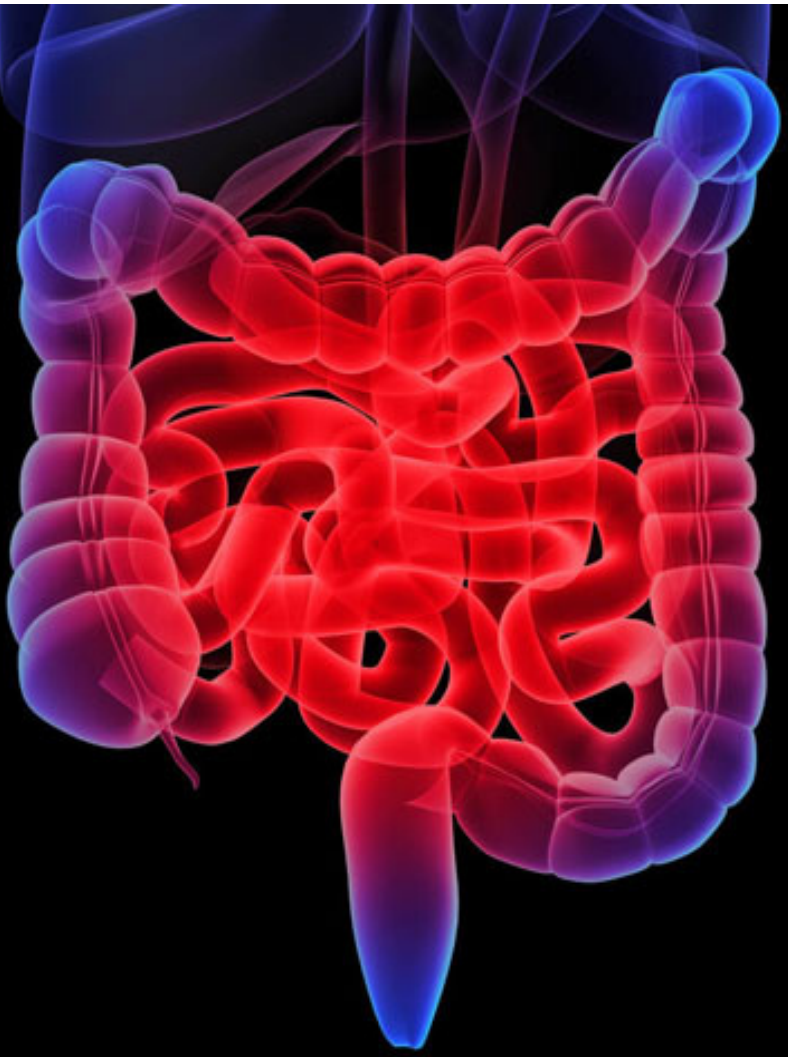

INFLAMMATORY BOWEL DISEASE

MEDDOCS
International

Inflammatory Bowel Disease: An Overview

Glauber Rocha Lima Araújo; Lorena Sousa de Carvalho; Jonathan Santos Apolonio; Beatriz Rocha Cuzzuol; Ronaldo Teixeira da Silva Junior; Elise Santos Vieira; Maria Luísa Cordeiro Santos; Breno Bittencourt de Brito; Filipe Antônio França da Silva; Fabrício Freire de Melo*

Multidisciplinary Health Institute, Federal University of Bahia, Vitória da Conquista 45029-094, Bahia, Brazil.

Corresponding Author: Fabrício Freire de Melo

Multidisciplinary Health Institute, Federal University of Bahia, Vitória da Conquista 45029-094, Bahia, Brazil.

Tel: +55-77-991968134;

Email: freiremelo@yahoo.com.br

Published Online: Jul 07, 2020

eBook: Inflammatory Bowel Disease

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

Abstract

Inflammatory Bowel Disease (IBD) is a worldwide health problem and comprises Crohn's Disease (CD) and Ulcerative Colitis (UC) as the two most prevalent pathologies. It has a direct connection with industrialized societies and all the changes imposed on individuals in this context, such as stress and dietary changes, in addition to the genetic predisposition and immunological factors. The future prospects are worrying because IBD affects not only the quality of life of its patients, but also generates significant expenses in health systems and direct and indirect impacts on the economy. When a disorder impairs the homeostasis of the gastrointestinal tract, IBD can occur. Factors such increased permeability of the epithelial layer, genetic mutations, changes in TLR expression, interleukin production, NOD2 variants, and imbalance in the suppression of the immune response are linked with CD and UC pathophysiology. Abdominal pain, diarrhea and perianal changes are the most often manifestations, furthermore, arthritis is the main extra-gastrointestinal manifestation. The diagnosis for IBD should be based in anamnesis, physical examination and invasive and non-invasive methods, as blood and stool collection, that may be indicated inflammatory markers. In addition, non-invasive procedures, such as magnetic resonance and video capsule endoscopy, and invasive ones, as endoscopy, are important in diagnosis of IBD besides assisting in differential diagnosis. The treatment for UC and CD should take into account disease severity, extension, and disease behavior. The medical therapy aims for inflammatory reduction and mucosal healing, focusing, mainly, in relief of the symptoms and improvement of quality of life for the patients. Surgery also is an option; however, its risks and benefits must be well-balanced.

Concepts and epidemiology

Inflammatory Bowel Disease (IBD) is a worldwide health problem that comprises two specific and more prevalent pathologies: Crohn's disease and Ulcerative colitis [1]. This chapter presents the concept, epidemiology, pathophysiology, clinical manifestation and treatment of Crohn's Disease (CD) and Ulcerative colitis (UC).

Crohn's disease is a transmural inflammation that can affect any part of the gastrointestinal tract, from the mouth to the perianal area. According to the affected site, Crohn's disease can be divided into colitis only (25%); only ileitis (25%) and ileocolitis (50%) [2]. Abdominal pain, fever and signs of intestinal obstruction or diarrhea typically characterize CD, and it is possible to occur mucus, blood, or both in the stool [3]. CD has

a higher incidence in Ashkenazi Jews, urban populations, and inthe northern hemisphere. It mainly affects individuals from 20 to 40 years old with no significant difference between sexes. The causes behind CD development involve genetic, environmental, and immunological factors [4].

Ulcerative colitis is the chronic and idiopathic inflammation of the intestinal mucosa, which begins in the rectum and extends to the nearby regions, potentially reaching all the colon extension. It is characterized by painful episodes in the abdominal region, bloody diarrhea and episodes of tenesmus. In addition, some extra intestinal conditions can also occur with primary manifestations in the skin, eyes, liver and joints [5]. The exact causes are still unknown, but genetic, immunological, and environmental factors appear to influence UC onset.

To understand the current worldwide distribution of IBD, it is indispensable to comprehend how socio-geographical changes have occurred throughout history. In this sense, it is necessary to return to the 18th century Industrial Revolution, which started in Western Europe, mainly in Great Britain and, later, in its colonies in North America and Oceania [6]. Inthat period, a great rural exodus that provided a considerable increase in population density occurred. That process led to drasticenvironmental and individual changes, including lifestyle and diet modifications, what probably contributed to the onset of the first cases of IBD [7]. At the end of the 20th century, several regions of the globe had already undergone those considerable industrialization processes, and regions from South America, Middle East, and Asia also experienced an increase in the number of IBD patients [8,9].

A study on the prevalence and incidence of IBD worldwide revealed that in the above-mentioned precursor countries of the 18th century Industrial Revolution, mainly in Europe and North America, IBD notifications tends to stabilize.On the other hand, increasing IBD incidence levels have been observedin countries located in newly industrialized continents, such as Asia, South America, and Africa [10].

Regarding the total cases from 1990 to 2016, Europe, North America, and Oceania presented the highest values per 100,000 inhabitants for CD and UC (>135.6 and >198, respectively). In its turn, newly industrialized countries, such as Brazil, presented prevalence values around0.6 - 6.75 (CD) and 2.42-21 (UC) for every 100,000 inhabitants [11].

However, the IBD numbers in the regions of the globe can vary due to a series of factors such as differences in access to health care, inadequate notification, and improper database usage. Given the background, future prospects are alarming, not only due to the increase in the number of cases, but also due to the numerous impacts that can be caused by IBD, which includethe economic burden to the health systems. Thus, preventive measures tend to have a positive impact on the current scenario of IBD.

Pathophysiology

The Inflammatory Bowel Disease (IBD) pathogenesis mechanism is not completely understood. Studies indicate that the main risk factors for the development of IBD are related to the association of genetic predisposition with environmental factors [12].

Regarding the genetic aspect, there is a connection between genes decoding and cytokines, chemokines and antimicrobial peptides activation, in addition to other molecules related to the immune response [13]. Furthermore, environmental factors, such as smoking, infections, stress, air and water pollution, food and drugs, have been associated with the development and worsening of IBD [14].

Crohn's disease (CD)

The pathogenesis of CD is associated with an inadequate immune response, and factors such as the integrity of the epithelial barrier and the constitution of the intestinal microbiota may contribute to this process [15].

