

Crohn's Disease in Adults for the Primary Care Physician

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ABSTRACT

Crohn's disease is an inflammatory bowel disease of unclear etiology, associated with an excessive immune response with stages of remission and activation. It can affect the entire gastrointestinal tract from the mouth to the anus; the most frequent symptoms are abdominal pain and diarrhea. The impact that lifestyle modification and good treatment have on the patient's life is so crucial that primary care physicians must learn to recognize it and not confuse it with similar gastrointestinal pathologies.

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INTRODUCTION

A bibliographic review of Crohn's disease (CD) was carried out to recognize the essential aspects of CD due to its high prevalence in Western society in the 21st century, affecting 1 in 500 individuals. It is an inflammatory bowel disease (IBD) with an etiology not fully understood, with serious health, economic and social implications, due to its high frequency in the population. Diarrhea, weight loss, and abdominal pain are usually observed, although it is not limited to gastrointestinal symptoms. Diagnosis is based on typical endoscopic features such as ulcerations, irregular lesions, and cobblestone appearance. The treatment aims to induce remission and must be adapted to each patient depending on its severity and location. It is generally treated with corticosteroids, steroid-sparing agents, and immunomodulators up to surgical treatment, although it is not generally curative. Its most common complications include malabsorption, vitamin and mineral deficiency, intestinal stenosis and obstruction, abscesses and intra-abdominal fistulae, and an increased risk of gastrointestinal cancer.

EPIDEMIOLOGY

The prevalence of individuals affected by Crohn's disease is approximately 1 case per-500 inhabitants in the United States and has an incidence of 6 new cases per-100,000 inhabitants per year; there is a bimodal distribution where the first affected age peak is 15-35 years and the second age peak of 55-70 years. [1, 2, 3]

Although there is a difference in incidence in age groups, gender does not seem to be a significant factor in the

development of the disease. Even so, a higher incidence is observed in patients of northern European descent, as well as in patients of Ashkenazi Jewish descent. [4]

ETIOLOGY

Although the etiology of Crohn's disease is not completely clear, it has been possible to relate immune deregulation and dysbiosis to the promotion of chronic inflammation, coupled with inherited family risk factors with genetic predisposition, NOD2 gene mutations, and an association directly with HLA-B27. [3, 4]

PATHOPHYSIOLOGY

Research indicates that the chronic inflammation present in Crohn's disease is due to immune dysregulation in IL-23-Th17 signaling, with failure of IL-23 signaling in Th17 cell function resulting in unrestricted function, which promotes inflammation, which chronically causes local tissue damage characterized by edema, erosions, ulceration, necrosis, and subsequent fibrotic scarring, stenosis, intestinal strangulation and finally obstruction. The failure in IL-23 signaling points to be caused by mutations in Nucleotide Oligomerization Binding Domain 2 (NOD 2). [4]

For the formation of fistulas and abscesses, intestinal aphthous ulcers must form, which will progress to transmural fissures and inflammation of the intestinal walls, causing adherence of other organs, which causes tissue penetration, existing in two types: 1) Tissue microperforation and formation of abscesses, or 2) tissue macroperforation and fistula formation. [4]

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CLINICAL CHARACTERISTICS

Crohn's disease can affect any part of the gastrointestinal tract, from the mouth to the anus; However, unlike ulcerative colitis, rectal involvement is rare; the most frequent site of involvement is from the terminal ileum to the colon. The clinical manifestations most commonly found in Crohn's disease are constitutional symptoms that include low-grade fever, unexplained weight loss, and fatigue; gastrointestinal symptoms include chronic diarrhea of variable characteristics; abdominal mass and pain generally in the lower right quadrant; lower GI bleeds are rare. However, they can occur. Complications are often part of the initial clinical picture because the formation of fistulas and perianal abscesses are usually the first signs of Crohn's disease. Malabsorption may be suspected when weight loss, anemia, or growth retardation occurs. [5, 6]

The clinical manifestations of Crohn's disease are not limited to constitutional and gastrointestinal symptoms. Extraintestinal manifestations are present in up to 30% of patients diagnosed with Crohn's disease. Arthritis enteropathy can be observed, a seronegative spondyloarthritis that develops in conjunction with IBD and naturally affects the joints of the lower limbs and the spine, and fingernails can be seen in some patients.

