Intestinal Crohn's disease: management

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Degrees of recommendation and evidence strength:

A: Experimental or observational studies of better consistency.

B: Experimental or observational studies of lesser consistency.

C: Case reports (non-controlled studies).

D: Opinion without critical evaluation, based on consensus, and on physiological or animal models studies.

Concept and epidemiology

Crohn's disease is a chronic inflammatory process of unknown etiology affecting the gastrointestinal tract, uni- or multifocal, of variable severity, transmural[1], and it is not curable by clinical or surgical treatment (C)[2,3] (D). The small and large intestines are affected more often. Perianal manifestations can be seen in more than 50% of the patients[1] (C). Associated or isolated extraintestinal manifestations can occur, affecting the skin, joints, eyes, liver, and urinary tract more commonly[4] (B)[5] (D). The disease affects individuals of any age, but the diagnosis is more common in the second or third decades[6] (D).

Diagnosis

The diagnosis of Crohn's disease results of the analysis of clinical (anamnesis, and complete physical and proctologic exams), endoscopic, radiologic, laboratorial, and histological data[2] (D). Clinical manifestations are more commonly of an inflammatory, obstructive, and/or fistulizing nature, which carry greater or lower prognostic value[7] (D). Symptoms of chronic diarrhea, abdominal pain, weight loss, and rectal bleeding direct the anamnesis. Clinical signs include malnutrition, cutaneous-mucous parlor, pain, abdominal mass, and distension or fistulization into the abdominal wall. Proctologic exam can be positive for anal fissure(s), edematous anal **plicomas**, fistulae, and cellulitis or abscesses and can, initially, be isolated, as well as extraintestinal manifestations[1] (C)[2] (D).

Toxic and acute colon dilation (toxic megacolon) is an acute and severe, but uncommon presentation[8] (B). The presentation of diarrhea requires differential diagnosis with infectious colitis (viral or bacterial) and protozoal bowel disorders. Acute ileitis requires differential diagnosis with acute appendicitis. The differential diagnosis of Crohn's disease includes ulcerative rectocolitis[9] (B). In up 20% of the cases, once current available investigative resources are exhausted, a diagnosis is not possible, being classified as undetermined colitis[10] (D). The diagnosis of intestinal Crohn's disease also requires the differential diagnosis with other enterocolitis (ischemic, actinic, or antibiotic-induced) and with irritable bowel disease[6] (D).

The most common extraintestinal manifestations are directly related to the inflammatory bowel process, and they can affect the skin (erythema nodosum and gangrenous pyoderma), peripheral (arthritis) or axial (ankylosing spondylitis and sacroiliitis) joints, eyes (conjunctivitis and uveitis), and liver (primary sclerosing cholangitis). Cholecystolithiasis and nephrolithiasis can also result from malabsorption[1] (C).

Contrast-enhanced exams (intestinal transit, barium enema, and double contrast study) are necessary to confirm the location and extent, as well as diagnosis, of complications. Barium-enhanced exams should not be performed in acutely ill patients or those who require hospitalization. Ultra-sound of the abdomen and computerized tomography (CT) should be performed, preferentially, during crisis or exacerbations, in the presence of abdominal mass, or suspected abscess. Besides, those exams are useful in the evaluation of abdominal and pelvic complications. They can be useful in preoperative planning and also to guide punctures. Magnetic resonance imaging (MRI) can be used in patients who are allergic to iodinated contrast and in gravidas, and it seem to make a difference in the evaluation of anorectal disease in some studies. High-resolution MRI has good accuracy in detecting anal fistulae in Crohn's diseases, providing important information for preoperative planning of recurring fistulae[11] (B). X-Rays of the abdomen should be performed to evaluate patients with acute abdomen or suspicion of toxic megacolon[12,13] (D).

