

Crohn's disease. Review and current concepts

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RESUMEN

La incidencia y la prevalencia de la enfermedad de Crohn (EC) han aumentado en todo el mundo. La carga económica y el impacto en la calidad de vida de los pacientes nos obligan a realizar un diagnóstico precoz, para así inducir y mantener la remisión, previniendo las complicaciones a largo plazo. Se ha descrito un gradiente Norte-Sur de la prevalencia de la EC; sin embargo, existen pocos reportes acerca de la epidemiología de esta entidad en los países latinoamericanos, por lo tanto, la prevalencia real y el desarrollo de la enfermedad en nuestra población se desconocen. Durante los últimos años, expertos han hecho importantes avances en el diagnóstico y manejo de la EC; no obstante, actualmente, no contamos con un tratamiento curativo. El conocimiento reciente de las terapias inmunomoduladoras y biológicas ha establecido nuevas metas para la inducción y mantenimiento de la remisión en la enfermedad inflamatoria intestinal. En este artículo revisamos los aspectos epidemiológicos y clínicos más actuales, enfocándonos en la evaluación del paciente; asimismo, hacemos un breve repaso del tratamiento de la EC.

Palabras clave. Enfermedad inflamatoria intestinal. Enfermedad de Crohn. Terapias inmunomoduladoras. Terapia biológica.

ABSTRACT

The incidence and prevalence of Crohn's disease (CD) is increasing worldwide. The economic burden and impact on patients' quality of life, make an early diagnosis of Crohn's disease, a priority to induce and maintain remission and prevent long-term complications. It has been described a North to South gradient of prevalence, however, there are only a few reports about the epidemiology of this disease in Latin-American countries, therefore the real prevalence and behavior of the disease in our population is unknown. During the last years, experts have made important advances in the diagnosis and treatment of the disease. However, despite this advances, currently, there is no curative treatment for CD. Recent knowledge of immunomodulatory and biologic therapies in the treatment of inflammatory bowel diseases (IBD) has established new goals in the induction and maintenance of remission of these diseases. This article reviews current knowledge of epidemiological and clinical aspects, an approach in the evaluation of the patient and a brief review on treatment of Crohn's disease.

Key words. Inflammatory bowel disease. Crohn's disease. Immunomodulatory therapies. Biologic therapy.

INTRODUCTION

Crohn's Disease (CD) and ulcerative colitis (UC) are the two main presentations of inflammatory bowel diseases (IBD). Crohn's disease is characterized by the involvement of the gastrointestinal tract from mouth to anus, with a transmural pattern of inflammation of gastrointestinal wall layers. The incidence of CD in Latin America is low; however, a rising incidence has been reported in the past 50 years in western countries. The origin of the disease is not entirely clear however several

involved mechanisms have been postulated such as genetic predisposition and disruption of homeostasis regulation in the gastrointestinal tract. Clinical manifestations are numerous and the vast majority are secondary to the inflammatory process that damages intestinal mucosa and deeper layers, causing loss of surface absorption, wall thickening, obstruction or fistulation. Differential diagnosis includes intestinal tuberculosis and malignancies. In cases where there is a strong suspicion, special image techniques, and serum and fecal biomarkers must be performed. Currently, there is no definitive treatment for

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CD; however, the development of biological therapies has allowed the approach of new therapeutic targets, which ameliorate symptoms, delay progression of complications and improve quality of life. This review focuses on current knowledge on Crohn’s Disease.

MATERIAL AND METHODS

We used the terms “inflammatory bowel disease” and “Crohn’s disease” to search the EMBASE and MEDLINE, OVID and HINARI databases for publications that included meta-analyses, systematic reviews, clinical trials and review articles.