The maintenance of the intestinal epithelial layer is essential for the defense of the organism, considering that it functions as a physical barrier between the immune system and the external environment and there is a high concentration of lymphocytes in the lymph tissue of the gastrointestinal tract mucosa. However, individuals with CD have a greater permeability of the epithelial layer, facilitating the entry of pathogenic microorganisms to layers below the mucosa. The increase of pathobionts in the mucous layer interacting with the antigenic receptors of the submucosal layer can trigger an inflammatory process [16].

Paneth cells also act in the defense of the mucosa, by excreting antimicrobial substances in the intestinal lumen, such as α-defensins that act against pathogens. In addition, according to studies carried out in mice, α-defensins also regulate the composition of the microbiota, performing a homeostatic function [17]. It is evident that there is a risk allele for CD in the ATG16L1 gene, andhomozygous patients for this allele have abnormal Paneth cells with disorganized or decreased granules [18].

Another factor linked to the mucosal immune balance is the antigen recognition. The immune system recognizes Pathogen-Associated Molecular Patterns (PAMPs) through receptors such as TLR (Toll-Like Receptor) and NOD (Nucleotide-Binding Oligomerization Domain). When triggered, these receptors activate signaling pathways, inducing the expression of genes and the release of substances that act in the inflammatory response. Together, TLRs recognize most of the intestinal microbiota, probably distinguishing commensal microbes from pathogenic bacteria, thus maintaining the bacterialbalance of the mucosal epithelium [19]. However, individuals with CD express TLRs differently from those who do not have the disease. As an example, a lower expression of TLR3 and an increase in the expression of TLR4 was noted [20]. Regarding NOD receptors, studies show that NOD2 variants are associated with the CD pathogenesis, since certain NOD2 polymorphisms are linked to the suppression of IL-10 transcription (anti-inflammatory cytokine). In addition, activities that depend on that receiver can also be affected [21]. NOD2 induces autophagy in dendritic cells influencing the antigenic processing and presentation for TCD4+ cells. Individuals who express risk variants of NOD2 or ATG16L1 associated with Crohn's disease have a dysfunction in autophagy induction, impairing the proper activation of TCD4 + cells. This could cause bacterial persistence and trigger an abnormal immune response [22].

In association with these factors, CD may be associated with the imbalance between effector T cells (in particular, the Th1 subgroup that mainly releases IFN-γ acting against intracellular pathogens or the Th17 subgroup that mainly releases interleukin (IL)-17 acting against extracellular bacteria and fungi) and Tregulatory cells (suppress the immune response) [3,23].

The interaction between genetic and environmental factors can be understoodby means of epigenetic mechanisms, such as changes in acetylation and methylation of histones and DNA methylation, which can interfere in genes expression. The epigenetic profile is susceptible to modifications according to environmental influences and it may play a role in IBD when affected by some factors, such as food, stress, and chemical substances [24].

Ulcerative colitis (UC)

The pathophysiology of UC is associated with the homeostasis disturbance in the colon environment. In Ulcerative Colitis, the mucus production is decreased while the lumen permeability is increased [25]. Once the intestine epithelium synthesizes antimicrobial peptides and works as a barrier between the microbiome and pathogenic bacteria, the interruption of this barrier function results in an increased interaction between microorganisms and immunologic system, inducing an exaggerated immune response [26].In this scenario, the cells of the innate and adaptive response are activated, producing cytokines and chemokines. Consequently, a high number of immune response cells such as dendritic cells, T cells, and macrophages is observed in the rectum lamina propria in UC as well as increased IgG [27].

The dendritic cells also express TLRs but, in an ideal environment, they present decreased or absent TLR2 and TLR4, which are increased in UC. TLR4 D299G polymorphism is identified as a possible risk factor for UC, considering that this gene is responsible for the balance between the tolerance of the immune system to the microbiome and the attack towards pathogenic bacterias [26-28].

The balance between T cells is also changed. In this case, Th2 induction mediated by NK cells is affected, producing IL-13, which exerts cytotoxic functions on epithelial intestinal cells, as well as changes in tight-junctions and apoptosis [29]. Thus, one of the consequences of this process is the increased permeability of the intestinal lumen.

Concomitantly, the complement system is also activated, which stimulates cytokines, chemokines and leukotrienes. The release of lymphocytes and cytokines into the circulation also explains the extra-intestinal responses of the UC, like fever [30]. All of these factors combined produce an intense immune response that contributes to the aggravation of the inflammation.

The inflammatory reaction influences the motility of the rectum, resulting in increased bowel movements and secretion production. The intestinal mucosa also changes, causing diarrhea, which can also happen with blood and pus. Another relevant process is the mechanism of colic distension, due to the ulcerations coming from the inflammatory process. These injuries can induce infections that result in smooth muscle relaxation and in the absence of contraction [31]. Thus, they trigger colic and reduce the absorption of water and sodium. Ulcers can also cause loss of protein and other nutrients [32].

Clinical manifestations

In general, IBD manifestations are highly dependent on the areas of gastrointestinal tract involvement. UC and CD may present with similar clinical complaints and symptoms among both children and adults [33]. The clinical manifestations in pediatric inflammatory bowel disease are nonspecific. Colonoscopy examination and biopsy are valuable in establishing the diagnosis of pediatric ulcerative colitis [34].

IBD most often manifests with symptoms from the digestive tract, including abdominal pains of various intensities and locations, diarrhea (stools passes with pus and/or blood), nausea, bloating, flatulence, vomiting, and perianal changes [35]. The most common clinical symptoms of CD include weakness, fatigue, long-term diarrhea with abdominal pain, weight variations and rectal bleeding [36]. As an extra-intestinal manifestation, the artritis is the most common outcome and the nodosum erythema is the most common cutaneous lesion [37].

Diagnosis

Anamnesis and physical examination

During anamnesis, the attendant should pay attention to the clinical condition of the patient through a well-constructed history of the present illness and antecedents. In physical examination, the attendant should proceed with the palpation of the four quadrants of abdomen and anal inspection [38].

Non-invasive methods

Blood count

Some bloody inflammatory markers can be used to measure the presence or curse of the inflammatory bowel disease. C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) as well as the groups of antibodies ANCA and ASCA are some biomarkers applied in clinics [39].

CRP test

The production of CRP occurs almost exclusively in the liver by the hepatocytes as part of the acute phase response upon stimulation at the site of inflammation [40]. Tests for CRP are more representative for infectious and inflammatory processes than the ESR test, sincetheir levels increase faster and are less affected by anemia and pregnancy, for example.It is important to highlight thatalterations in these testsare not specific for IBD [41,42].

ESR

Erythrocyte Sedimentation Rate is a non-specific inflammatory marker. May be elevated in inflammatory processes but it is also influenced by age, sex, anemia, infection, pregnancy and globulin levels [42].

ANCA

Antineutrophil Cytoplasmic Antibodies (ANCAs) target granules of neutrophil cytoplasm, and atypical perinuclear ANCA (pANCA) is DNase sensitive and significantly increases in UC patients [39]. They are determined by indirect immunofluorescence using neutrophils fixed in ethanol. Three intracellular stippling patterns can be identified: Cytoplasmic, perinuclear and atypical [43].

ASCA

Anti-Saccharomyces Cerevisiae Antibody is another serologic marker of IBD, being commonly present in CD patients. These antibodies consists of IgG and IgA immunoglobulins against thecell wall components of the yeast *Saccharomyces cerevisiae* [43].

Stool examination

Among the intestinal inflammation markers present in stool samples, the main are Fecal Calprotectin and Lactoferrin [44].

Fecal calprotectin

Fecal Calprotectin is a protein that binds calcium and zinc, and it is responsible for transporting these minerals in the organism. It is able to resist room temperature for seven days [45]. Determining the level of FC in stool samples may help distinguish non-inflammatory disorders from IBD and, in most cases, a negative calprotectin rules out IBD [46].

Lactoferrin

Lactoferrin is aniron-binding protein found in neutrophils granules and it is secreted by mucous membranes. It is resistant to degradation and proteolysis (although less than Calprotectin), becoming it a useful marker of intestinal inflammation. It is sensible and specific to detect inflammation in patients with abdominal pain and diarrhea [45,47].

Non-invasives procedures

Transabdominal ultrasound

Transabdominal ultrasound is clinically useful in the initial diagnosis of IBD by evaluating bowel wall thickness and surrounding structures and it helps to better characterize the course of the disease in individual patients and can guide therapeutic decisions [48]. Bowel US is aneffective method in assessing CD, being a non-invasive and easy-to-use tool in the management of CD patients in clinical practice [49].

Intestinal transit

In this exam, the patients ingest a bariumsolution andradiologic registries of the gut are made with small intervals until the colon becomes full. Biopsy may be required by endoscopic methods after detection of alteration in this exam [50].

Tomography enterography

This is a computed tomography-similar exam, however the patient ingest the neutral contrast orally that will dilate the intestinal loops and allow to evaluate the thickening of slim intestinal walls andinflammatory activity as well as fistulas, abscess and malignancy. It lasts about ten minutes inside the CT device [50].

