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# CONSENSUS GUIDELINES FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Brazilian Study Group of Inflammatory Bowel Diseases*

**ABSTRACT** - This is the first Brazilian Consensus on inflammatory bowel disease, carried out by the Brazilian Study Group of Inflammatory Bowel Disease, and discusses the treatment of Crohn's disease and ulcerative colitis in acute and remission phases. The first part of the text, brings out a review on the main drugs used in the treatment of inflammatory bowel disease, as well as their mechanisms of action and cautions during their use. In the second part, the committee's opinions about the most recommended medical and surgical approaches for both diseases are presented on the basis of disease activity, location and behaviour status. The recommendations here presented were widely discussed in several scientific meetings with active participation of all members of the group and were highly based on scientific evidence covered by the literature.

**HEADINGS** – Crohn disease. Colitis, ulcerative. Consensus.

**TABLE OF CONTENTS**



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## 1. INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the main inflammatory bowel diseases. They are caused by the interaction of genetic factors, intestinal microbiota and mucosal immunoregulation[12, 24, 45, 81].

UC compromises the rectum and colon, whereas CD may occur in any part of the digestive tract, from the mouth to the anus, but the ileal and ileocecal region are its main targets. CD involves the whole intestinal wall (transmural inflammation) and causes a non-caseating granulomatous reaction.

UC clinical picture depends on the extension and severity of the disease. UC is best evaluated using a colonoscopy (Figure 1), while its severity, by means of a clinical evaluation or using the Truelove and Witts index (Figure 2).

| | |
|---|---|
| Distal UC | Proctitis- inflammation of the rectal mucosa within 15 cm of the dentate line |
| | Proctosigmoiditis – mucosal inflammation of the mucosa within 25-30 cm of the dentate line |
| Left-sided UC | Mucosa inflammation up to splenic flexure (sometimes up to distal transverse colon) |
| Pancolitis | Mucosal inflammation up to proximal transverse colon and beyond |

**FIGURE 1.** Ulcerative colitis (UC) classification according to the anatomic extension of the inflammation (colonoscopic evaluation)

| | Mild | Moderate | Severe |
|---|---|---|---|
| 1. Number of evacuations/day | ≤4 | 5 | ≥6 |
| 2. Bright-red blood in stool | ± | + | + + |
| 3. Temperature (°C) | Normal | Intermediate values | Average temperature at night >37.5 °C or ≥37.8° C in 2 days within 4 days |
| 4. Pulse (bpm) | Normal | Intermediate | >90 bpm |
| 5. Hemoglobin(g/dL) | >10 | Intermediate | ≤10.5 |
| 6. *HSS (mm,1st hour) | ≤30 | Intermediate | >30 |

*HSS = Hemosedimentation speed

**FIGURE 2.** Classification of nonspecific ulcerative colitis (UC) according to severity of acute episode (Truelove & Witts[93])

An easy way to classify UC as severe is to consider six or more bloody evacuations a day with at least one of the following alterations: a) fever (>37.5°C); b) tachycardia (>100 bpm); c) anemia (red blood cells <10 g/dL); d) HSS >30 mm, 1st hour; e) albumina <3.5 g/dL[6].

Fulminant UC is diagnosed when the patient has more than 10 bloody evacuations (enterorrhagia), fever, tachycardia, need for blood transfusion, marked alterations in inflammatory bowel disease (IBD) activity tests (e.g., HSS >30 mm, 1st hour), with or without toxic megacolon, (dilated transverse colon >6 cm) or intestinal perforation.

UC is evaluated according to the extension of the disease, as follows:

**a) Distal UC:** usually mild and moderate cases often with rectal bleeding and mucus and pus in stool and tenesmus. Diarrhea occurs in 80% of cases, however there may be constipation. Abdominal pain is usually cramp-like, preceding evacuations and is not fully relieved after colon rectal emptying. Patients may complain of urgency, incontinence and anorectal pains. Extraintestinal manifestations are less frequent (Figure 3).

| Manifestations | UC | Crohn | Relationship with disease activity |
|---|---|---|---|
| Rheumatologic | | | |
| • Arthralgia/arthritis | 6%–30% | 15%–35% | + |
| • Sacroiliitis | 5%–15% | | - |
| • Ankylosing spondilitis | 1%–6% | | - |
| Dermatologic | | | |
| • Oral aphthae | 4%–25% | 10%–30% | + |
| • Nodous erythema | 2%–5% | Up to 15% | + |
| • Gangrenous pyoderma | 1%–5% | 1%–2% | + or- |
| Ophthalmologic | | | |
| • Episcleritis | 2%–4% | | + |
| • Uveitis | 0.5%–3.5% | | + or - |
| Hepatobiliary | | | |
| • PSC | 2%–8% | 1%–2% | + or - |
| • Cholelithiasis | — | 15%–30% | - |
| Nephrologic | | | |
| • Nephrolithiasis | 2% – 5% | 5%–20% | - |
| • Amyloidosis | rare (1%) | | - |