General aspects of Crohn’s disease (CD)

Definition

UC and CD are the two main types of inflammatory bowel diseases. UC affects only colon mucosal layer with continuous ascending pattern, while CD is characterized for affecting the entire gastrointestinal tract, from the mouth to the anus with a transmural affection, mainly with a patchy pattern (Table 1).^{1,2} Up to 10-15% of patients with IBD cannot be classified in none of these types, therefore pathologists described the term of “indeterminate colitis” (IC) for colectomy specimens in which no specific features of CD or UC were seen.³

Recent evidence suggests that an inflammatory process which involves pro-inflammatory cytokines such as TNF- α and a wide variety of interleukins, damages the

layers of the gastrointestinal tract in patches, leaving some undamaged segments of mucosa (Figure 1).

Epidemiology

A “North to South gradient” of incidence has been suggested previously in several publications. North America (7 to 10.3/100, 00 per year), United Kingdom (8.3 to 9.1/100,000 per year) and Northern Europe (5.8-6.3/100,000 per year) have the highest incidence of CD; similar behavior has been seen in prevalence: 207/100,000 per year in North America, 156/100,000 per year in the United Kingdom and 90/100,000 per year in Northern Europe.⁴⁻⁹

However, this gradient is not widely accepted since the lack of information of IBD in southern countries.

Regarding epidemiology in Latin America, there are only a few reports about the incidence and prevalence of this disease. Although the incidence of CD in South America has been reported to be lower compared to North America, in the last 50 years, occidental countries have reported a rising in both, incidence and prevalence, of IBD.¹⁰ The lowest incidence has been reported in Puerto Rico.¹¹ In Mexico a study carried out by Yamamoto-Furusho, showed an increased incidence of ulcerative colitis from 1987 to 2006, with a 2.6-fold increase from 1997 to 2006, compared to the previous decade, suggesting this increase being caused by the environmental factors and the unique genetic mosaic of the Mexican population.¹² However, there is no information regarding CD in Mexico.

Table 1. Differences between Crohn’s disease and ulcerative colitis.

	Crohn’ disease	Ulcerative colitis
Common site	Terminal ileum	Rectum
Distribution	Mouth to anus	Rectum
Spread	Discontinuous	Continuous
Gross feature	Focal aphthous ulcer with intervening normal mucosa, linear fissures, cobblestone appearance, thickened bowel wall, creeping fat.	Extensive ulceration pseudopolyps.
Microscopy	Non-caseating granulomas	Crypt abscesses
Inflammation	Transmural	Limited to mucosa and sub-mucosa
Complications	Strictures, string sign on barium studies, abscesses, sinus tract, obstruction, fistulas	Toxic megacolon
Extraintestinal manifestations	Uncommon	Arthritis, spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum
Cancer risk	1-3%	5-25%



Figure 1. Post-contrast coronal image of the abdomen showing distal ileal mural thickening, with prominence of the mesenteric vasculature (comb sign).

A recent retrospective observational study in United States compared the incidence of IBD in Caucasian and Hispanic population, where Hispanics represented 60% of the population of study. In this study, the authors observed that the diagnosis of UC is more frequent than CD in Hispanic population. However, the diagnosis of IBD is done at a more advanced age in Hispanic population, this may be caused by delay in seek of health attention or more frequent extra-intestinal manifestations. In Hispanic patients there is a lower number of intestinal resection due to IBD.¹³

Etiology and risk factors

Although the etiology is not completely understood, multiple mechanisms have been described. Genetic predisposition and disruption of the intestinal homeostasis are two of the most studied etiological factors.¹⁴

CD affects predominantly females, with an incidence peak around the second and third decades of life.^{10,15}

Previous studies have described that CD is more prevalent in Ashkenazi Jewish, and it has been associated with multiple genetic variants such as Nucleotide-binding Oligomerization Domain containing 2 (NOD2), which is the first susceptibility gene strongly associated. This gene is expressed in the intestinal epithelium,

especially in Paneth cells, which are responsible for defense against enteric pathogens. Three genetic variants within the gene CARD15 / NOD2 are present in up to 30% of Caucasian patients with CD (A702W, G908R and L1007fsinsC). For homozygotes and compound heterozygotes, the risk of developing CD is 10 to 42 times higher compared to individuals without the mutation. Moreover, the variants mentioned are associated with an increased frequency of ileal disease, stenosis and earlier onset.¹⁶