Colonoscopy is used to confirm the clinical suspicion of Crohn's disease and to obtain biopsies. Endoscopy is more sensitive than contrast-enhanced exams regarding extension of the disease. When a strong suspicion of coli-

tis exists and sigmoidoscopy or barium enema findings are negative, colonoscopy with multiple biopsies can determine the presence and severity of colon inflammation, as well as to allow the visualization of the mucosa of the terminal ileus. Colonoscopy with biopsy is also effective in the differential diagnosis between Crohn's colitis and ulcerative rectocolitis, as well as in the evaluation of other forms of colitis (actinic, ischemic, and microscopic)[14] (C)[15] (D). Even though endoscopic evaluation is not related with disease activity[15] (D), colonoscopy evaluation of intestinal anastomosis can be related with the possibility of recurrence after surgical treatment[10] (D). Histological studies of biopsies obtained by colonoscopy allows diagnostic proof, differential diagnosis between Crohn's colitis and ulcerative rectocolitis, as well as the diagnosis of dysplasia and cancer in cases of long-standing colitis[15] (D).

Measuring disease activity

Measuring the activity in Crohn's disease can be difficult due to different location patterns, as well as the presence of complications[6] (D). A standard indicator of disease activity does not exist. Somewhat objective parameters, such as suspension of corticotherapy or activity without surgical indication, can be used[6] (D). Differentiation between activity and remission can be done by the Crohn's Disease Activity Index (CDAI), detailed in Chart 1.

The disease is considered in remission when the CDAI is below 150; mild to moderate, when the CDAI is between 150 and 219; moderate to severe, when the CDAI is between 220 and 450; and severe or fulminating, when the CDAI is above 450.

Treatment

Treatment is not indicated for asymptomatic patients or those in remission and who never underwent surgical treatment[6] (**D**). Recommendations for clinical or surgical intervention result from location of the disease, severity, response to prior drug therapy, and diagnosis of complications. The initial objective of clinical treatment is to induce remission. Patients in remission should be considered for maintenance treatment. Symptomatic patients and those undergoing corticotherapy or with fever, vomiting, abdominal pain, or suspected bowel obstruction or malnutrition should be hospitalized[6] (**D**).

Surgical treatment of Crohn's disease by resection or enteroplasty is indicated for complications and when clinical intractability of refractory disease is indentified. For patients with perianal disease, drainage of abscesses is indicated, as well as fistulotomy or drainage seton in more symptomatic cases. Proctectomy is indicated for cases of severe suppuration associated with severe proctitis and anal incontinence[1] (**C**).

Enteritis and ileocecal involvement

Ileal or ileocecal disease should be treated by the administration of oral aminosalicylate (mesalazine, 3 to 4 g/day)[16-18] (**A**). Ileocecal disease can be treated with oral sulfasalazine, 1 to 4 g/day[19] (**A**). Alternatively, oral ciprofloxacin, 1 g/day, can be used for at least 6 weeks, and ideally from 3 months to 1 year[20] (**A**). For patients with ileocecal disease who do not respond to aminosalicylates, treatment with oral metronidazole, 10 to 20 mg/kg, can be offered for a maximum of 4 months[21] (**A**) to try to postpone the introduction of corticotherapy. Evidence indicates that the combination of ciprofloxacin and metronidazole can produce results superior than each drug alone[22] (**B**).

For patients with little or no response after the initial therapy with aminosalicylates (or alternatively, antibiotics), corticotherapy should be instituted with oral prednisone, 40 to 60 mg/day[19] (**A**). Oral budesonide, 9 mg/day, can be used instead of prednisone[23] (**A**).

Immunosuppressive therapy in Crohn's disease is indicated in patients dependent on corticosteroids or those refractory to corticotherapy. Oral azathioprine and 6-mercaptopurine are used in doses of 2 to 2.5 mg/kg/day and 1 to 1.5 mg/kg/day, respectively. Their effectiveness in inducing remission has been proven; however, they should be used for at least 4 months to classify the response[24] (**A**). There is no recommendation on the duration of treatment. The use of immunosuppressors requires some experience, and leukocyte count should be done at the end of the first

Chart 1.

