUT2 variants that limit the secretion of ABO antigens [29]. Adhesion molecules, integrins, and chemokines that drive the production of proinflammatory cytokines play an important role in pathogenesis. Of particular importance are MAdCAM-1 and the remodeling of the extracellular matrix involving CD44, CD26, and metalloproteinases (MMP-1, MMP-3), which promote leukocyte activation [30]. In the CD mucosa, there is a strong dysregulation of the immune response, primarily T-cell hyperactivity and a predominance of the Th1 phenotype, characterized by increased production of IL-12, IFN-γ, and TNF-α. Increased TNF-α concentration also correlates with an increase in the number of Treg cells in the mucosa. The disease is also associated with impaired expression of many interleukins, particularly TNF, IL-12, IL-23, but also IL-34 (increased in active disease) and IL-25 (decreased). IL-34 enhances the expression of TNF-α and IL-6 and induces the chemokine CCL20 via the M-CSFR1 receptor present in the inflamed mucosa. Therapies blocking IL-12/IL-23 or TNF-α, despite their effectiveness in some patients, remain insufficient and may cause adverse effects. Frequent lack of response to biological drugs, such as infliximab, is associated with, among other things, alternative signaling pathways and cell migration [29].

3.4. Clinical manifestations

Clinical manifestations of CD may be highly variable due to many different phenotypes of the disease. The mean time between the onset of symptoms and diagnosis is longer in CD than other IBDs such as ulcerative colitis (UC) [31]. The greater delay in diagnosis may be due to smaller frequency of alarming symptoms in CD and unspecific, systemic symptoms, which may be confused with other etiologies [32]. The most commonly occurring clinical manifestations of CD are weakness, fatigue, diarrhea, abdominal pain, weight loss, and rectal bleeding. [33] Depending on disease phenotype patients may present other symptoms such as fistulas or abscesses in penetrating disease, bowel obstructions in stricturing disease leading to vomiting, nausea and hyperactive bowel sounds [34]. Extraintestinal manifestations of CD occur commonly. CD mostly affects musculoskeletal system (e.g. enthesitis, axial arthritis), skin (e.g.

erythema nodosum), eyes (e.g. anterior uveitis, iritis) and hepatobiliary tract (primary sclerosing cholangitis), but might present symptoms from almost every organ [35].

3.5. Diagnosis

The diagnosis of Crohn's disease requires a strategy that integrates clinical evaluation, laboratory testing, cross-section imaging, and endoscopic visualization with tissue biopsy and histopathologic examination, which remains the gold standard. According to Maaser et al., the diagnosing process should begin with biochemical assessment such as full blood count, inflammatory markers (C-reactive protein [CRP]), electrolytes, liver enzymes, and microbiological analysis of a stool. Raised inflammatory markers highly correlate with clinical severity of CD [36]. Fecal calprotectin is the most sensitive marker of intestinal inflammation and highly correlates with endoscopic indicators of disease activity [37]. Some symptoms of infectious colitis may mimic CD, so it should be ruled out by microbiological stool analysis, including C. difficile. Performing an endoscopy with biopsy of tissues from the edges of ulcers is essential for diagnosis and maximizes the chance to find granulomas, which are pathognomonic for CD, even though they can be found only in about 20% of biopsies taken from patients with CD [38]. The hallmarks of CD seen in endoscopy are skip lesions – areas of inflammation located between normal mucosa. Ulcers in CD tend to be longitudinal with the cobblestone appearance of the colon [39]. To evaluate the disease severity in small intestine, computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are recommended. Both have sensitivity and specificity above 90% detecting lesions associated with CD [40]. MRE is preferred over CTE due to radiation dose reduction in patients who might need serial imaging [40]. For grading the severity of Crohn's disease using endoscopy, there are scoring systems, which can be used, such as SES-CD and Crohn's disease Endoscopic Index of Severity [41,42]. Gaining results from tests mentioned above allows to use Montreal or Paris (for children) Classification to stratify risk of exacerbations, complications and surgery-requiring treatment [43,44].