Smoking typically has been thought as a risk factor for CD, but a protector factor in UC. In some studies, cigarette smoking has been associated with exacerbations and it is believed to be a risk factor for having IBD, although it is controversial.¹⁷

Appendectomy demonstrates a divergent influence on IBD. In a meta-analysis published in 2008, they found that appendectomy increased the risk for the development of CD.¹⁸ However, the risk for CD decreased, while patients were operated before 10 years of age. Andersson, *et al.* found that appendectomy due to perforating appendicitis may increase the risk for subsequent intestinal resection, while appendectomy due to other reasons reduced the risk for CD.¹⁹ The relationship between appendectomy and CD is still not conclusive.

Pathophysiology

It is known that there are genetic factors (gene CARD 25/NOD2 mutations and polymorphisms of TLR) and environmental factors (smoking, drugs, social status, stress, microorganisms, diet, appendectomy and intestinal permeability) that participate in the physiopathology of this disease. The most accepted theory suggests that intestinal inflammation is produced by an abnormal response from the lymphocytes T against enteric bacterial flora in genetic susceptible people.¹⁶

In CD overexpression of toll-like receptors (TLR) could induce an alteration in the recognition and discrimination of their own bacterial flora, resulting in activation of cytokines such as NF- κ B. Such alteration of the innate immunity leads to an uncontrolled activation of lymphocytes T helper, especially Th1 response, and the release of pro-inflammatory mediators such as TNF- α , culminating in tissue destruction.

Finally, there is an exaggerated production of antibodies (ASCA), and both regulatory lymphocytes T and lymphocyte apoptosis are altered, thereby limiting anti-inflammatory mechanisms.^{2,20}

Clinical manifestations

There are a vast number of clinical manifestations, including abdominal pain, diarrhea, nausea, vomit, fever and weight loss, among other manifestations.^{20,21} It is believed they are mainly due to the inflammatory process in the gastrointestinal tract which causes alteration of the intestinal mucosa, decreasing the absorption of micronutrients.²²⁻²⁴

It is important to have in mind the intestinal complications which include low intestinal bleeding, perforation, intraabdominal abscesses, stenosis and intestinal obstruction. The presence of anal fistulas is highly suggestive of CD²⁵ (Table 2).

Extra-intestinal manifestations occur in 30% of the patients and affect organs apart from the gut, such as the joints (peripheral arthritis, ankylosing spondylitis, sacroiliitis), skin (pyoderma gangrenosum, erythema nodosum), eyes (uveitis, episcleritis) and hepatobiliary system (primary sclerosing cholangitis) (Table 3). EIMs are most common when the colon (as opposed to the small bowel) is inflamed. Some EIMs appear directly related to the activity of the bowel disease and others appear to follow a distinct course.²⁶ Anemia and arthropathy are the most common EIMS. Anemia of IBD is a unique model characterized by overlap of chronic disease anemia and iron deficiency anemia with other causes of anemia, such as vitamin B12 deficiency, folate deficiency and effects of medications.²⁷

On the other side, arthropathy can have peripheral (pauciarticular and polyarticular arthritis) or axial (spondylitis and sacroiliitis) articular involvement, and may precede, be synchronous with, or develop following the diagnosis of CD. Peripheral arthritis classically is seronegative, non-deforming, non-erosive, involves large joints and is

asymmetric. Type 1 peripheral arthritis is pauciarticular (knees, ankles, hips, wrists, elbows and shoulders), involving fewer than 5 joints, and is strongly associated with disease activity and other EIMs. Type 2 peripheral arthritis is polyarticular (metacarpophalangeal joint, proximal interphalangeal joint, metatarsophalangeal joint, knees, ankles, and shoulders), independent of disease activity, and not usually associated with other EIMS. Axial involvement is independent of gut pathology.²⁸

Although primary sclerosing cholangitis (PSC) is the most common hepatobiliary disorder associated with IBD, it is more common in UC than in CD, however, gallstones (incidence from 13-14%), medication-associated liver disease and fatty liver seem to be higher in patients with CD compared with patients with UC and general population.²⁹