Magnetic resonance (MRI)

Magnetic resonance enables clear visualization of the entire length of the intestinal tract along with various extra-and intra-intestinal complications, and the lack of non-ionizing radiation exposure is an important advantage of this imaging modality [51]. In addition, MRI would be helpful for detecting mesenteric inflammatory changes and bowel wall edema and it is sensitive for detection of perianal abscesses requiring urgent intervention [52].

Video capsule enteroscopy (VCE)

VCE directly visualizes the mucosal surface of the small intestine and does it in a minimally invasive manner. The capsule is ingested and images are transmitted from the attached system to a data recorder, through which real-time images can be viewed [53]. Capsule endoscopy has few adverse events, with capsule retention being the most serious complication [54].

Invasives procedures

Endoscopy

Endoscopy is the principal modality used and has the advantage of allowing tissue acquisition for histologic assessment and therapeutic procedures, in addition to avoiding the radiation risk [55]. It is often included in the diagnostic evaluation of suspected IBD, and at least two biopsies should be taken from the esophagus, stomach, and duodenum for suspected upper tract IBD [56].

Colonoscopy

In patients with clinical presentations suggestive of IBD, the initial evaluation should include a colonoscopy with intubation and examination of the terminal ileum and allow biopsies to be performed for necessary [56].

Double-balloon enteroscopy (DBE)

Double-balloon enteroscopy is a novel endoscopic technique developed to investigate small bowel diseases [57]. This method allows visualization of the small bowel mucosa and biopsy of the lesion as well as therapeutic interventions, being indicatedforIBD diagnosis [58].

Differential diagnosis

Infectious colitis

The investigation of pathogenic bacteria, virus, parasites and *Clostridium difficile* toxin is necessary for differentiation between inflammatory bowel disease and infectious colitis. The stool examination to exclusion of the infectious etiology should be repeated during relapse and before administration of the immunosuppressive therapy [37]. Many papers reveal the role of bowel infection-triggering bacteria, such as *Mycobacterium*, *Campylobacter*, *Listeria*, *Escherichia*, *Salmonella*, *Clostridium*, *Yersinia*, and *Chlamydia*, as they directly lead to mucosa membrane lesion [35].

Intestinal tuberculosis

The intestinal tuberculosis is usually a complication of primary pulmonary disease, by swallowing of infected sputum. Palor, weight loss, night sweats and fever are the most common findings to the physical examination [59]. Weight loss and mucosal nodularity were associated with ITB. Abdominal pain and excessive intestinal involvement were associated with CD [60]. The commonest sites of tuberculous involvement of the GI tract are the ileocecal area and if the area of affected gut is within the reach of the flexible endoscope, rapid diagnosis may be possible with biopsy [61].

Crohn's disease Vs Ulcerative colitis

No single gold standard is available for the diagnosis and the distinction of IBD. The diagnosis should be based on clinical evaluation integrated with a combination of endoscopic, histological, radiological, and/or biochemical investigations [62]. Other endoscopic findings, such as macroscopic cobblestoning, segmental colitis, ileal stenosis and ulceration, perianal disease, and multiple granulomas in the small bowel or colon more strongly suggest a diagnosis of CD [63]. Rectal urgency, tenesmus and, occasionally, severe constipation represent the classical complaints of rectal involvement, while chronic diarrhea with nocturnal defecation and crampy abdominal pain are

typical of left-sided or extensive UC [62]. The IgG ASCA is usually detected in patients with CD and p-ANCA is found in 60-70% of UC cases, moreover, patients with pANCA-positive CD exhibit a clinical phenotype resembling that observed in UC [64].

Treatment

The choice of Inflammatory Bowel Diseases (IBD) treatment should consider some factors like severity level, lesion extension, and patient's age. Therefore, the therapeutic interventions could vary from immunosuppressive drugs usage to surgical resections or newer biological therapies [65].

Crohn's disease (CD)

Some aspects should guide the outset of the treatment for CD. Therefore, according to evidence-based consensus of the Brazilian Study Group of Inflammatory Bowel Disease, it is advised to collect some data about the patients in a clinical pre-treatment evaluation, such as activity level, extension and behavior of disease, which may be gathered from clinical, endoscopic and laboratorial exams [66]. It is also reasonable to establish the therapeutic recommendations based on disease prognosis (from low to high risk of progression to a more virulent course) [67].

Currently there is no "gold standard" for measuring the CD activity, but the Crohn's Disease Activity Index (CDAI) [68] is still the mostly used tool in clinical studies. The Harvey-Bradshaw Index (HBI) [69] is also recommended for differentiating clinical remission from active disease, and subtyping it. The Montréal classification of CD [70] is indicated specially for classifying the disease phenotype, which can be useful for describing the diagnosis and accompanying the disease behavior and response during the treatment.

In that context, CD is classified as mild to moderate, moderate to severe, or severe to fulminant. This subtyping, which can be also associated with the site of disease, may suggest the best medical approaches for each group. Surely, the treatment must be individualized and guided by symptomatic response as well as by the patient's tolerance to the care protocols, demanding physician's expertise to develop the suitable adjustments. Moreover, the treatment steps must be organized in a continuum process, starting from the management of acute disease (or clinical remission induction), and next, to response/remission maintenance.

Disease modifiers: General recommendations

Some publications on IBD literature, despite eventual low level of evidence, strongly advocate additional caution for CD patients care, such as:

1. Avoiding cigarette smoking due to risks of disease activity exacerbation and disease recurrence acceleration, what can even increase the rate of surgical interventions or hospitalizations [71].
2. Avoiding Nonsteroidal Anti-Inflammatory Drugs (NAIDs) administration, especially due to their side effects on gastrointestinal mucosa which may lead to greater chances of CD exacerbation [72].
3. Admitting lesser restriction to antibiotic usage when intended to prevent disease flares, especially in septic complications, symptoms attributable to bacterial overgrowth or perianal disease [73].
4. Including stress, depression and anxiety management in CD patient's broad care, in order to ease disease damage for well-being, improve quality of life and decrease greater risks of surgery or high-complex care needs related to these comorbidities [74].

Drug classes discussed for CD therapy

Salicylic derivatives

Mesalazine (also known as mesalamine or 5-aminosalicylic acid) is a topic agent capable of modulating proinflammatory cytokines release and limiting leukotriene and prostaglandin synthesis, besides other mechanisms [66].

Alternatively, Sulphasalazine (SSZ) has been pointed as a more effective option for some cases, mainly for mild to moderate CD [75]. The side effects are usually related to high serum levels of sulphapyridine, which may be aggravated by low drug metabolism in patients with hepatic limitations [66].

Overall, despite the current prescription, there is not enough evidence of aminosalicylates efficacy over placebo in reference to mucosal healing in patients with CD [76].

Corticosteroids

Conventional corticosteroids, such as hydrocortisone, prednisone or prednisolone, are commonly elected for CD flares management. Their mechanisms are especially useful to induce clinical remission rather than histological or endoscopic improvement. Even so, its quick symptom control is essential until effective immunomodulators or biological agents have time to act and show their results over inflammation, especially in moderate to severe CD. For sure, treatment duration, dose and route of drug administration are some factors that influence side effects severity and should be balanced to prevent them [77].

Controlled Ileal Release (CIR) budesonide is currently a well-indicated oral drug due to its action more restricted to intestine sites (especially, terminal ileum and right colon), rapid metabolism after first passage through liver and efficacy for symptom relief in patients with mildly to moderate CD activity [78].

It is not recommended to extend corticosteroid treatment for over 2-3 months, neither its usage as maintenance treatment. For patient's safety, corticosteroid "weaning" must be gradual. During this period, the potential adverse effects are acute adrenal insufficiency, a syndrome of pseudo-rheumatism or intracranial pressure rise [79]. In case of CD relapses, the previous dosage must be re-established. For those corticosteroid-dependent or intolerant patients, immunomodulatory therapy may behave as an "weaning" strategy or alternative care.

Antibiotics

Antimicrobial therapy usage is based on the hypothesis that CD may be associated with abnormal response to microbiota agents in genetically vulnerable hosts. Some of its supposed mechanisms involve immunosuppression, bacterial overgrowth blocking, and elimination of antigenic trigger mediated by bacteria. However, its effectiveness has not been assured for mucosal healing or remission induction [80].

Though recent trial outcomes report that rifaximin may benefit remission induction in mild to moderate CD, in general, antibiotics are recommended specially for septic complications, clinical reaction derived from bacterial overgrowth or perineal

disease [73]. Besides that, antimycobacterial therapy cannot be widely advocated for CD, due to its lack of evidence for induction or maintenance of remission or mucosal healing.

Immunomodulators

Thiopurines

AZA and its metabolite (6-mercaptopurine), followed by methotrexate, are first-line immunosuppressant drugs indicated for CD patients who are resistant or refractory to corticosteroids, present early relapse after corticosteroid withdrawal, reports CD recurrence after bowel resection or who have diagnosis of fistulizing or small bowel extensive disease [66].