**FIGURE 3.** Main extraintestinal manifestations of the inflammatory bowel disease, their frequency and relationship with disease activity. UC = ulcerative colitis; PSC = primary sclerosing cholangitis; + = relationship with the disease inflammatory activity; - = no relationship with the disease activity

**b) Left-sided hemicolon UC and pancolitis:** in such cases, patients usually suffer from moderate or severe forms of the disease. Fever, asthenia and weight loss with anorexia are common. Diarrhea with mucus, pus, blood and tenesmus may also be present. The fulminant form may occur. Extraintestinal manifestations happen in 20% to 30% of cases (for example: arthralgia, arthritis, sacroiliitis, oral aphtae, nodous erythema, episcleritis and gangrenous pyoderma).

CD can also be classified according to severity, extension and disease behavior[82]. There are several activity indexes for CD and CDAI (Crohn's Disease Activity Index)[9] (Figure 4) is the most used in clinical studies. However, in clinical practice the doctor's impression is enough to evaluate the severity of the disease. Such impression must consider location, extension, behavior, age, extraintestinal manifestations and the patient's life history.

More recently the Montreal classification (modified from the Vienna classification) was described so as to homogenize case description mainly in clinical studies[82] (Figure 5).

Clinical data obtained only from anamneses and physical exams are also effective to classify CD and at the same time they help to provide guidance for the treatment[6]. CD may thus be divided in:

**1) Mild to moderate CD -** outpatients able to tolerate enteral feeding without dehydration, toxicity, abdominal discomfort, painful mass, obstruction or weight loss higher than 10% of bodyweight;

| | Weighing factor |
|---|---|
| 1) Number of liquid or soft stools each day for seven days | x2 |
| 2) Abdominal pain (none = 0; mild = 1; moderate = 2; severe = 3) Consider total sum of individual data during the last week | x5 |
| 3) General well-being (excellent = 0; good = 1; average = 2; bad = 3; terrible = 4) Consider total sum of individual data during the last week | x7 |
| 4) Number of associated symptoms (list by category): a) Arthralgia/arthritis; b) Inflammation of the iris/ uveitis; c) Nodous erythema/ oral aphthae; d) Anal fissure, fistulae or abscesses; e) Other types of fistulae; f) Fever | x20 (maximum value = 120) |
| 5) Use of antidiarrheic drugs (No = 0; Yes = 1) | x30 |
| 6) Abdominal mass (none = 0; questionable =2; definite =5) | x10 |
| 7) Absolute deviation of hemotocrit: men 47-Ht; women 42-Ht (subtract instead of adding if patient's Ht is higher than standard) | x6 |
| 8) Weight*: percentage deviation from standard weight (subtract instead of adding if patient's weight is higher than expected) | x1 |
| Total (Crohn's Disease Activity Index) = <150 = Remission<br>150 - 250 = Mild<br>250 - 350 = Moderate<br>>350 = Severe<br>*Expected or ideal weight = height $(m)^2$ x 25.5 = _____ kg (men)<br>Height $(m)^2$ x 22.5 = _____ kg (women) | |

**FIGURE 4.** Crohn's Disease (CD) inflammatory activity index (AI) (known as CDAI = "Crohn's Disease Activity Index")

**1. Age at diagnosis:**
( ) **A1** <16 years of age
( ) **A2 between 17 and 40 years of age**
( ) **A3** >40 years of age
**2. Location**
**L1** ileal
**L2** colonic disease
**L3** ileocolic
**L4** Isolated upper GI tract disease (modifier that can be added to L 1-L3, in case there is concomitant disease involving the upper GI tract)
**3. Behavior**
**B1** – Non-stenosing, non-penetrating
**B2** – Stenosing
**B3** - Penetrating
**P** – Modifier for perianal disease (added to B1-B3 in case of concomitant perianal disease)

**FIGURE 5.** Montreal classification for Crohn's disease[82]

2) **Moderate to severe CD -** unresponsive patients to the treatment or those with more conspicuous symptoms of fever, weight loss, abdominal pain, nausea or intermittent vomiting (without evidence of bowel obstruction) or marked anemia;
3) **Severe to fulminant CD** – patients with persistent symptoms despite use of corticosteroids and/ or biological therapy (such as infliximab, adalimumab, etc) or individuals with fever, persistent vomiting, evidences of bowel obstruction, signals of peritoneal irritation, cachexia or evidences of abscesses.