Some other important manifestations are failure to thrive, renal lithiasis, and osteoporosis, all these related to malabsorption.^{30,31}

Diagnosis and classification

In our media, owing to the fact that CD has a low prevalence, CD is an exclusion diagnosis, but it must come to mind in the workup of chronic diarrhea, weight loss, lower gastrointestinal bleeding, abdominal pain, and intestinal obstruction, once malignancies and tuberculosis have been ruled out (Table 4).^{13,32}

In high suspicion cases, some diagnostic studies that may be useful are a colonoscopy and serologic test. Colonoscopy may show important macroscopic characteristics like deep linear ulcers with patchy distribution, which may affect the whole gastrointestinal tract or just a segment. Other suggestive findings are abscesses, fistulas or stenosis. Histological findings are non-necrotizing granulomas and signs of chronic inflammation.

Table 2. Clinical manifestations depending on the location in Crohn's disease.

Location	Symptoms	Comments	Frequency (%)
Ileum and colon	Diarrhea, cramping, abdominal pain, weight loss	Most common form	35
Colon	Diarrhea, rectal bleeding, perirectal abscess, fistula, perirectal ulcer	Skin lesions and arthralgias	32
Small bowel	Diarrhea, cramping, abdominal pain, weight loss	Fistula or abscess formation	28
Gastroduodenal region	Anorexia, weight loss, nausea, vomiting	Rare form. May cause bowel obstruction	5

Table 3. Extra-intestinal manifestations in Crohn's disease.

Sites	Extraintestinal manifestations
Musculo-skeletal (20%)	Arthritis: colitic type, ankylosing spondylitis, isolated joint involvement. Hypertrophic osteoarthropathy: clubbing, periostitis.
Skin and mouth (10%)	Miscellaneous manifestations: osteoporosis, aseptic necrosis, polymyositis, osteomalacia. Reactive lesions: erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizing vasculitis, Sweet syndrome. Specific lesions: fissures, fistulas, oral Crohn's disease, drug rashes.
Hepatobiliary (5%)	Nutritional deficiencies: acrodermatitis enteropathica (zinc), purpura (vitamin C and K), glossitis (vitamin B), hair loss and brittle nails (protein). Associated diseases: vitiligo, psoriasis, amyloidosis, epidermolysis bullosa acquisita. Specific complications: Primary sclerosing cholangitis, bile-duct carcinoma, small duct PSC, cholelithiasis. Associated inflammation: autoimmune chronic active hepatitis, pericholangitis, portal fibrosis, cirrhosis, granulomatous disease.
Ocular (5%)	Metabolic manifestations: fatty liver, gallstones associated with ileal Crohn's disease. Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease, retrobulbar neuritis, Crohn keratopathy.
Metabolic	Growth retardation, delayed sexual maturation.
Blood and vascular	Anemia, leukocytosis, thrombocytosis, thrombophlebitis, thromboembolism, arteritis, arterial occlusion, polyarteritis nodosa, Takayasu arteritis, cutaneous vasculitis, anticardiolipin antibody, hyposplenism.
Renal and genitourinary	Calcium oxalate stones, amyloidosis, drug-related nephrotoxicity, renal tubular damage with increased urinary excretion of various enzymes.
Neurologic	Peripheral neuropathy, myelopathy, vestibular dysfunction, pseudotumor cerebri, <i>Myasthenia gravis</i> , cerebrovascular disease.
Airway and lungs	Pulmonary fibrosis, vasculitis, bronchitis, acute laryngotracheitis, interstitial lung disease, sarcoidosis.
Cardiac	Pericarditis, myocarditis, endocarditis, heart block, cardiomyopathy, cardiac failure.
Pancreas	Acute pancreatitis.
Autoimmune	Drug-induced lupus, positive DNA, anti-double-stranded DNA.

Table 4. Differential diagnosis in Crohn's disease.