Among the side effects, the main one is dose-dependent myelotoxicity, commonly noticeable through leucopenia, which makes necessary additional caution and monitoring (hemogram, AST, ALT and amylase exams) especially during the beginning of the treatment. In addition, other events such as nausea, vomits, abdominal pains, allergic reactions such as fever, rash, myalgia and articulation pain are also reported [66]. Lymphoma risk is another concern about immunosuppressant long-term usage; however, expectation and quality of life seem to be improved by this treatment [81].

On balance, the main role of thiopurines is in maintenance treatment, whereas their function in active CD may be restricted to adjunctive therapy or steroid-sparing action. When compared, remission induction in CD is clearly better and faster achieved through anti-TNF therapies, for instance [82]. Azathioprine should be used for over 3.5 years if the patient presents an established remission and absence of complications [83].

Methotrexate (MTX)

The mechanisms of MTX over inflammation is probably related to the inhibition of cytokine and eicosanoid synthesis [84]. Systematic review outcomes have shown MTX efficacy as an steroid-sparing agent for patients with active CD [85]; despite this, methotrexate has been reserved to treat patients with active or relapsing CD who are insensitive or intolerant to thiopurines or anti-TNF agent.

Because of its orally irregular absorption, MTX must be firstly administered through parenteral routes (intramuscular or subcutaneous) to be more effective [85]. Liver tests and blood count monitoring are important during the treatment, and additional caution to individual response should be applied when switching the administration to enteral forms. Besides that, it is also valid to remember that MTX has teratogenic properties, which makes its usage contraindicated for pregnant women [86].

Even though there is no specific data about this, it is advisable to co-prescript folic acid with methotrexate during CD treatment, in order to limit its early toxicity effects, which usually are responsible for treatment interruption. The main long-term concerns are hepatotoxicity, bone marrow suppression, and pneumonitis [87].

Biological therapies

Biological therapy is the general term designed for approaches with activity based on natural mediators and physiological phenomena.

Anti-TNF agents

Anti-TNF therapy for CD remission is based on the activity of chimeric monoclonal antibodies (IgG-1) against tumor necrosis factors. Basically, these antibodies bind to soluble or transmembrane TNF-α, inhibiting its coupling to TNF receptors and neutralizing its role in inflammation [88].

Risks and benefits must be balanced before anti-TNF therapy onset, mainly concerning the elevated vulnerability to opportunistic infections and malignancy risk associated with its usage. For this reason, it is advisable to check patient health conditions, before initiating any anti-TNF therapy, especially looking for presence of active or latent tuberculosis, opportunistic infection (e.g. histoplasmosis or blastomycosis) and viral hepatitis [67].

In general, these anti-TNF agents are well-tolerated, despite their related side effects, like headache, skin rash, respiratory tract infections, gastro intestinal-related effects, besides other relevant concerns such as cardiac dysfunction, anemia, leukopenia and increased risk of lymphoma [88].

Infliximab

Among researchers, there is no objection to infliximab potential of inducing CD remission, considering the wide compilation of high-level evidence available, but infliximab-with-AZA therapies have seemed to afford more promising results [89].

Adalimumab and certolizumabpegol (certolizumab)

Both drugs can be useful alternative therapies to infliximab-intolerant or -insensitive patients. Adalimumab is similar to infliximab in many aspects and effective on mucosal healing induction, whereas certolizumab pegol is a pegylated anti-TNF antibody form and probably less effective for induction treatment in CD [82]. There are fewer studies about their efficacy when co-prescribed with immunomodulators, but this approach likely has positive outcomes for inhibiting eventual immune reactions to treatment (antibodies against anti-TNF) through immunomodulating action.

Leukocyte trafficking inhibitors

Anti-integrin antibodies can be effective for inflammation relief when interfere in the physiology of leukocytes response, which is increased in CD. Natalizumab (anti-α4 integrin antibody) prevents leukocytes from connecting to both vascular cell adhesion molecule-1 and mucosal addressing cell adhesion molecule-1. Alternatively, vedolizumab only binds to α4β7, preventing interference with leukocyte trafficking out of the gut and potential complications attributable to this [90].

Medical Management for inducing clinical remission

In general, acute disease treatment should be extended until symptoms remission or clinical progression failure, what may direct more advanced approaches. The major goal is to quickly relieve inflammation and its secondary damage to the organism, usually in over 3 months or less [67].

Mild to moderate activity disease / low-risk disease

The treatment for mild CD is very particular, since there is a concern of protecting the patient from over treating and unnecessary exposure to riskier therapies, while on the other hand, there is also a wide prescription of “ineffective” agents, like 5-ASA, based on its low advantage over placebo. Therefore, oral mesalamine should not be used. Nevertheless, sulfasalazine doses of 3-6 g/day can be used for colonic or ileocolonic CD, but not for small intestine isolated disease [91].

Symptomatic medication and dietary manipulation are also acceptable [92], especially in cases with limited risk of disease progression and under careful monitoring. For mildly active ileocecal CD, oral budesonide 9 mg once daily is the preferred therapy [78,93].

Moderate to severe activity disease / moderate-to-high risk disease

This clinical condition requires more potent agents for induction of inflammation relief and mucosal healing. Therefore, oral corticosteroids should be part of a short-term treatment scheme, if sparingly used (up to 60 mg/day).

Enteric-coated budesonide may be appropriate, mainly for ileocecal CD, but prednisone is highly effective for serious cases [94]. Oral prednisone 40-60mg/day is mostly recommended, but higher prednisolone doses (1 mg/kg body weight daily) are also eligible for clinical response [95]. It is advisable to avoid corticosteroid therapy in patients with perforating complications [96].

Azathioprine (1.5–2.5 mg/kg/day) and 6-mercaptopurine (0.75–1.5 mg/kg/day) are not first-line therapies for symptomatic remission but should be considered as steroid-sparing agents in CD or for maintenance remission [97]. Besides these above-mentioned roles, methotrexate (15–25 mg SC/IM once weekly) is also acceptable for symptoms relief in patients with steroid-dependent active CD [98].

Biosimilar anti-TNF agents are available, effective, and may improve accessibility due to their lower costs, but require monitoring of clinical response [67]. Anti-integrin therapies, such as vedolizumab (with immunomodulators or not) and natalizumab, are clearly effective over placebo and advised for achieving clinical response, clinical remission, and corticosteroid-free remission especially in patients who have presented inadequate response or intolerance to TNF-blockers [90]. Ustekinumab (anti-p40 antibody that inhibits IL-12 and -23) is also effective for inducing and maintaining remission of moderate-to-severe CD, being recommended for those patients that have presented loss of response to previous medication (corticosteroids, thiopurines or anti-TNF agents) or have not undergo biological therapies yet [99].

Severe / fulminant disease

The primary therapy for acute severe CD should be with systemic corticosteroids, including prednisolone, hydrocortisone. Methylprednisolone may be effective at doses of 40-60mg/day [100]. For those relapsed, anti-TNF agents are appropriated. Infliximab is mostly suitable for fulminant disease, with greater advantages if combined with azathioprine [89]. For infrequently relapsing disease, it is convenient to reinitiate therapy based on steroids combined to immunomodulators. Vedolizumab is advocated as a “last-line” therapy appropriated for those non-responsive to steroids and/or anti-TNF [90].

Management of fistulizing crohn’s disease

Fistulas are recurrent in around 33% of patients with CD and require a careful treatment. Though perianal fistulas are the most typical forms, other internal or external locations can also be damaged. The presence of abscess prompts its drainage before initiation of immunosuppressive therapy, unless it is small and does not need to be drained [101].

Asymptomatic perianal fistulas do not require treatment, but when symptoms are present, associated with major internal fistulas, diarrhea or bacterial overgrowth in the small intestine, then patient, physician and surgeon should joint for establishing the best available care procedures [102].

Symptomatic simple perianal fistulas in patients with CD may be satisfactorily treated with either non cutting setons, fistulotomy or mucosal advancement flap surgery [103]. Besides this, immunomodulators, vedolizumab or anti-TNF agents (infliximab rather than others) may be considered [104]. Simple fistulas may also respond well to initial antibiotic therapies, such as oral metronidazole (20 mg/kg/day or 750–1500 mg/day) and/or oral ciprofloxacin (500-1500 mg daily) within an usual period of 6 to 12 weeks, which can relief fistula symptoms and even induce its healing [104,105].

Currently, the best recommendation for treating complex perianal fistulas is to combine surgery with anti-TNF therapy [103]. A surgical approach is necessary for recognizing presence of abscess and fistula extension, besides draining the involved tissues from infection. The placement of seton, a common method for continued drainage, followed by infliximab infusion and immunosuppressive drugs seems to induce greater fistula healing response [106]. Despite its low long-term success, bowel diversion may be elected for refractory perianal disease, and then anti-TNF therapy (combined or not to immunomodulators) should be reintroduced, as an attempt to achieve perianal healing.

