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CROHN'S DISEASE: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, MANAGEMENT – A LITERATURE REVIEW

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ABSTRACT

Introduction and purpose: Crohn's Disease (CD) is a condition characterized by chronic granulomatous inflammation that penetrates all layers of the intestinal wall and can affect any part of the gastrointestinal tract – from the oral cavity to the anus. This condition may be accompanied by extraintestinal manifestations. CD carries numerous complications that negatively impact patients' well-being. The course of the disease is chronic with alternating periods of exacerbation and remission; nevertheless, symptoms are often persistent. This review summarizes the current knowledge, focusing on pathophysiology, epidemiology, diagnosis and treatment. By integrating current knowledge and new findings, it aims to enhance and optimize patient care.

Description of the State of Knowledge: Crohn's disease is a condition with an incompletely understood etiopathogenesis, in which disturbances in the microbiota – modulated by environmental factors (including diet) – are considered a likely cause, with genetic mutations contributing to susceptibility. Clinical diagnosis of the disease can be challenging, and faecal calprotectin may be a useful tool not only for diagnosis but also for monitoring disease activity. The introduction of biological therapies, particularly anti-TNF antibodies, has demonstrated satisfactory therapeutic efficacy.

Conclusions: The „treat-to-target” strategy in therapy provides optimal conditions as long as continuous monitoring and assessment of treatment outcomes are maintained. The lack of standardized treatment methods allows for a wide range of therapeutic approaches; nevertheless, complications leading to surgical interventions remain a major clinical challenge.

Materials and methods: A review of recent clinical studies and scientific articles was conducted, focusing primarily on pathophysiology, epidemiology, clinical presentation, diagnosis and treatment, supplemented with the latest findings.

KEYWORDS

Crohn's Disease, Inflammatory Bowel Disease, Infliximab, Adalimumab, Calprotectin

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Introduction

Crohn's disease (CD), alongside ulcerative colitis, is one of the main components of inflammatory bowel disease (IBD) [2]. It was first described by Crohn, Ginzburg and Oppenheimer and subsequently presented at the American Medical Association meeting in 1932 [16]. CD is characterized by granulomatous inflammation, which begins in the mucosal layer and then extends through all layers of the intestinal wall [28]. Lesions can occur in any part of the gastrointestinal tract – from the mouth to the anus – and are separated by healthy tissue. The pathogenesis of the disease may result from a combination of various factors, including environmental influences, immune system dysfunction, genetic alterations and fluctuations in the gut microbiota [16]. It has been proven that living in an urban environment, smoking, antibiotic use, oral contraceptive use, regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) [37] are associated with an increased risk of developing Crohn's disease, whereas sharing a bedroom, having more than two siblings, contact with domestic and farm animals – particularly dogs [25], a high-fiber diet and maintaining physical activity are associated with a lower risk of the disease [37]. An increase in the incidence of CD has been observed in both adults and children [1,4,28], with most cases diagnosed in young individuals between 18 and 35 years of age [28]. The diagnosis of CD is a challenging clinical task due to its nonspecific nature. The diagnosis is based on symptoms, endoscopic and radiologic findings, while histopathological examination can confirm the diagnosis [27]. Treatment is founded on suppressing the inflammatory process affecting the involved tissues and managing the resulting complications with the aim of achieving and maintaining remission – using immunosuppressants, biologic therapies and surgical treatment – while simultaneously minimizing the adverse effects of treatment on the patient's health and functioning [1,2].

Objective of the work

The aim of this study is to provide an overview of Crohn's disease, focusing primarily on its pathophysiology, etiology, and clinical presentation, as well as on diagnosis and a critical analysis of the effectiveness of treatment and maintenance of the remission.

Materials and Methods

A review of clinical studies and scientific articles published between 2011 and 2025 was conducted. The source of these materials was the PubMed database. The reports were compared, focusing primarily on pathophysiology, epidemiology, clinical presentation, diagnosis and treatment.

Pathophysiology

The exact cause of Crohn disease remains unclear; however, the intestinal microbiota is believed to play a significant role in its pathogenesis [2,11]. It has been shown that, compared to healthy individuals, patients with CD exhibit reduced microbiota diversity, mainly involving a decrease in Bacteroides and Firmicutes, while an increase in Proteobacteria and Actinobacteria has been observed [28]. A three-stage theory has been proposed, in which the initial trigger is a gastrointestinal infection leading to the formation of ulcers. The second stage involves an abnormal inflammatory response of the body to bacteria that penetrate the damaged tissue along with faecal material. Finally, the third stage is characterized by granulomatous inflammation and an adaptive immune response resulting from the migration of immune cells and uncontrolled production of pro-inflammatory cytokines, leading to local inflammation and systemic symptoms [17]. Genetic factors also play a crucial role in the pathogenesis of CD. A mutation in the NOD2 gene, which regulates macrophage responses to bacterial lipopolysaccharides, increases susceptibility to CD [1,2,17], and the presence of two mutated NOD2 alleles is associated with 20-40-fold higher risk of developing the disease [1,36]. Other important genetic factors include IRGM and ATG16L1, which are involved in the activation of T lymphocytes within the adaptive immune system [17]. This sequence of events leads to the development of granulomatous inflammatory lesions in a non-contiguous pattern that may affect any section of the gastrointestinal tract and fibrosis within the intestinal wall, which in turn may result in the formation of fistulas or strictures [9,18,35].