Infectious	Non-infectious (inflammatory)	Non-infectious (toxic)	Non-infectious (malignant)	Non-infectious (other)
<i>Yersinia</i> spp	Diverticulitis	Postoperative diversion colitis	Colorectal cancer	Irritable bowel syndrome
<i>Mycobacterium tuberculosis</i>	Ulcerative colitis	Bile acid loss	Small-bowel cancer and lymphoma	Ischaemic colitis
Atypic micobacterias	Microscopic colitis	Overuse of non-steroidal anti-inflammatory and other drugs		Chronic pancreatitis and malabsorption
	Behçet syndrome	Excessive or misuse of laxatives		
	Radiation enteritis			
	Sarcoidosis			
	Celiac disease			
	Ulcerative jejunoileitis			

Laboratory findings that are useful in CD are hypoalbuminemia, elevation of the ESR and RCP, anemia or leukocytosis.³³ The serologic markers of clinical importance are the anti-*Saccharomyces cerevisiae* antibodies (ASCA) which are commonly positive in CD and antineutrophil cytoplasmic antibody (p-ANCA) negative for CD.³⁴

These tests are suggestive of CD but are not meant to be interpreted as a diagnostic test, as up they could be positive in a healthy population.³⁵ The main utility of these antibodies is in patients with characteristics of CD and other diseases including UC, for differential diagnosis (Table 5).

Treatment and prognosis of the disease depend on several factors, the Montreal Classification considers age of onset, location, behavior of the disease and presence of perianal disease for categorization; many decisions regarding diagnostic approach, treatment, follow-up, and prediction of several outcomes from response to therapy, to long-term prognosis, depend on this classification (Table 6).³⁶

Table 6. Montreal classification.

Age at diagnosis	A1: less than 16 years A2: between 17 and 40 years A3: over 40 years
Location	L1: ileal L2: colonic L3: ileocolonic L4: isolated upper digestive
Behavior	B1: non strictureing, non penetrating B2: strictureing B3: penetrating P: perianal disease

Table 5. Diagnosis of Crohn's disease and chronic ulcerative colitis.

Diagnosis	Ulcerative colitis	Crohn's disease
Suspected	Presence of typical clinical manifestations, further investigation required	
Suggested	Presence of clinical features + either positive image or endoscopic findings	
Rule out	*Chronic schistosomiasis *Amoebiasis *Intestinal tuberculosis *Ischemic colitis *Radiation colitis *Clostridium difficile	*Chronic intestinal infections (small intestinal tuberculosis, amoebiasis, Yersinia) *Lymphogranuloma venereum *Intestinal lymphoma *Chronic diverticulitis *Ischemia colitis *Behcet's disease *NSAID enteropathy
Definite	Suggested diagnosis + other causes rules out + typical histopathology of resected specimen. In areas of high tuberculosis prevalence: a negative culture (biopsy or resected bowel).	

Table 7. Crohn's disease activity index (CDAI).

Variable (n)	Variable description	Multiply	Total
1	No. of liquid or soft stools (each day for 7 days)	X2	
2	Abdominal pain, sum of 7 daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe)	X5	
33	General well-being, sum of 7 daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	X7	
4	Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8 °C).	X20	
5	Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes)	X30	
6	Abdominal mass (0 = no, 2 = questionable, 5 = definite)	10	
7	Hematocrit - (males 47%, females 42%)	X6	
8	Body weight (1-weight/standard weight) x 100 (add or subtract according to sign)	X1	

Add the 8 variables. A total of < 150 points denotes disease remission and a better outcome. > 450 points implies severe disease.

On the other hand, for classification of severity, there is an extensive number of validated scores like the Crohn's disease activity index (CDAI), mainly used in clinical trials because of complexity, and the Harvey-Bradshaw activity Index used in the clinical setting due to its simplicity (Table 7).³⁷⁻³⁹

TREATMENT OF CROHN'S DISEASE

Treatment of CD should be guided by severity, behavior, disease location, appearance of complications, treatment refractoriness and dependency to steroids. CD treatment is divided into drugs inducing remission and for maintenance of remission (Table 8).²

First line drugs in the treatment for Crohn's disease

- **5-Aminosalicylates.** This kind of drugs are the classic first line treatment, there are oral and rectal

Table 8. Pharmacotherapy used in Crohn's disease treatment.