As is common in immunological diseases, there is ocular involvement, ranging from uveitis and iritis to episcleritis; in the oral mucosa, the formation of oral thrush and pyostomatitis vegetans can begin, and there is an increase in cholelithiasis and urolithiasis, the latter generally caused by due to calcium oxalate stones. Erythema nodosum can manifest on the skin, as well as acrodermatitis enteropathica. On some occasions, a neutrophilic dermatosis (pyoderma gangrenosum), generally associated with rheumatoid arthritis, trauma, and IBD, is observed as the formation of painful and highly progressive red spots to pustules purulent or deep ulceration with central necrosis, commonly located on the extensor side of the lower extremities. [7, 8, 9]

DIAGNOSIS

A complete history and physical examination should be performed, including a digital rectal examination, a search for extraintestinal signs and symptoms mentioned above, and the presence of perianal fistulas should be evaluated. [5, 10, 11] The endoscopic evaluation of the small intestine is of the utmost importance in the initial diagnostic study of Crohn's disease; almost a third of patients have Crohn's disease limited to the small intestine, and its evaluation can be limited with ileocolonoscopy. [10, 12]

Ileocolonoscopy is indicated for all patients with suspected Crohn's disease to evaluate its distribution, severity, and differentiation from ulcerative colitis. Jumping lesions (discontinuous lesions), serpiginous or aphthous ulcers, erythema, fissures, fistulas, and strictures (ileoscopy can be used therapeutically for dilation of strictures), as well as the cobblestone sign (edematous lesions with frank inflammation

interspersed with deep, cobblestone-like ulcerations). [10, 11, 13]

Cross-sectional images allow the evaluation of the entire gastrointestinal tract (including the small intestine) and serve to identify and evaluate complications and assess differential diagnoses. Its indications include:

- Suspected Ulcerative Colitis
- Location of lesions in the small intestine
- Evaluation of therapeutic response
- Evaluation of acute outbreaks and/or complications

The preferred cross-sectional imaging study for Crohn's disease is cross-sectional enterography, in which edematous thickening of the intestinal wall, mucosal growth, mesenteric fat stranding, stenosis, fistulas, abscesses, cholelithiasis, etc. can be observed. Urolithiasis, and assessment of therapeutic response. Unlike ileocolonoscopy, transverse enterography can assess the small intestine, identifying luminal complications such as internal fistulas and narrow segments of the intestine, called the thread sign. [5, 10, 12, 14, 15, 16, 17]

Other modalities, such as abdominal ultrasound, may be considered for initial evaluation of suspected Crohn's disease and follow-up. Intestinal wall thickening >4mm is indicative of active disease. Plain abdominal radiography can be used for a rapid assessment of complications. [11, 12]

Laboratory studies have different objectives. It can be used to rule out differential diagnoses. Stool analysis can be helpful to rule out gastrointestinal infections; for example, in *C. Difficile* infection, serology can include increased ASCA (Antibodies anti-Saccharomyces cerevisiae, where it is generally higher in Crohn's disease than in ulcerative colitis, and conversely in pANCA (anti-neutrophil cytoplasmic antibody myeloperoxidase), although the use of serology is not routinely recommended due to a low sensitivity [5, 10, 18]

Fecal calprotectin and/or fecal lactoferrin are proteins associated with neutrophil activation and can be used as a marker of intestinal inflammation, as a mechanism to monitor disease and therapeutic response; it is also useful for differentiating IBD from syndrome irritable colon. Inflammatory markers such as C-Reactive Protein, erythrocyte sedimentation rate, or platelet count may be normal in patients with mild Crohn's disease. In contrast, increased platelets serve as an indicator of active disease. [5, 10, 16, 19, 20]