Epidemiology and Clinical Presentation

The diagnosis of CD is most commonly made within two age ranges: a larger peak between 18-35 years and a smaller one between 50-60 years [28]. The incidence rates of CD in adults are approximately 13.9 per 100,000 per year in the United States and 15.4 per 100,000 per year in Europe [28]. About 25% of all CD cases are diagnosed in children [5,11], and the incidence in this group is rising rapidly compared to adults [28].

The most common symptoms of CD are nonspecific, including abdominal pain, diarrhea, the presence of blood or mucus in stool, fever, weight loss and fatigue [1]. In children and adolescents growth impairment related to malabsorption of nutrients may occur, affecting 65-85% of diagnosed children [5]. It should be noted that growth retardation or delayed puberty in this age group may sometimes be the only manifestation of CD [28]. Extraintestinal symptoms may occur in up to 50% of patients, most commonly involving the joints, eyes, and skin [1,28]. Skin manifestations (including pyoderma gangrenosum and erythema nodosum) appear in 22-44% of patients at some stage of the disease [2,7]. Local symptoms depend on the severity, location and extent of the lesions [1]. Depending on the location of the affected area, specific symptoms tend to predominate (Table 1) [3].

Table 1. Predominant symptoms depending on the location of the lesions [3].

Location	Symptoms
Gastroduodenal region	weight loss, anorexia, vomiting, nausea
Small bowel only	cramping, diarrhoea, weight loss, abdominal pain
Colon only	rectal bleeding, diarrhoea, perirectal abscess, fistula
Ileum and colon	diarrhoea, abdominal pain, weight loss, cramping

Long-standing CD may be complicated by abscesses, fistulas or strictures resulting from fibrosis of the intestinal wall, and these changes may occur in the perianal region in about one-fifth of patients [28].

Diagnosis

The diagnosis of Crohn's disease can be a challenging task due to its nonspecific symptoms [1,2,27]. The presence of blood in the stool, diarrhea, abnormal cramps and fever are symptoms that warrant ordering a faecal calprotectin (FC) test [3]. A result below 40 µg/g allows CD to be ruled out with high probability [28]. FC is the most commonly used biomarker in CD [20]. An FC value equal to or greater than 1000 µg/g indicates active disease, whereas a value below 250 µg/g strongly correlates with endoscopic remission. Another useful marker is faecal lactoferrin (FL), which can also help determine whether CD is in an active or inactive phase [20]. In addition, laboratory findings may reveal abnormalities such as anaemia, leucocytosis, thrombocytosis, elevated serum CRP (although not in all patients, even with active intestinal inflammation), hypoalbuminemia and decreased levels of: iron, vitamin D, B6, B9 and B12 [27,28]. Studies show that no serological biomarker is sufficiently sensitive or specific to be used as a diagnostic or monitoring tool in CD [19,27]. The gold standard for diagnosis remains endoscopy with direct assessment of lesions and biopsy for histopathological examination, where the classic finding is a non-caseating granuloma, present in only about 20% of biopsy samples and it is not specific to this condition [27,28]. Imaging studies such as computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are also helpful, aiding both in diagnosis and evaluating complications such as abscesses or fistulas [1,2,27,28]. Research indicates that the use of intestinal ultrasound (IUS) – particularly for assessing the terminal ileum – shows sensitivity comparable to that of MRE for the same segment [27]. Considering its low invasiveness and cost-effectiveness, regular disease monitoring via ultrasound could be a more accessible and practical option [29].

Management

The current „treat-to-target” (T2T) approach in CD therapy emphasizes initiating treatment at the earliest possible stage of the disease to maintain optimal long-term outcomes [19,22,29]. The introduction of biologic therapies has led to the development of new therapeutic pathways and the establishment of more rigorous treatment strategies for CD patients. This approach is supported by the STRIDE II protocol, which defines specific treatment goals [Table 2] and assists in therapeutic decision-making within the T2T strategy [28,29].

Table 2. Therapeutic goals according to STRIDE II [28,29].