Drug	Induction	Medical therapies used in Crohn's disease			Crohn's disease	Fistulating disease
		Maintenance	Ileocaecal disease			
Budesonide	Yes	No	Yes	Possibly	No	
Mesalazine	No	Possibly	No	No	No	
Prednisolone	Yes	No	Yes	Yes	No	
Immunomodulator	Yes	Yes	Yes	Yes	Yes	
Biological therapy	Yes	Yes	Yes	Yes	Yes	
Ciprofloxacin	No	No	No	No	Yes	
Metronidazole	No	No	No	Yes	Yes	
Primary nutritional*	Yes	No	Yes	Possibly	Possibly	

*Primarily for paediatric patients.

Table 9. Immunomodulatory therapy for Crohn's disease.

Drug	Dosage	Immunomodulatory therapy for Crohn's disease	
			Common adverse effects
Steroids Prednisone	20 a 40 mg by mouth per day (up to 60 mg)		Hypertension, fluid retention, hyponatremia, osteoporosis, depression, increased risk of infection.
Budesonide	9 mg PO every morning for up to 8 weeks (induction)		Diarrhea, nausea, arthralgias, headache, respiratory tract infection, sinusitis.
Thiopurines Azathioprine	50 mg PO per day (maximum 2.5 mg/kg/day)		Gastritis, nausea, vomiting, lymphoma, fever, leukopenia, anemia, thrombocytopenia. Risk of cancer in elderly patients.
6-Mercaptopurine	50 mg PO per day (maximum 1.5 mg/kg/day) hepatic encephalopathy, pancreatitis, rash, hyperpigmentation, lymphoma, fever.		Myelosuppression, hepatic toxicity, immunosuppression,
Methotrexate	25 mg SC or IM once a week		Alopecia, photosensitivity, rash, diarrhea, anorexia, nausea, vomiting, stomatitis, leukopenia, pneumonitis. May also cause hyperuricemia, gastrointestinal hemorrhage, myelosuppression, hepatotoxicity, lung fibrosis, renal failure.
Anti TNF agents Infliximab	5 mg/kg IV once at weeks 0, 2 y 6, then 5 mg/kg every 8 weeks		Infusion-related reactions (dyspnea, flushing, headache, rash, chest pain, hypotension, urticaria, anaphylaxis), delayed reactions (serum sickness, myalgia, arthralgia), infections, pneumonia, abscess, sepsis, lupus-like syndrome, lymphoma.
Adalimumab	160 mg SC at week 0, 80 mg at week 2, then 40 mg every 4 weeks		Injection site reactions, infection, tuberculosis, malignancies, lupus-like syndrome.
Certolizumab pegol	400 mg SC once at weeks 0, 2, and 4, then 400 mg every 4 weeks		Injection site reactions, upper respiratory tract infection, headache, hypertension, rash, infections.

preparations. Some of these drugs are Sulfalazine, Mesalazine, Olsalazine and Balsalazide. Rectal presentations are only useful when CD is active in colon and rectum.

Mainly used in reactivation and for induction to remission, when activity of the disease is mild to moderate. For CD the preferred aminosalicilate is Mesalazine 4-6

g/day, for its activity in small intestine, also it is the best tolerated.⁴⁰

Most common side effects of these drugs (10-40%) are headache, nausea, epigastric pain, diarrhea, Oligospermia (Sulfasalazine). Rarely Steven's Johnson syndrome, pancreatitis, agranulocytosis and alveolitis. It is recommended to start treatment with Folinic acid, to avoid