3.6. Treatment

3.6.1. Anti-TNF

Tumor necrosis factor alpha is a proinflammatory cytokine, which takes part in acute phase response. TNF-α is released by Th1 cells together with other cytokines such as IL-1, IL-6, and IL-17 [45]. These mediators promote the recruitment of intestinal fibroblasts, neutrophils, and macrophages to the gastrointestinal tract. The accumulation of fibroblasts contributes to intestinal fibrosis, ultimately resulting in stricture formation. Neutrophil infiltration leads to the secretion of elastase, which facilitates degradation of the extracellular matrix. In addition,

macrophages that accumulate within the intestinal tissue produce TNF-α, IL-1, and IL-6, collectively driving matrix breakdown, epithelial injury, endothelial activation, and vascular impairment [46,47].

Adalimumab is an IgG1 monoclonal antibody that binds specifically to TNF-α. Beyond neutralizing TNF-alpha, its therapeutic effect in Crohn's disease also appears to involve the induction of apoptosis. Studies have shown that adalimumab triggers apoptosis in transmembrane TNF-expressing monocytes and T cells [48].

Infliximab is a chimeric IgG1 monoclonal antibody targeting both soluble and transmembrane tumor necrosis factor alpha [49]. It is the first monoclonal antibody approved by the FDA for CD treatment in 1998 [49].

In a Danish population-based study comparing adalimumab and infliximab in patients diagnosed with Crohn's disease no significant differences in rate of CD-related hospitalization or major abdominal surgery were found between patients treated with any of the compared antibodies. Although patients using adalimumab, were hospitalized for reasons unrelated to CD less often [50].

Another retrospective cohort study comparing adalimumab to infliximab in CD showed that patients treated with infliximab were at lower risk of hospitalization related to CD, abdominal surgery, and corticosteroid use than patients treated with adalimumab [51].

3.6.2. Corticosteroids

Corticosteroids suppress the transcription of genes responsible for producing proinflammatory cytokines, including interleukin (IL)-1, IL-6, NF-κB, and TNF-α, and reduce the expression of adhesion molecules within inflamed tissues, thereby limiting the migration and activity of activated immune cells [52]. Systemic steroids due to their severe adverse effects are used only for remission induction.

Budesonide is a locally acting corticosteroid with 80-90% first-pass hepatic metabolism and due to that systemic absorption is significantly lower than conventional corticosteroids [52].

In a Rezaie et al. meta-analysis including studies, which compared budesonide to placebo and to systemic corticosteroids, budesonide was superior to placebo for induction of clinical remission. Remission rates in budesonide-treated patients and placebo group were respectively 47% and 22%. Conventional steroids were more effective than budesonide for induction of remission. In the budesonide-treated group, 52% of patients achieved remission compared to 61% in the group of patients who received conventional steroids. Adverse events were less common in patients treated with budesonide than systemic steroids [53].

In Faleck et al. meta-analysis of randomized trials comparing anti-TNF and corticosteroids polytherapy to anti-TNF monotherapy in CD remission induction, the combination of corticosteroids and an anti-TNF agent was found to be less effective than anti-TNF monotherapy showing superiority of anti-TNF monotherapy in induction of remission [54].

3.6.3. Janus kinase inhibitors

Upadacitinib is a selective, oral JAK-1 inhibitor.

In a clinical trial conducted in 2023, comparing upadacitinib to placebo, upadacitinib was significantly more effective than placebo in achieving clinical remission (38.9% compared with 21.1%) and an endoscopic response (34.6% compared with 3.5%) [55]. Patients with clinical remission were qualified for maintenance trial to receive lower doses (15 mg or 30 mg) of upadacitinib or placebo for 52 weeks. Patients using 30 mg upadacitinib achieved clinical remission more often than 15 mg upadacitinib or placebo groups (47.6%, 37.3%, 15.1%, respectively). Also, the endoscopic response was similar to clinical remission outcomes. [55]

3.6.4. 5-aminosalicylates

Aminosalicylates exhibit multiple mechanisms of anti-inflammatory action that may have a desirable effect on inflammatory bowel diseases. They interact with pathways of inflammation, cancer development, apoptosis, and have antimicrobial properties [56].

The meta-analysis published in 2016 evaluated efficacy of 5-aminosalicylic acid (mesalamine) to placebo, corticosteroids and other 5-aminosalicylates for inducing remission of CD. 45% of sulfasalazine patients entered remission compared to 29% of placebo patients. Corticosteroids were superior to sulfasalazine for inducing clinical remission, 60% of corticosteroid-treated patients achieved remission compared to 43% of sulfasalazine patients. Olsalazine and low dose mesalamine were found to be less effective or at least not superior to placebo. High dose controlled-release mesalamine (4 g/day) also was not superior to placebo and less effective than budesonide [57].