Short-term	Clinical response: <ul style="list-style-type: none"> • ≤50% in patient reported-outcomes of abdominal pain and stool frequency
Intermediate-term	clinical remission: <ul style="list-style-type: none"> • abdominal pain score ≤1 and a stool frequency score ≤3, or Harvey Bradshaw Index <5 • normalisation of biomarkers (CRP and faecal calprotectin)
Long-term	<ul style="list-style-type: none"> • endoscopic healing (SES-CD <3) • normalised quality of life • absence of disability • restoration of growth for children

Regular assessment of disease activity within predefined treatment goals is crucial, as it determines whether therapy should be continued or modified [29]. Therefore, patient education and collaboration are essential, since the introduction of biologic agents offers a broad and complex range of therapeutic pathways, primarily depending on the location, severity and activity of the disease [27,28]. One of the most commonly prescribed drugs for CD patients is mesalamine, although studies indicate that due to its low efficacy in inducing and maintaining remission, it should no longer be used [27,28]. Antibiotic therapy is indicated exclusively for treating complications of the disease – intra-abdominal abscesses and perianal lesions (abscesses and fistulas), most commonly using metronidazole with or without ciprofloxacin [1,28]. It has been observed that adding ciprofloxacin to therapy enhances the efficacy of infliximab and adalimumab [1]. Systemic corticosteroids (prednisone, hydrocortisone, methylprednisolone) are used in moderate to severe forms of the disease, whereas in milder forms, often limited to the ileal or ileocecal region, oral budesonide is preferred due to its low bioavailability [28]. One of the key therapeutic goals is achieving steroid-independent remission, which remains a significant clinical challenge due to the need to avoid repeated steroid cycles, their adverse effects and the development of steroid dependency [1,28]. The addition of immunomodulators – thiopurines and methotrexate – aims to maintain remission in steroid-dependant CD and

to reduce the risk of anti-TNF antibody formation [27,28]. This combination should be used with particular caution in elderly patients, as an increased risk of malignancy has been observed in this population [1,28].

Biologic therapy plays a crucial role in the treatment of CD, with ant-TNF agents – infliximab and adalimumab - demonstrating the highest efficacy in both inducing and maintaining remission [28], as well as in reducing the risk of postoperative disease recurrence [23,24,26,34]. Studies have identified specific effects of both, infliximab showing particular efficacy in the treatment of perianal CD, while adalimumab has been proven effective in fistula healing process [28]. Other biologic agents used in CD treatment include vedolizumab (an anti- $\alpha 4\beta 7$ integrin monoclonal antibody) and ustekinumab (an anti-IL-12 and IL-23 p40 antibody), both of which are approved for treatment of moderate to severe CD. Due to their low risk of immunogenicity, they do not require combination therapy with immunomodulators [28,31]. Vedolizumab is gut-selective, which contributes to its favorable tolerability and long-term safety profile [27,30]. In the case of ustekinumab, its use has been confirmed to be effective in patients with secondary loss of response to infliximab [32].

Some patients will require surgical intervention during the course of CD. Indications for surgery include both emergent and non-emergent situations. In the abdominal region, emergent indications include symptomatic acute bowel obstruction and intestinal perforation, whereas non-emergent indications involve disease unresponsive to medical therapy and complications not amenable to conservative treatment. When the disease affects the perianal area, pelvic abscess is considered an emergent indication, while fistulas and abscesses may be treated electively [28]. A major clinical challenge faced by patients is that, after 20 years of disease activity, over 50% of individuals with CD require surgical intervention [1,27,28]. Patients with childhood-onset disease have a 43-53% risk of undergoing surgical resection before the age of 30 [6,8]. Surgical procedures are not curative and most patients experience clinical recurrence, manifested by symptoms or endoscopic relapse, which occurs in 83-100% of cases within three years after surgery [10].

Appropriate nutritional therapy also affects the course of the disease and can be used either as a primary treatment strategy or for the management of malnutrition as a complication of the disease [13-15]. Exclusive enteral nutrition (EEN), particularly in children, can be used as an alternative to corticosteroids [15,28]. However, studies have shown that the combination of partial enteral nutrition (PEN) and the Crohn's Disease Exclusion Diet (CDED) – a phased introduction of natural foods aimed at limiting those that negatively affect the gut microbiota – is more effective. Among the nutritional interventions studied, the PEN + CDED combination proved to be the most effective approach for inducing and maintaining remission [15]. Studies suggest that eliminating harmful dietary factors identified through IgG4 ELISA testing provides clinical benefits in patients with the most active form of CD, which may be related to a reduction in intestinal wall inflammation [12].

It has also been shown that patients with higher vitamin D level undergoing infliximab therapy had a greater likelihood of achieving remission [33].

Conclusions

The „treat-to-target’ approach utilizing biological therapy yields satisfactory treatment outcomes in patient with Crohn's disease. These patients require a multidisciplinary approach due to the potential presence of comorbidities, disease-related complications or treatment-associated adverse effects. The latter, often necessitating surgical intervention, remain a significant challenge for patients, as the disease profoundly affects their quality of life and demands considerable self discipline. An appropriate diet may serve as an optimal complement to the therapy. Before initiating biological treatment, it is advisable to correct vitamin D levels to achieve more favorable therapeutic outcomes.

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