anemia and other pathologies associated with its deficit.⁴¹

- **Steroids.** These are the most used when there is severe activity, lack of response to treatment with 5-ASA or when a quick inflammatory response is needed. Different types of steroids may be used in a flare, however steroids should not be used as a maintenance therapy in long term, because of systemic side effects. For induction of remission, Prednisolone 40 mg/day, in a reduction regimen, achieves quick clinical response. The evidence shows higher doses do not give greater benefit and do elevate the number of adverse reactions. Drug suspension must be done through a reduction scheme, with an approximate duration of 8 weeks, as abrupt reductions are associated to more reactivations. On the other hand, doses < 15 mg/day have been useless for induction to remission. Budesonide is an intraluminal steroid, with little systemic absorption, and it seems to be as useful as prednisolone specially in low or moderate activity.⁴² Administration route of steroids depends on location and severity of the disease.
 - a) **Intravenous.** Methylprednisolone 60 mg/day, hydrocortisone 400 mg/day in severe activity or with contraindication for oral administration.
 - b) **Oral.** prednisolone, prednisone and budesonide, in moderate to severe activity.

There is a group of patients that will fail to steroid therapy; these are known as refractory and those who do not achieve remission without the use of steroids known as steroid dependent. We can use Thiopurines as Azathioprine or 6-mercaptopurine as sparing steroid.

Second line drug therapy in Crohn's disease: immunomodulators

A standardized reduction scheme helps to identify refractory patients, and who may need an adjuvant therapy. Resistance and lack of response to steroid therapy should make us consider surgery. Some second line medical therapies include an immunosuppressor appropriate for the severity and type of disease. Therapy escalation should be considered in patients having a severe reactivation or frequent events, patients requiring two or more steroid courses in a 12-month time lapse, those with activation when the steroid dose falls below 15 mg/day and those presenting relapse in the first 6 weeks after steroid cessation (Table 9).

- **Thiopurines.** Azathioprine in a 2-2.5 mg/kg/day dose or 6-mercaptopurine in a 0.75 to 1.5 mg/kg/day dose, might be useful for inducing remission or as a maintenance therapy in patients that fail or are intolerant to 5-ASA and that require recurrent steroid cycles. Although its effect is delayed, between 4-6 weeks, and its use alone is not recommended, it is useful as a sparing steroid agent and in the treatment of CD with fistulas of any type. It is important to exclude other complications as occlusion or abscesses. The more common side effects are allergic reactions, leucopenia, pancreatitis, bone marrow and liver toxicity.⁴³
- **Methotrexate.** This drug has shown its utility in the induction and maintenance treatment of patients with CD in those patients intolerant or resistant to thiopurine treatment. Methotrexate should be administered with 5 mg of folic acid after three days of administration, to diminish its adverse effects associated with the inhibition of the dihydrofolate reductase.⁴⁴⁻⁴⁶ The most common adverse effects of this drug are gastrointestinal symptoms (nausea, vomit, diarrhea or stomatitis), hepatotoxicity, pneumonitis and infection associated with opportunistic agents. Methotrexate is also a teratogenic agent and is contraindicated during pregnancy or in women on reproductive age without an effective anticonception therapy. Pregnancy should be planned up to 6 months after the drug suspension. It is also not recommended during breast feeding and ethanol consumption should be also avoided.
- **Calcineurin inhibitors.** Cyclosporine and Tacrolimus are examples of this type of drugs. They both suppress humoral and cellular immunity, preventing the clonal expansion of T cells. These drugs are useful in the treatment of UC, although they have not shown to be useful in the treatment of CD.
- **Tumor necrosis factor alpha inhibitors.** Almost all current guidelines recommend Anti TNF as second line therapy for IBD the use of these drugs. Anti TNF used for treatment of CD are adalimumab, infliximab and certolizumab pegol.⁴⁷⁻⁴⁹ There is some recent information that suggest that these drugs may be used as first-line therapies in CD of recent diagnosis, especially infliximab and azathioprine, this strategy is known as "top-down", treatment and the evidence shows quick remission in patients with this therapy mode.^{50,51}
- **Anti-integrin monoclonal antibodies.** Currently there are three useful drugs for patients with CD, natalizumab, vedolizumab and ustekinumab. Current guidelines still not consider the use of these drugs for the treatment of IBD, but there is recent evidence that has shown its utility.⁵²

Adjuvants, prevention and other therapies

IBD frequently coexists with mood disorders, especially depression and anxiety disorders. When reactivation occurs they commonly find themselves frustrated as their quality of life change. The Quality of life at one year of diagnosis is worst for CD over UC. It is important to consider these aspects and to offer a multidisciplinary treatment that includes a psychiatrist and a psychologist.