The reviews of studies that compared 5-aminosalicylic acid (mesalamine) to placebo concluded that 5-aminosalicylates are superior to placebo for the maintenance of surgically induced clinical remission in patients with CD, but found no evidence for 5-aminosalicylates to be superior to placebo for maintenance of medically induced clinical remission of CD [58,59].

3.6.5. Antimetabolites

6-mercaptopurine and its prodrug, azathioprine act as antimetabolites for purine bases, leading to impaired DNA synthesis and preventing the proliferation of cells involved in the immune response.

Methotrexate is an antimetabolite, a folic acid antagonist. It inhibits the synthesis of purine nucleotides and thymidylates necessary for DNA synthesis and repair, and cell replication. Methotrexate acts specifically on proliferating cells, mainly in the S phase of the cell cycle.

Meta-analysis conducted in 2016 that included 13 studies found azathioprine and 6-mercaptopurine not superior to placebo for induction of remission or clinical improvement in active CD, although antimetabolite treatment may lead to limit usage of corticosteroids and their adverse effects [60].

Other meta-analysis including 11 studies from 2015 concluded that azathioprine is more effective than placebo for maintenance of remission in Crohn's disease, but quality of the evidence is low [61].

According to Patel et al. review, evidence suggests that giving methotrexate intramuscularly at 15 mg per week is more effective than placebo for maintaining remission in Crohn’s disease. In contrast, low-dose oral methotrexate (12.5–15 mg per week) does not seem to help sustain remission. Using methotrexate together with infliximab does not appear to provide any additional benefit compared with infliximab alone for ongoing remission maintenance [62]. Infliximab seems to be more effective than antimetabolites in combination or alone with similar risk of adverse effects. [63]

3.6.6 . Anti-IL12, Anti-IL23 antibodies

Ustekinumab targets the p40 subunit, shared by interleukins IL-12 and IL-23, preventing them from binding to their respective receptors. In this way, it inhibits signal transduction and the processes of cytokine differentiation and secretion, which are important in the development of inflammation [64].

Risankizumab is a humanized IgG1 monoclonal antibody that specifically targets the p19 subunit of the cytokine IL-23, blocking its binding to the IL-23 receptor. This results in a reduction of IL-23 activity, which leads to a decrease in inflammatory and immune responses [65].

In a clinical trial comparing the efficacy of risankizumab and ustekinumab, patients treated with risankizumab achieved clinical remission and endoscopic remission more often than patients using ustekinumab (58.6% vs. 39.5% and 31.8% vs. 16.2%, respectively). Frequency of adverse effects did not vary in both groups [66].

Data from clinical trials and early real-world evidence indicates that risankizumab might be a breakthrough therapeutic option for patients with inadequate response to anti-TNF drugs in moderate to severe CD and act as second line treatment better than older immunosuppressive therapies [67].

3.6.7. Surgical management

Despite advances in the treatment of Crohn's disease, approximately 80% of patients require surgery during the course of the disease. Due to the high recurrence rate within a year after surgery, surgical treatment is mainly aimed at treating complications related to stricturing or penetrating disease [68]. Indications for surgery depend on disease patterns and location, the most important is failure of medical management, but also fistulas leading to secondary symptoms, abscesses, bowel perforations, obstructive symptoms, toxic megacolon, refractory GI bleeding and others [69].

4. Conclusions

Crohn's disease affects an increasing number of people worldwide, dispelling the notion that it is mainly limited to high-income countries, and becoming a global public health problem. Its diagnosis and management require interdisciplinary cooperation between gastroenterologists, surgeons, pathologists, endoscopists, and radiologists. An increasingly better understanding of its pathogenesis enables research into new therapeutic possibilities. Due to the multidirectional nature of the inflammatory process and the neutralizing mechanisms of monoclonal antibodies, targeted therapy is often ineffective. There is a clear need for further research and improving therapies for inducing and maintaining remission, as well as for maintaining remission after surgical treatment, which, despite advances in pharmacotherapy, remains necessary for most patients with Crohn's disease.

Disclosure:

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