A complete metabolic panel is used to identify malnutrition as a complication of malabsorption, a decrease in total protein or an increase in creatinine can be observed in kidney damage and/or dehydration, blood counts, iron and B12 studies, serve to the evaluation of anemia and micronutrient deficiency. Anemia can result secondary to chronic disease and not solely due to active bleeding. [19]

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PATHOLOGY

Taking a biopsy during the endoscopic evaluation is essential, in which a transmural inflammation can be observed where all the mucosa of the intestinal wall is involved, where non-caseating granulomas, giant cells, and lymphoid aggregates of the lamina propria can be observed; it is not rare to find a hyperplastic growth of adipose tissue resulting in the accumulation of mesenteric fat around the circumference of the intestine, as well as hypertrophic lymph nodes. [twenty-one]

TREATMENT

The treatment of Crohn's disease is complex and includes medication with drugs with multiple adverse effects; treatment must be adapted to the severity, phase, and risk of progression of Crohn's disease; in some circumstances, surgery may be necessary to control complications and works as an option for an isolated manifestation, lifestyle modifications are essential to minimize potential complications. [11, 15]

The progression of the disease should be monitored. Fast-acting corticosteroids in acute outbreaks are useful for acute control, although maintenance treatment based on biological products and immunomodulators must be maintained. [10, 15, 22]

Thus, drug therapy is divided into the induction phase (control of acute outbreak) and the maintenance phase (maintain remission). The evaluation of the activity and progression of Crohn's disease cannot be done based on symptoms; objective markers such as biomarkers, imaging, or endoscopy must be used to evaluate the activity or remission of the disease. [22, 23]

Corticosteroids are mainly used to induce the remission phase; drugs such as ileal controlled release budesonide (to control inflammation of the ileum or ascending colon), oral prednisolone, or IV methylprednisolone are used. Corticosteroids should be discontinued once the acute flare is controlled; failure to discontinue them results in poor mucosal healing and increases the risk of complications. Up to 20% of patients are refractory to steroids. [10, 15]

Biologics such as anti-TNF- α antibodies (adalimumab, infliximab, certolizumab) are increasingly being used as the principal remission-inducing agent, and as maintenance drug treatment in patients with Crohn's disease refractory to immunomodulators, as another product biological used in Crohn's disease we have antibodies against leukocyte trafficking (vedolizumab) and anti-p40 antibody (ustekinumab), used to induce and maintain moderate or severe Crohn's disease. [10, 15]

The most used immunomodulators are methotrexate and thiopurine analogs (azathioprine, 6-mercaptopurine), and they are mainly used to maintain remission of the disease. However, it can be used as a steroid-sparing regimen in the induction phase. [10, 15]

5-aminosalicylic acid derivatives (sulfasalazine or mesalamine) can be considered for the remission of mild severity of colonic or ileocolonic Crohn's disease and are ineffective in isolated small bowel disease. [10]

As shown in this treatment section, this is based on the severity of the disease. Table 1 shows the treatment regimens based on the symptom severity of Crohn's disease: [10, 15, 23, 24, 25]

Table 1

Pharmacological management of Crohn's disease			
Gravity	Characteristic clinic	Common regime	
		induction phase	maintenance phase
Mild-Moderate	outpatient normal dietary intake Weight loss < 10% No major complications	Limited to the ileum and right colon: Ileal controlled release budesonide colonic disease Oral systemic corticosteroids (prednisone) Consider Sulfasalazine	Supportive therapy is necessary for asymptomatic patients and/or at low risk of progression. High risk of CD progression or ongoing inflammation: consider anti-TNF- α antibodies.
Moderate-Severe	Fever significant weight loss Abdominal pain intermittent nausea	Combination therapy: Oral systemic corticosteroids (prednisone) PLUS an immunomodulator (azathioprine) OR anti-TNF- α antibodies (infliximab) Steroid-sparing regimen: Anti-TNF- α antibodies (infliximab) PLUS an immunomodulator (thiopurine analogs, methotrexate) Monotherapy A biologic (anti-TNF- α antibodies, ustekinumab, or vedolizumab) is preferred. Consider methotrexate (IV or subcutaneous).	Taper and discontinue corticosteroids. Continue nonsteroidal agents that resulted in remission.