Cigarette smoking cessation is one of the most important measures, as it is associated with a greater risk of exacerbation.

Problems due to malabsorption, such as anemia, vitamin D deficiency, and/or osteoporosis, should be recognized and treated. It is recommended, even in active patients, to have enteral nutrition. Parenteral nutrition is not recommended as first line nutrition strategy.

Antibiotics are useful in the treatment of abscesses or when it is difficult to distinguish between disease activity from infectious diarrhea. Ciprofloxacin and Metronidazole are useful in CD for the treatment of perineal activity. Probiotics and prebiotics are not recommended 53.

Non-steroidal anti-inflammatory drugs should be avoided, as they have been found as exacerbating agents. Also, there are some associations between the regular use of aspirin and the development of CD.

Surgical therapy

This therapy is useful in refractory disease and when complications develop such as occlusion, abscess, and fistulas. Before a surgical treatment is planned, we must first come to a consensus between doctors and patient, since it is not a curative therapy, and the disease might reactivate we must make an informed and bilateral decision.⁵⁴

Prognosis

Almost all patients with CD have complications; the perianal disease is present in approximately 50%. Approximately, 40% will develop active disease within the first 3 years and only a small percentage remains inactive over time. The majority will require bowel resections and several surgeries. A review showed that after 10 years of diagnosis, 85% had the same location; however, the initial pattern will change after 25 years. 55 Stenosis or penetrating complications will be found in 60% of patients in the first 5 years, which will require intensive medical treatment (immunomodulatory and /or biological therapy).

Over time, 77% of patients will show intermittent activity, 10% a prolonged remission and 13% a chronic activity.

Age under 40 years, presence of perianal disease and premature need for corticosteroid therapy are predictors of aggressive disease. The presence or absence of these, represent a guide for decision making to regulate management and treatment.

CONCLUSIONS

We have done an extensive review of the available medical literature regarding CD. Although it is a rare multifactorial disease, the incidence and prevalence are increasing.

It frequently affects young patients, making it an economic and social expensive disease. Complications can be severe; prompt diagnosis and early treatment are essential to yield a better prognosis. Even though the pathophysiology and risk factors have been exhaustively studied, definite etiology has not been demonstrated. Treatment is intended to induce remission and to maintain the disease inactive. Nevertheless, improvement and development of novel treatment agents is targeted for improving prognosis and quality of life.

HIGHLIGHTS

- Crohn's disease is characterized by the involvement of the gastrointestinal tract from mouth to anus, with a transmural pattern of inflammation of gastrointestinal wall layers.
- A "North to South gradient" of incidence has been suggested previously in several publications. However, this gradient is not widely accepted since the lack of information of IBD in southern countries.
- Although the etiology is not completely understood, multiple mechanisms have been described. The Nucleotide-binding Oligomerization Domain containing 2 (NOD2) is the first susceptibility gene strongly associated with CD, expressed in the intestinal epithelium, especially in Paneth cells. Three genetic variants within the gene CARD15/NOD2 are present in up to 30% of Caucasian patients with CD.
- In our media, owing to the fact that CD has a low prevalence, CD is an exclusion diagnosis, but it must come to mind in the workup of chronic diarrhea, weight loss, lower gastrointestinal bleeding, abdominal pain, and intestinal obstruction.
- Treatment of CD should be guided by severity, behavior, disease location, anatomic site, appearance of

complications, treatment refractoriness and dependency to steroids. CD treatment is divided into drugs inducing remission and for maintenance of remission.

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