Internal fistulas, such as rectovaginal or enterovesical (i.e. colovesical), have similar management, starting with immunomodulator therapy, usually followed by surgical intervention [107]. Immunomodulators (AZA, 6-MP), anti-TNF agents or both can be applied, as a strategy to induce mucosal inflammation healing. Then, excision of the fistula (for rectovaginal form) or of inflamed bowel (for colovesical form) with tissue reconstruction are usually performed [67].

Medical management for maintenance of remission in Crohn’s disease

After the initial management of acute Crohn’s disease, the establishment of sequential treatment requires a careful assessment of patient clinical condition and clinical history. Important factors to take into consideration are the course and extent of disease, as well as the response of the patient to prior treatments applied to induce and/or maintain remission [86]. Besides that, other limitations and patient’s active participation should be considered for guiding the process.

First presentation of localized disease

For those patients who have achieved remission with corticosteroids, AZA (2–2.5 mg/kg daily) is the preferred prescription, followed by 6-MP (at doses 1-1.5 mg/kg/day), another thiopurine, which should be also considered before methotrexate [108]. Moreover, no maintenance treatment is conceivable for some patients.

Relapse of localized disease

In this case, azathioprine should be a primary therapy for preventing disease progression. Corticosteroids are contraindicated for maintenance therapy even budesonide usage should be avoided [93]. If relapse occurs when patient is already receiving thiopurines as maintenance therapy, their doses can be swelled (AZA > 2.5mg/kg/day or 6-MP > 1.5mg/ kg/day) with correct monitoring of leukopenia and/or 6-thioguanine concen-

trations [108].

Extensive disease

AZA (2–2.5 mg/kg day) remains as first-line maintenance therapy [108]. If disease presents a severe behavior or poor prognosis, anti-TNF therapy should be considered.

Steroid-dependent disease

The current data that supports maintenance therapy for patients with steroid-dependent CD and without previous exposure to immunosuppressive therapies suggests 2 possible options: A "step-up" approach, with introduction of immunomodulators (AZA, 6-MP or MTX), and then, adding anti-TNF if necessary [100]; or a "top-down" approach, including early introduction of biological therapy [109]. Thereafter, if clinical remission is achieved, maintenance therapy should follow the same established regimen, either with biological monotherapy or combined to thiopurines [86].

Duration of maintenance therapy in CD

Maintenance therapy based on thiopurine usage may be discontinued if sustained remission is achieved in lack of objective signs of inflammation. For greater assurance, endoscopic assessment is advised, even when symptoms are not reported, since factual mucosal healing is associated with diminished hospitalization and surgery in the future [86].

Anti-TNF therapy may be extended if needed, despite its association with increased risk of melanoma and lymphoproliferative disorders, especially when combined with thiopurines [110,111]. In case of loss of response to anti-TNF therapy, the first strategy should be dose optimization or moving to another anti-TNF formula if remission is still unachievable [109].

Surgery in crohn's disease

The primary treatment for Crohn's disease is reserved to gastroenterologists and medical management. However, it is important to consider the value of surgery and its risks and benefits for symptom relief, quality of life and efficient therapy [112]. Therefore, it is convenient that the therapeutic set should be agreed among patient, physician and surgeon. So, when needed, an early surgical consultation is recommended.

Surgery is usually indicated in Crohn's disease for those patients with complications derived from strictures, fistulizing disease, intestinal perforation, intra-abdominal abscess, gastrointestinal hemorrhage, malignancy, growth restriction in children and medically non-responsive disease [113].

It is currently stated that extensive resection is unnecessary and may be harmful [112]. So, segmented bowel resections have been mostly indicated in case of small bowel obstruction or penetrating CD. Intra-abdominal abscess concomitant to luminal CD may also require surgical resection, but the best recommendation is introducing antimicrobial therapy and draining it before any intervention [113]. Percutaneous drainage procedures, like ultra sonographic or computed tomography-guided drainage, can be efficient as less invasive approaches and then may be followed for delayed surgical resection, or even CD medical treatment in some patients [101,114].

Postoperative Crohn's disease

One of the major concerns about intestinal resection in patients with CD is avoiding recurrence, i.e. reappearance of lesions or symptoms after surgical resection. Because of this, some risk factors (e.g. presence of penetrating disease, previous surgeries) should be considered and avoided when possible, especially tobacco smoking after surgery [115]. Besides that, prophylactic medication should be introduced.

No treatment is acceptable for non-smokers without risk factors or significant risk of recurrence. For patients with moderate risk of CD recurrence, thiopurine-based monotherapy or combined with an antibiotic should be initiated [116]. Metronidazole (1g/day) combined to AZA (100-150mg/day) may be suitable for this role [117].

However, despite having prophylactic medical treatment or not, all patients should undergo a colonoscopy at 6 months after surgery, in order to assess intestinal mucosa and investigate eventual CD recurrence [116]. If there is indication of CD, then anti-TNF agents may be added to therapy [118].

For those patients with high-risk of CD recurrence or intolerant or refractory to immunomodulators, anti-TNF is stated as the best primary therapy for preventing postoperative Crohn's disease [116]. In this case, combining infliximab with azathioprine is also suggested for reducing loss of response to treatment and even achieving greater outcomes. The same regimen is valid if the patient has a history of previous resection in the last 10 years.

Ulcerative colitis

The therapy for ulcerative colitis is expressively focused on the improvement of patients' quality of life, since, until nowadays, the etiology of this intestinal disease is not well-explained, which limits better results and still makes the cure hard to conceive. Its treatment, as in other IBDs, is based on the disease degree (mild, moderate or severe) and in its extension, since inflammation proportion must be analyzed. The main goals of treatment are the symptoms relief and reducing inflammation [119].

Proctitis-mild or moderate

In this type of clinical manifestation of ulcerative colitis, the inflammation is limited to the rectal area and is usually considered less severe. Because of disease localization, its treatment is based on the usage of topical medications, as mesalazine suppositories, which may guarantee higher drug concentrations locally. For this therapy, the recommended dose is of 1g daily. In addition, others therapies such as the use of combined oral and topical aminosalicylates might be more effective in the treatment, mainly in cases where there is no improvement with use of topical mesalazine and the proctitis is persistent, must being treated as extensive colitis [120]. This medicine works by blocking production of prostaglandins and leukotrienes by colon epithelium, interfering in inflammatory response and lessening it, making possible the improvement of the symptoms [121].

Left sided colitis-mild or moderate

The treatment recommended for this type of manifestation is the usage of mesalamine topical and oral combined, since studies have demonstrated significant improvements in clinical condition of those patients in use of this combination in comparison with the oral use only. For this therapy, the oral use recommended ranges from 2,4g to 4.8g daily, sendo this last most beneficial for patients with moderate degree of disease. The stated topical dose is 1g per day, and can be elevated based on the patient's necessity [122]. If disease remission does not

happen, the usage of corticosteroids, such as prednisone, might be an alternative, not exceeding 60 mg per day. So, after patient condition improvement, the doses of the drugs must be decreased approximately 5 - 10 mg weekly, aiming not to generate negative effects [123]. These drugs work similarly to aminosalicylates blocking the production of prostaglandins, besides interfere in production of pro-inflammatory cytokines, change vascular permeability, among others, causing immunosuppression [121]. Lastly, in cases where corticotherapy and aminosalicylates have no significant effects on patient's response, such as in more severe degrees, the introduction of immunomodulators, like azathioprine and infliximab, might be a solution [124].

Pancolitis-mild or moderate

"Pancolitis'' means that inflammation has extended for the areas of proximal colon and rectum. Patients with this type of clinical manifestation might make use of oral sulfasalazine and mesalazine, being reserved to doctor the choice of what medication should be used to start therapy. The sulfasalazine dose recommended is in the range of 2 - 4g daily, which may be administered once or divided in twice. The mesalamine oral doses remain between 2 - 4.8g daily, while the topical dose of this medication stayed at 1g per day. If patient's condition improvement and symptoms relief are not achieved, it is recommended to progress for corticotherapy of 1 mg/kg/day and then for azathioprine 2-2,5 mg/kg/day if the condition persists. Lastly, if the patient does not respond to therapies cited before, biological therapies might be used [125].

Severe colitis

In this situation, the primary therapy may be based on oral corticosteroids and aminosalicylates. Alternatively, patients with corticosteroid addiction risk must start with immunosuppressant [126]. When there is no good response for conventional treatment, biological therapies, with infliximab dose 5mg per day, might be an alternative. Besides that, studies have demonstrated improvement in results of patients who made use of infliximab and azathioprine combined, instead of monotherapy with infliximab. Another possible biological therapy is the use of adalimumab, where it demonstrated best results in comparison with placebo. The recommended dose is 160 mg initially, 80 mg in the second week and maintenance with 40 mg every two weeks [125].