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Severe-fulminating	severe fever Signs of intestinal obstruction persistent vomiting Peritoneal signs abscess formation	Systemic IV corticosteroids (methylprednisone IV) PLUS infliximab.	
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COMPLEMENTARY THERAPY

The pain of the symptomatic patient should be managed by avoiding the use of NSAIDs, cessation of smoking, and joint management to control triggering emotional factors such as stress, depression, and anxiety. For cases with diarrheal symptoms, loperamide or cholestyramine can be administered (it should not be used in patients with intestinal obstruction, abdominal pain, or signs of systemic infection). Enteral nutrition is preferred over parenteral nutrition. Micronutrient deficiency should be identified and treated; iron deficiency, vitamin D, and B12 are common in patients with Crohn's disease. If a malabsorption syndrome is identified, the necessary calories, proteins, and micronutrients should be supplied. [26, 27, 28, 29]

Half of the patients with Crohn's disease require major abdominal surgery within the first ten years after diagnosis; it is indicated in case of complications such as intestinal obstruction, intra-abdominal abscess, or perianal abscess when medical therapy is unsuccessful or in Crohn's disease. Isolated Crohn's, surgical drainage of the abscess, laparoscopic resection of the diseased intestinal segment, and stricturoplasty must be performed. However, surgery can lead to remission. It is not curative and can cause short bowel syndrome. [11, 16, 30]

LONG-TERM MANAGEMENT

Chronic inflammation increases the risk of suffering intestinal cancer, so surveillance colonoscopy with biopsy should be scheduled in patients with onset of the disease eight years ago, colon involvement >30%, and biopsy should be performed at the time of diagnosis in patients with primary sclerosing cholangitis. [5, 10, 15]

Dual X-ray absorptiometry should be performed in patients with >3 months of lifetime cumulative exposure to corticosteroids looking for evidence of osteoporosis. [10, 15] The nutritional and anemic status of the patient should be assessed with complete blood count, iron-binding studies, folate, vitamin B12, vitamin D, and albumin. [5, 10, 15]

COMPLICATIONS

Fistula Crohn's disease occurs in up to a third of patients; usually, the perianal region is involved, internal fistulas can affect the bladder, vagina, and/or another portion of the intestine, and recurrences are frequent. Clinical characteristics depend on the location of the fistula. [31]

In the case of pancolitis, it is not uncommon for it to progress to colorectal cancer; in cases of intestinal perforation, it can progress to peritonitis. Intestinal stenosis progresses to

intestinal obstruction that may require surgery. In patients undergoing surgery (with or without stenosis), it is not uncommon to find associated problems such as short bowel syndrome. Impaired bile acid reabsorption causes steatorrhea and fat-soluble vitamin deficiencies. [31]

Signs of malabsorption syndrome can be seen as weight loss, developmental and growth retardation in children, and anemia of different indoles, including but not limited to iron deficiency anemia, anemia of chronic disease, megaloblastic anemia, and can coexist with osteoporosis. [31]

CLINICAL PROGNOSIS

Crohn's disease, as can be seen in the treatment section, is a pathology for which there is currently no curative treatment. Patients with any of the following characteristics lead a high risk of severe disease progression and may require further treatment: specialized and aggressive: [10, 15, 22]

- Young age at diagnosis (<30 years)
- The early need for steroid use
- small intestine compromise
- Perianal or rectal disease
- Stenosis, fistula, and/or abscess
- visceral adiposity

DISCUSSION

Crohn's disease is an inflammatory disease of the gastrointestinal tract that can range from the mouth to the anus in its location, being most frequent between the terminal ileum and colon, rarely involving the rectum [1,5,6]. Although its etiology is unknown, it has been found to be associated with an autoimmune cause; among the sources consulted for this review, mutations in the NOD2 gene and HLA-B27 stand out. [1, 3, 4] The relevance of this disease transcends its high prevalence in the Western society of our century, one in 500 people in the United States present it, especially young adults (15-35 years) and elderly adults (55-70) with certain increases in incidence depending on etiology, higher in Ashkenazi Jews and Northern European areas [1,2,3].