Crohn's Disease Activity Index	
Number of liquid stools (daily for 7 days)	x 2
Abdominal pain (none = 0, mild = 1, moderate = 2, severe = 3)	x 5
Sense of well-being (well = 0, slightly below par = 1, poor = 2, very poor = 4, terrible = 4)	x 7
Number of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula or abscess, fever > 37.8° C)	x 20
Taking diphenoxylate or loperamide (no = 0, yes = 1)	x 30
Abdominal mass (no = 0, questionable = 1, present = 5)	x 10
Hematocrit (males: 47 – HT%, females: 42 – Ht%	x 6
Weight (1 – weight / standard weight x 100). Add or subtract according to the sign	x 1
Total	

week of treatment to detect hematologic toxicity of mercaptopurine metabolites. Complete blood count and liver function tests should be done every 45 days, in the beginning of treatment, and later every 3 months.

Biologic therapy with infliximab has been approved by the FDA (Food and Drug Administration) for induction and maintenance of remission in patients with Crohn's disease, with moderate to severe activity, who had inadequate response to conventional therapy. In three doses of 5 mg/kg, it is effective in inducing remission[25] (**A**), and also the dose of 5 mg/kg every 8 weeks, for maintenance[26] (**A**).

Colitis

Clinical treatment should be initiated with oral sulfasalazine, 1 to 4 g/day. Oral mesalazine, in the dose of 1 to 4 g/day, should be used in cases of sulfasalazine intolerance[27] (**B**). For individuals who do not respond to aminosalicylates, oral prednisone, 20 to 60 mg/day, should be added[19] (**A**). In association with immunosuppressors, infliximab, three doses of 5 mg/kg, is effective for inducing remission[25] (A) and, for maintenance, 5 mg/kg every 8 weeks[28] (**A**).

Maintenance therapy

Indication of maintenance therapy in Crohn's disease should be determined case by case. Maintenance therapy seems specially indicated in patients whose remission required corticotherapy, those who evolved with early symptomatic relapse after induction of remission, and also for those who underwent surgical treatment[29] (**B**). For individuals with chronically active, steroid-dependent, or steroid refractory Crohn's disease, azathioprine (oral, 2 to 2.5 mg/kg/day) or 6-mercaptopurine (oral, 1 to 1.5 mg/kg/day), without aminosalicylates, is beneficial after corticotherapy-induced remission[30] (**A**). Evidence indicates the efficacy of oral sulfasalazine or mesalazine, in doses higher than 3.0 g/day, in preventing relapses after ileocolic resection[31] .(**A**)

Perianal disease

Anorectal abscess is treated by surgical drainage. Patients with **plicomas**, anal fissures, or fistulae with little suppuration, should undergo clinical treatment[1] (**C**). Oral metronidazole, 20 mg/kg/day, divided in two doses, is indicated in the presence of fistulae, with a response rate higher than 90%. Duration of treatment with metronidazole should not be higher than 4 weeks[21] (**A**). Alternatively, oral ciprofloxacin, 1 g/day, can be used for at least 6 weeks, and ideally between 3 months and 1 year[21] (**A**). Oral prednisone, 20 to 60 mg/day, is indicated in case of little response to antibiotics, and it should be associated with them[19] (**A**). To decrease the dose of prednisone or to discontinue corticotherapy, azathioprine (oral, 2 to 2.5 mg/kg/day) or 6-mercaptopurine (oral, 1 to 1.5 mg/kg/day), results in healing of fistulae and symptomatic improvement, which is superior to placebo, and it can be used in association with antibiotic therapy. At least three months of treatment are required to evaluate response[33] (**A**).

In patients with little or no response to antibiotics, corticosteroids, and immunosuppressors, intravenous infliximab, 5 mg/kg, after two and six weeks (three doses) produces benefits when compared to placebo, with a mean duration of three months[32] (**A**). Maintenance is achieved with a dose of 5 mg/kg every eight weeks and, if failure is observed, 10 mg/kg is effective[28] (**A**).

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