Severe acute colitis

Initially, the patients must be taken to intensive care units, where they will receive, firstly, hydrolytic support, research for anemia, nutritional assessment and, obligatorily, they must receive therapy against thromboembolic events [127]. The medication recommended is prednisone, with intravenous doses within 300-400 mg daily, portioned in three or four administrations. Subsequently, if treatment does not have good results, it is started the use of intravenous cyclosporine 2 mg/kg/day for seven days. After this, if treatment has good results, it is switched to oral cyclosporine 5 mg/kg in two doses for 12 weeks. Then, azathioprine 2 a 2,5 mg/kg might be used for gradual reduction of corticosteroid doses, aiming to remove it without generating negative effects for the patient. Cases in which cortico therapy has not shown good results or does not have results, cyclosporine or infliximab might be used as rescue therapy, at recommended doses of 2 and 5 mg/kg/day, respectively. During all therapy, the patients must be monitored, since there is a possibility of treatment failure and not clinical remission, requiring surgical intervention, such as colectomy [126].

Surgery in ulcerative colitis

Normally, drug therapy can control the symptoms and ensure the remission of inflammation, no need for surgical intervention; however, some patients do not present improvement with therapy or exhibit worsening of case. The surgery happens in a minority of cases, ranging from 23% to 45% of patients and might be optional in some cases, such as patients who do not respond anymore to non-surgical treatments [128]. Besides, there are cases where the surgery is obligatory, such as cancer risk, where cancer of colorectal can lead to death, emergency problems, due crisis in condition clinical of patient or when the medications themselves cause more troubles to quality of life of patient than treat the disease [129].

Before the realization of surgical intervention, it is very important to evaluate the clinical condition of the patient, considering the benefits as much as the harms, aiming at the best prognosis for the patient. The proctocolectomy is one of the available procedures and it can be done in two ways. In the first one, occurs the removal of the rectum, all colon, and anal canal, whereas the small intestine is anastomosed to an external-collector bag, performing an ileostomy. Another option is the restorative method, in which there is no removal of the anus, butonly of the colon and rectum and, posteriorly, the ileum is connected to the anus. The colectomy, another surgical alternative, can also be performed in two ways, with or without ileorectal anastomosis. When this last one is chosen, the ileostomy can be definitive or temporary, being the small intestine, posteriorly, connected to the rectum [130].

Important points

- Inflammatory bowel disease aggregates two specific conditions: Crohn's Disease and Ulcerative Colitis; both with worldwide distribution.
- CD has a higher incidence in Ashkenazi Jews, in urban populations and in regions located in the northern hemisphere; being more prevalent in individuals from 20 to 40 years old.
- UC can lead to extra intestinal symptoms in eyes, liver, joints, and skin.
- IBD is a condition of industrialized societies. Being registered since the 18th century Industrial Revolution.
- The first countries to register IBD cases were located in Western Europe, North America and Oceania. Today, it presents a growing prevalence in South America, Africa and Asia newly industrialized countries.
- The pathophysiological process occurs through the contribution of genetics and environmental factors.
- In CD, some factors interfere with the harmonic relationship between the intestinal microbiota and the mucosal immune system:

  Greater permeability of the epithelial layer, facilitating the entry of pathogenic microorganisms to layers below the mucosa.

  Abnormal Paneth cells with disorganized or decreased granules.

  Fewer expressions of TLR3 and an increase in expression

of TLR4.

Expression of risk variants of NOD2 or ATG16L1 linked to Crohn's disease.

Imbalance between effector T cells and Treg cells.

- In UC, mucus production is decreased while the colon permeability is increased, which induces an exaggerated immune response.
- In UC, innate and adaptive immune cells are highlyactivated in the lamina propria.
- Th2 production is affected, producing IL-13, which affects tight-junctions and causes apoptosis. Consequently, the lumen permeability is increased.
- The interruption of the barrier function induces an amplified immune response.
- The inflammatory reaction affects the rectum motility, increasing bowel movements and secretion production that leads to diarrhea, which can occur with blood and pus.
- During the relapses the severity of symptoms of Inflammatory Bowel Disease (IBD) varies from mild to severe and during remissions many of them may disappear or decrease.
- Abdominal pain, diarrhea, blood to the defecation, abdominal masse and distension and perianal disease and fistulas can be appearance in patients with inflammatory bowel disease.
- The main inflammatory bowel disease is CD and UC. Both are idiopathic and with clinical conditions that may extend for years with diarrhea of prolonged and recurrent evolution.
- The extra-intestinal most common IBD manifestation is the arthritis and the nodosum erythema is the most common cutaneous lesion.
- A well-constructed history of the present illness and physical examination can assist in the diagnosis of IBD and decide on invasive or non-invasive methods to help guide clinical management.
- The main non-invasive diagnostic methods are:

  Blood count, with CRP test, ESR, ANCA and ASCA

  Stool examination, with analysis of markers of inflammatory processes such as Fecal Calprotectin and Lactoferrin.
- As non-invasive procedures, transabdominal ultrasound, intestinal transit, tomography enterography, MRI and capsule endoscopy can be used in the diagnosis.
- Endoscopy, colonoscopy and double-balloon enteroscopy can be used as invasive procedures in the diagnosis of inflammatory bowel disease.
- Infectious colitis and intestinal tuberculosis are differential diagnosis for IBD and should be analyzed.
- Patterns of ANCA and ASCA tests can indicate the development of Crohn's Disease or Ulcerative Colitis.

Usually, the positive test for p-ANCA and negative tests for ASCA suggest UC and positive tests for ASCA and negative tests for p-ANCA suggest CD.

- Treatment guidelines for both Crohn's disease and Ulcerative colitis share similar approaches and drug classes.
- The appropriate diagnosis and classification of IBD activity level, behavior and extension should guide a better therapeutic itinerary.
- The medical management of CD may be organized in induction of remission, followed by maintenance therapy.
- Relapses or inadequate response may require dose optimization or therapy switching.
- Risks and benefits of each medical therapy available should be discussed and balanced before prescription.
- Antibiotics should be reserved for fistulizing CD treatment or postoperative CD prophylaxis.
- Corticosteroid long-term usage is not recommended, due to its harmful side effects and low effectiveness for maintenance therapy in CD.
- Immunomodulators can be useful as steroid-sparing agents or adjunctive therapy with anti-TNF agents.
- Biological therapies are usually the last-line medical therapy, though its early usage may be effective in some cases.
- Surgical intervention may be suitable for enteric complications of CD and clinical remission induction.
- Colonoscopy is recommended for all patients at 6 months after surgery, in order to investigate eventual CD recurrence.
- The focus of therapy for Ulcerative Colitis is, mainly, the improvement of patient'squality of and relief of symptoms.
- The drugs used for therapy of Ulcerative Colitis are based in the inflammation localization and disease degree.
- In proctitis, due to localization distal of inflammation, the recommended treatment is the use of topical aminosalicylates.
- Patients with proctitis in mild or moderate degree who did not respond to conventional therapy and made use of the therapies based on the use of oral and topical aminosalicylates combined, presented best results. This combination might be used for the treatment of left sided colitis too.
- The biological therapy might be used for the treatment of pancolitis mild and moderate, in cases in which the initial therapy did not present good results.
- Patients with cases of severe colitis and with corticosteroids addiction risk can make use of immunosuppressant initially, instead conventional therapy.

- In the severe acute colitis, the patients must be taken to intensive care units to be examined and received the necessary support. They must be monitored during all treatment, since failures in therapy might lead to surgical interventions.
- The surgical intervention of Ulcerative Colitis is recommended in cases wherein drugs therapy did not succeed. Must consider the impacts positive and negative of this procedure in patients' lives before its realization.