The NOD2 gene mutation has been demonstrated to participate in the pathophysiology of this disease, related to the malfunction of interleukin 23, which then fails in its signaling to TH17 Lymphocytes, which physiologically restrict the magnitude of the immune response, when missing, produces the edema, erosion and ulceration that chronically produces fibrosis and that characteristic cobblestone appearance [4]. Due then to this uncontrolled immune activation the systemic symptoms of low-grade fever,

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unexplained weight loss and fatigue occur, among the gastrointestinal symptoms we can find abdominal mass and pain generally in the lower right quadrant, bleeding is uncommon, associated more with the principal differential diagnosis, Ulcerative Colitis. The diagnosis may initially be discovered as perianal abscesses and fistulas or clinically secondary to malabsorption [5,6]. Finally, being part of the group of autoimmune diseases its manifestations may include arthritis, uveitis, iritis, episcleritis, oral thrush and pyostomatitis vegetans, cholelithiasis, urolithiasis, showed to be caused due to calcium oxalate stones. Erythema nodosum acrodermatitis enteropathica. Although uncommon neutrophilic dermatosis has been registered in some patients with Crohn disease [7, 8, 9].

CONCLUSIONS

The diagnostic procedures recommended in this review are complete history and physical examination, including a digital rectal examination [5, 10, 11]. The endoscopic evaluation of the small intestine (almost a third of patients have the disease limited to this location) [10, 12] Ileocolonoscopy to evaluate its distribution, severity, and differentiation from ulcerative colitis, to diagnose jumping lesions (discontinuous lesions), serpiginous or aphthous ulcers, erythema, fissures, fistulas, and strictures, as well as the cobblestone sign can be seen in this exam [10, 11, 13]. Ultrasound, may be considered for initial evaluation and follow-up. Plain abdominal radiography can be used to look for acute complications [11, 12].

Stool analysis can be helpful to rule out gastrointestinal infections; for example, in *C. Difficile* infection, serology can include increased ASCA (Antibodies anti-Saccharomyces cerevisiae), which is generally higher in Crohn's disease than in ulcerative colitis, and conversely pANCA (anti-neutrophil cytoplasmic antibody myeloperoxidase). Although the use of serology is not routinely recommended due to a low sensitivity [5, 10, 18] Fecal calprotectin and/or fecal lactoferrin are markers of intestinal inflammation. Inflammatory indicators such as C - reactive protein, erythrocyte sedimentation rate, or platelet count may be normal in patients with mild Crohn's disease. In contrast, increased platelets serve as an indicator of active disease [5, 10, 16, 19, 20]

Treatment should be individualized for each patient, the bases we recommend from the sources consulted are as follows, fast-acting corticosteroids in acute outbreaks, like budesonide oral prednisolone, or IV methylprednisolone, and maintenance based on biological products such as anti-TNF- α antibodies (adalimumab, infliximab, certolizumab), antibodies against leukocyte trafficking (vedolizumab) and anti-p40 antibody (ustekinumab), and immunomodulatory, the most used are methotrexate and thiopurine analogs (azathioprine, 6-mercaptopurine) [10, 15, 22]. 5-aminosalicylic acid derivatives (sulfasalazine or mesalamine)

have been proven to be beneficial for the remission of mild severity of colonic or ileocolonic Crohn's disease and are ineffective in isolated small bowel disease [10]. For symptoms, NSAIDs, smoking cessation, stress, depression and anxiety management have been shown to be helpful. For diarrhea, loperamide or cholestyramine may be prescribed. And replenishment of flattening nutrients in malabsorption syndromes such as iron and vitamin D and B12 [5, 10, 15].

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