References

1. Borg-Bartolo SP, Boyapati RK, S atsangi J, Kalla R. Precision medicine in inflammatory bowel disease: Concept, progress and challenges. F1000Res. 2020; 9.
2. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Disease-a-Month. 2018; 64: 20-57.
3. Baumgart DC, Sandborn WJ. Crohn's disease. The Lancet. 2012; 380: 1590-1605.
4. Hugot JP, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, et al. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature. 1996; 379: 821-823.
5. Feuerstein JD, Cheifetz AS. Ulcerative colitis: Epidemiology, diagnosis, and management. InMayo Clinic Proceedings. 2014; 89: 1553-1563.
6. Frolkis A, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, et al. Environment and the inflammatory bowel diseases. Canadian Journal of Gastroenterology and Hepatology. 2013; 27: e18-24.
7. Z wi AB & Mills A. Health policy in less developed countries: Past trends and future directions. Journal of International Development. 1995; 7: 299-328.
8. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017; 152: 313-321.
9. Frolkis A, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, et al. Environment and the inflammatory bowel diseases. Canadian Journal of Gastroenterology and Hepatology. 2013; 27: e18-24.
10. Kaplan GG. The global burden of IBD: From 2015 to 2025. Nature Reviews Gastroenterology & Hepatology. 2015; 12: 720-727.
11. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, et al.Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. The Lancet. 2017; 390: 2769-2778.
12. Veauthier B, Hornecker JR. Crohn's Disease: Diagnosis and Management. Am Fam a Physician. 2018; 98: 661-669.
13. Neurath MF. Targeting immune cell circuits and trafficking in inflammatory bowel disease. Nat Immunol. 2019; 20: 970-979.
14. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Fatores de risco ambientais para doenças inflamatórias intestinais: Revisão da literature baseada em evidências. World J Gastroenterol. 2016; 22: 6296-6317.
15. Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Invest. 2007; 117:514-521.
16. Mazal J. Crohn disease: Pathophysiology, diagnosis, and treatment. Radiol Technol. 2014; 85: 297-316.
17. Salzman NH, Hung K, Haribhai D, Chu H, Karlsson-Sjöberg J, et al. Enteric defensins are essential regulators of intestinal microbial ecology. Nature immunology. 2010; 11: 76-83.
18. Cadwell K, Liu JY, Brown SL, Miyoshi H, Loh J, et al. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature. 2008; 456: 259-263.
19. Pinho M. A Biologia molecular das doenças inflamatórias intestinais. Revista Brasileira de Coloproctologia. 2008; 28: 119-123.
20. Baumgart DC, Carding SR. Inflammatory bowel disease: Cause and immunobiology. Lancet. 2007; 369: 1627-1640.
21. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: Current state of the art. Nat Rev Gastroenterol Hepatol. 2016; 13: 13-27.
22. Cooney R, Baker J, Brain O, Danis B, Pichulik T, et al. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. Nature medicine. 2010; 16: 90.
23. Abbas AK, Lichtman AH, Pillai S. Imunologiacelular e molecular. 8. ed. Rio de Janeiro: Elsevier. 2015.
24. Gabbani T, Deiana S, Marocchi M, Annese V. Genetic risk variants astherapeutic targets for Crohn's disease. Expert OpinTher Targets. 2017; 21: 381-390.
25. Hindryckx P, Jairath V, D'Haens G. Acute severe ulcerative colitis: From pathophysiology to clinical management. Nat Rev Gastroenterol Hepatol. 2016; 13: 654-664.
26. Ordás I, Eckmann L, Talamini M, Baumgart D, Sandborn W. Ulcerative colitis. The Lancet. 2012; 380: 1606-1619.
27. Head KA, Jurenka JS. Inflammatory bowel disease part 1: Ulcerative colitis-pathophysiology and conventional and alternative treatment options. Alternative Medicine Review. 2003; 8: 247-283.
28. Sarlos P, Kovesdi E, Magyari L, Banfai Z, Szabo A, et al. Genetic update on inflammatory factors in ulcerative colitis: Review of the current literature. World Journal of Gastrointestinal pathophysiology. 2014; 5: 304-321.
29. Lynch WD, Hsu R. Ulcerative Colitis. 2019.
30. Ardizzone S. Ulcerative colitis. Orphanet. 2003; 1-8.
31. Guyton AC & Hall JE (1956). Textbook of Medical Physiology (Tratado de FisiologiaMédica). 13ª ed. Rio de Janeiro, Elsevier, 2017.
32. Barbieri D. Doenças inflamatórias intestinais. Jornal de Pediatria. 2000; 76: 173-180.
33. Moazzami B, Moazzami K, Rezaei N. Early onset inflammatory bowel disease: manifestations, genetics and diagnosis. Turk J Pediatr. 2019; 61: 637-647.
34. Luo YY, Chen J. [Clinical and colonoscopic characteristics of pediatric inflammatory bowel disease]. Zhonghua E rKe Za Zhi. Chinese. 2009; 47: 129-133.
35. Derkacz A, Olczyk P, Komosinska-Vassev K. Diagnostic Markers for Nonspecific Inflammatory Bowel Diseases. Dis Markers. 2018; 2018: 7451946
36. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019; 12: 113-122.
37. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology. 2007; 133: 1670-1689.
38. Maranhão DDA, Vieira A, Campos T. Características e diagnóstico diferencial das doenças inflamatórias intestinais. Jornal Brasileiro de Medicina. 2015; 103.

39. Fengming Y, Jianbing W. Biomarkers of inflammatory bowel disease. Dis Markers. 2014; 2014: 710915.

40. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis. 2004; 10: 661-665.

41. Chang S, Malter L, Hudesman D. Disease monitoring in inflammatory bowel disease. World J Gastroenterol. 2015; 21: 11246-11259.

42. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: Useful, magic, or unnecessary toys? Gut. 2006; 55: 426-431.

43. Schappo F. Pesquisa de anticorpos contra estruturas citoplasmáticas do neutrófilo (ANCA) e contra o Saccharomyces cerevisiae (ASCA) na doença inflamatória intestinal. 2007. Dissertação (Mestradoem Gastroenterologia Clínica) - Faculdade de Medicina, Universidade de São Paulo, São Paulo. 2007.

44. Cappello M, Morreale GC. The Role of Laboratory Tests in Crohn's Disease. Clin Med Insights Gastroenterol. 2016; 9: 51-62.

45. Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. Gastroenterology. 2011; 140: 1817-1826.

46. Waugh N, Cummins E, Royle P, Kandala NB, Shyangdan D, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: Systematic review and economic evaluation. 2013; 17: xv-211.

47. Kane SV, Sandborn WJ, Rufo PA, Zholudev A, Boone J, et al. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. The American journal of gastroenterology. 2003; 98: 1309-1314.

48. Dietrich CF. Significance of abdominal ultrasound in inflammatory bowel disease. Dig Dis. 2009; 27: 482-493.

49. Allocca M, Fiorino G, Bonifacio C, Furfaro F, Gilardi D, et al. Comparative accuracy of bowel ultrasound versus magnetic resonance enterography in combination with colonoscopy in assessing Crohn's disease and guiding clinical decision-making. Journal of Crohn's and Colitis. 2018; 12: 1280-1287.

50. Associação Brasileira de Colite Ulcerativa e Doença de Chron. Ecames: Quaissão e comosãofeitosos principaismétodos de diagnósticos das Doenças Inflamatórias Intestinais. Revista da Associação Brasileira de Colite Ulcerativa e Doença de Crohn. Brasil. 2013.

51. Amitai MM, Ben-Horin S, Eliakim R, Kopylov U. Magnetic resonance enterography in Crohn's disease: A guide to common imaging manifestations for the IBD physician. J Crohns Colitis. 2013; 7: 603-615.

52. Gee MS, Harisinghani MG. MRI in patients with inflammatory bowel disease. J MagnReson Imaging. 2011; 33: 527-534.

53. Collins PD. Endoscopia com cápsula de vídeonadoença inflamatória intestinal. World J GastrointestEndosc. 2016; 8: 477-488.

54. Health Quality Ontario. Capsule Endoscopy in the Assessment of Obscure Gastrointestinal Bleeding: An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2015; 15: 1-55.

55. Tharian B, George N, Navaneethan U. Endoscopy in the Diagnosis and Management of Complications of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016; 22: 1184-1197.

56. Spiceland CM, Lodhia N. Endoscopia nadoença inflamatória intestinal: Papel no diagnóstico, tratamento e tratamento. World J Gastroenterol. 2018; 24: 4014-4020.

57. Pata C, Akyüz Ü, Erzın Y, Mercan A. Double-balloon enteroscopy: The diagnosis and management of small bowel diseases. Turk J Gastroenterol. 2010; 21: 353-359.

58. Huang Z, Liu X, Yang F, Wang G, Ge N, et al. Diagnostic efficacy of double-balloon enteroscopy in patients with suspected isolated small bowel Crohn's disease. BMC gastroenterology. 2020.

59. Mendes WB, Batista CA, Lima HA, Leite GF, Paula JF, et al. Tuberculose intestinal como causa de obstrução intestinal: Relato de caso e revisão de literatura. Revista Brasileira de Coloproctologia. 2009; 29: 489-492.

60. Larsson G, Shenoy T, Ramasubramanian R, Balakumaran LK, Småstuen MC, et al. Routine diagnosis of intestinal tuberculosis and Crohn's disease in Southern India. World Journal of Gastroenterology: WJG. 2014; 20: 5017-5024.

61. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol. 1993; 88: 989-999.

62. Tontini GE, Vecchi M, Pastorelli L, Neurath MF, Neumann H. Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives. World J Gastroenterol. 2015; 21: 21-46.

63. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; Colitis Foundation of America, Bousvaros A et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: Report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. J Pediatr Gastroenterol Nutr. 2007; 44: 653-674.

64. Mitsuyama K, Niwa M, Takedatsu H, Yamasaki H, Kuwaki K, et al. Antibody markers in the diagnosis of inflammatory bowel disease. World J Gastroenterol. 2016; 22: 1304-1310.

65. Turner JR, Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. São Paulo: Elsevier Editora. 2016.

66. Pontte ACA, Damião AOMC, Rosa AM. Consensus guidelines for the management of inflammatory bowel disease. Brazilian Study Group of Inflammatory Bowel Disease. Arquivos de Gastroenterologia. 2010; 47: 313-325.

67. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, et al. ACG clinical guideline: Management of Crohn's disease in adults. American Journal of Gastroenterology. 2018; 113: 481-517.

68. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976; 3: 439-444.

69. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980; 315: 514.

70. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut. 2006; 55: 749-753.

71. Kuenzig ME, Lee SM, Eksteen B, Seow CH, Barnabe C, et al. Smoking influences the need for surgery in patients with the inflammatory bowel diseases: A systematic review and meta-analysis incorporating disease duration. BMC gastroenterology. 2016;16: 143.

72. Singh S, Graff L, Bernstein C. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol. 2008; 104: 1298-1313.

73. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, et al. Antibiotic therapy in inflammatory bowel disease: A systematic review

and meta-analysis. American Journal of Gastroenterology. 2011; 106: 661-673.

74. Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, Rodríguez IV, Ferreiro R, et al. Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. Inflammatory bowel diseases. 2014; 20: 92-102.

75. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2010; 12: CD008870.

76. Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, et al. Efficacy of 5-aminosalicylates in Crohn's disease: Systematic review and meta-analysis. American Journal of Gastroenterology. 2011; 106: 617-629.

77. Irving PM, Gearry RB, Sparrow MP, Gibson PR. Review article: Appropriate use of corticosteroids in Crohn's disease. Aliment PharmacolTher. 2007; 26: 313-329.

78. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, et al. Canadian Inflammatory Bowel Disease Study Group: Oral budesonide for active Crohn's disease. N Engl J Med. 1994; 331: 836-841.

79. Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. British Society of Gastroenterology. Gut. 2000; 46: I1-8.

80. Borgaonkar MR, Mac Intosh DG, Fardy JM. A meta-analysis of anti mycobacterial therapy for Crohn's disease. Am J Gastroenterol. 2000; 95: 725-729.

81. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: Benefits outweigh the risk of lymphoma. Gastroenterology. 2000; 118: 1018-1024.

82. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: A network meta-analysis. Gastroenterology. 2015; 148: 344-354.

83. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005; 128: 1812-1818.

84. Chan ES, Cronstein BN. Mechanisms of action of methotrexate. Bull Hosp Jt Dis. 2013; 71: S5-8.

85. McDonald JW, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane database of systematic reviews. 2014; 8: CD003459.

86. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. Journal of Crohn's and Colitis. 2017; 11: 3-25.

87. Herfarth HH, Kappelman MD, Long MD, Isaacs KL. Use of methotrexate in the treatment of inflammatory bowel diseases. Inflammatory bowel diseases. 2016; 22: 224-233.

88. Gerriets V, Bansal P, Khaddour K. Tumor Necrosis Factor (TNF) Inhibitors. [Updated 2019 Dec 24]. In: StatPearls [Internet]. 2019.

89. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. New England Journal of Medicine. 2010; 362: 1383-1395.

90. McLean LP, Cross RK. Integrin antagonists as potential therapeutic options for the treatment of Crohn's disease. Expert Opin Investig Drugs. 2016; 25: 263-273.

91. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, et al. European Cooperative Crohn's Disease Study (ECCDS): Results of drug treatment. Gastroenterology. 1984; 86: 249-266.

92. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2007; 1: CD000542.

93. Kuenzig ME, Rezaie A, Kaplan GG, Otley AR, Steinhart AH, et al. Budesonide for the induction and maintenance of remission in Crohn's disease: Systematic review and meta-analysis for the Cochrane collaboration. Journal of the Canadian Association of Gastroenterology. 2018; 1: 159-173.

94. Rezaie A, Kuenzig ME, Benchimol EI. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2015; 6: CD000296.

95. Feldman PA, Wolfson D, Barkin JS. Medical management of Crohn's disease. Clin Colon Rectal Surg. 2007; 20: 269-281.

96. Warshaw AL, Welch JP, Ottinger LW. Acute perforation of the colon associated with chronic corticosteroid therapy. Am J Surg. 1976; 131: 442-446.

97. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews. 2015; 10: Cd000067 .

98. Rampton DS. Methotrexate in Crohn's disease. Gut. 2001; 48: 790-791.

99. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. New England Journal of Medicine. 2016; 375: 1946-1960.

100. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004; 53: v1-v16.

101. Nguyen DL, Sandborn WJ, Loftus Jr EV, Larson DW, Fletcher JG, et al. Similar outcomes of surgical and medical treatment of intra-abdominal abscesses in patients with Crohn's disease. Clinical Gastroenterology and Hepatology. 2012; 10: 400-404.

102. Levy C, Tremaine WJ. Management of internal fistulas in Crohn's disease. Inflamm Bowel Dis. 2002; 8: 106-111.

103. Marzo M, Felice C, Pugliese D, Andrisani G, Mocci G, et al. Management of perianal fistulas in Crohn's disease: An up-to-date review. World J Gastroenterol. 2015; 21: 1394-1403.

104. Gecse KB, Bemelman W, Kamm MA, Stoker J, Khanna R, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014; 63: 1381-1392.

105. Aguilera-Castro L, Ferre-Aracil C, Garcia-Garcia-de-Paredes A, Rodriguez-de-Santiago E, Lopez-Sanroman A. Management of complex perianal Crohn's disease. Ann Gastroenterol. 2017; 30: 33-44.

106. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, et al. Combined seton placement, infliximab infusion, and maintenance immune suppressives improve healing rate in fistulizing anorectal Crohn's disease: A single center experience. Dis Colon Rectum. 2003; 46: 577-583.

107. Kaimakliotis P, Simillis C, Harbord M, Kontovounisios C, Rasheed S, et al. systematic review assessing medical treatment for rectovaginal and enterovesical fistulae in Crohn's disease. Journal of clinical gastroenterology. 2016; 50: 714-721.

108. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's and Colitis. 2010; 4: 28-62.

109. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: When to start, when to stop, which drug to choose, and how to predict response? [published correction appears in Am J Gastroenterol. 2011; 106:375. Watermayer, G [corrected to Watermeyer, G]]. Am J Gastroenterol. 2011; 106: 199–213.

110. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology. 2012; 143: 390-399.

111. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immune modulator therapy for the treatment of Crohn's disease: A meta-analysis. Clin Gastroenterol Hepatol. 2009; 7: 874-881.

112. Gionchetti P, Dignass A, Danese S. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. Journal of Crohn's and Colitis. 2017; 11: 135-149.

113. Lewis RT, Maron DJ. Efficacy and complications of surgery for Crohn's disease. Gastroenterol Hepatol (NY). 2010; 6: 587-596.

114. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A Meta-analysis of Percutaneous Drainage Versus Surgery as the Initial Treatment of Crohn's Disease-related Intra-abdominal Abscess. Journal of Crohn's and Colitis. 2016; 10: 202-208.

115. Avidan B, Sakhnini E, Lahat A, Lang A, Koler M, et al. Risk factors regarding the need for a second operation in patients with Crohn's disease. Digestion. 2005; 72: 248-253.

116. Nguyen GC, Loftus EV, Hirano I, Falck–Ytter Y, Singh S, Set al. American Gastroenterological Association Institute guideline on the management of Crohn's disease after surgical resection. Gastroenterology. 2017; 152: 271-275.

117. D'Haens GR, Vermeire S, Van Assche G, Noman M, Aerden I, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: A controlled randomized trial. Gastroenterology. 2008; 135: 1123-1129.

118. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: A prospective pilot study. Inflamm Bowel Dis. 2009; 15: 1460-1466.

119. Associação Brasileira de ColiteUlcerativa e Doença de Crohn. Viver com a retocoliteulcerativa. Brazil. 2017.

120. Meier J, Sturm A. Current treatment of ulcerative colitis. World Journal Gastroenterology. 2011; 17: 3204-3212.

121. Santos Jr JCM. Reto colite ulcerativa-Diagnóstico e tratamento clínico-Parte II. Revista Brasileira de Coloproctologia. 1999; 19: 114-221.

122. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. Journal of Crohn's and Colitis. 2017; 11: 769-784.

123. Kornbluth A, Sachar DB, MACG. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. The American Journal of Gastroenterology. 2010; 105: 501-523.

124. Kayal M, Shah S. Ulcerative Colitis: Current and Emerging Treatment Strategies. 2020; 9: 94.

125. Teixeira FV, Hosnee RS, Sobrado CW. Management of ulcerative colitis: A clinical update. Journal of Coloproctology. 2015; 34: 230-237.

126. Comissão Nacional de Incorporação de Tecnologias no SUS. ProtocoloClínico e Diretrizes Terapêuticas Retocolite UlcerativA. Brazil. 2019.

127. Sobrado CW, Sobrado LF. Manejo da coliteulcerativa grave: Atualização terapêutica. Arquivos Brasileiro de Cirurgia Digestiva. 2016; 29: 201-205.

128. Associação Brasileira de Colite Ulcerativa e Doença de Crohn. Cirurgia para Doença de Crohn e Retolite Ulcerativa. Brazil. 2019

129. Bohl JL Bohl, Sobba K. Indications and Options for Surgery in Ulcerative Colitis. The Surgical clinics of North America. 2015 95: 1211-1232.

130. Crohn's & Colitis UK. Surgery for Ulcerative Colitis. England. 2014.