## 2. RECOMMENDATION GRADES

The grades standardized by the American Gastroenterological Association (AGA) were adopted by the present consensus guidelines[53] as follows:

a) **Grade A -** consistent evidences from well-designed controlled randomized trials with an adequate number of patients.
b) **Grade B** – evidences from at least a well-designed trial with or without randomization or from meta-analyses.
c) **Grade C -** evidences based on clinical experience or on publications by a committee of experts.

## 3. PRE-TREATMENT EVALUATION

Prior to beginning the IBD treatment, whenever possible it is advisable to get the following data from patients:

1) In case of UC – Evaluate: a) severity level: mild, moderate, severe or fulminant) using clinical, laboratorial and endoscopic data; b) the extension of inflammatory process using colonoscopy. Risk of perforation must be taken into consideration in case of severe cases; c) corticoid dependency.
2) In case of CD – Evaluate: a) activity level (mild, moderate or severe), using clinical, laboratorial and endoscopic data; b) extension of the disease by means of endoscopic and image exams; c) disease behavior (inflammatory, stenosing or penetrating), and d) corticoid dependency.

## 4. DRUG CLASSES

### Salicylic derivatives

In this group of drugs, we have included sulphasalazine (SSZ) and salicylic derivatives. SSZ is unfolded in the colon by the bacterial azoreductase enzyme into sulphapiridine and 5-aminosalicylic acid (5-ASA). The latter is the active principle of this drug. Among the several action mechanisms of the 5-ASA action are modulation of proinflammatory cytokines secretion, inhibition of leukotriene and prostaglandin production, ability to scavenge free radicals and decrease oxidative stress, reduction of nuclear factor k- B (NF-kB), cell proliferation inhibition and apoptosis promotion. More recently, it has been shown that a great part of 5-ASA (mesalazine) action is due to its ability to activate PPAR-g (peroxisoma proliferator-activated receptor-g), which plays a role in inflammation control, cell proliferation and apoptosis[63].

Side effects of SSZ are more commonly dose-dependent and related to sulphapiridine serum levels. Such effects occur mainly in individuals with low genetic ability of hepatic acetylation of the drug (slow acetylators) in up to 45% of patients. These side effects include: abdominal pain, nausea, vomits, anorexia, cephalea, hemolysis, male infertility, etc. Less frequently, SSZ side effects may occur as a result of hypersensitivity (allergy or idiosyncrasy): fever, rash, lymphadenopathy, Stevens-Johnson agranulocytosis, hepatitis, pancreatitis, diarrhea exacerbation, etc, There are several types of controlled-release mesalazine (5-ASA) allowing the drug to be released in specific sites of the gastrointestinal tract as follows: a) microgranule mesalazine coated with ethylcellulosis: release of mesalazine irrespective of pH along the whole gastrointestinal tract, and more recently a prolonged-release oral mesalamine 2 g, that allow to take once a day[19]; b) conjugation of 2 molecules of 5-ASA molecules (olsalazine) by an azo bind: release of the drug in the colon in a SSZ-like fashion (diarrhea in 10%-15% of cases owing to its secretagogue action on the small intestine and the colon); c) 5-ASA coated with acrylic resin (e.g., S or L eudragit) with

active principle release from the proximal (eudragit L) and distal ileo (eudragit S) on and more recently a compound formula or acrylic resin (eudragit S) and two kinds of matrixes (lipophilic and hydrophilic) allowing mesalazine to be released in the colon when taken only once a day (MMX)[40], thus increasing patient's adherence to the treatment.

Mesalazine is also available for topical use as suppositories, foam and enema. Most patients intolerant or allergic (80%-90%) to SSZ tolerate mesalazine, however some patients (10%-20%) present SSZ-like side effects when using mesalazine. A meta-analysis study published by Sutherland et al.[88] at the Cochrane library showed that despite being less tolerated, SSZ is as effective in maintaining UC as mesalazine new formulations and is also less costly. For patients with mild/moderate UC in the left-sided hemicolon or in extensive areas, a combination of oral and topical mesalazine (>2 g/day) is more effective than the use of each of them separately[60, 73].

## Corticosteroids

Corticosteroids (e.g., hydrocortisone, prednisone, prednisolone) are to date the drug of choice for moderate and severe cases of IBD.

In active UC and CD of moderate and mild intensity, oral prednisone (0.75-1 mg/kg/day, usually not necessary to exceed 60 mg/day) is indicated to induce the disease clinical remission. However its use must be avoided for long periods (>2-3 months) even if administered at low doses. Corticosteroids withdrawal (weaning) must be gradual, reducing 10 mg/week up to 20 mg/day, followed by 5 mg/week until total withdrawal is achieved. If a relapse occurs during withdrawal, the corticosteroid dose may be increased to the same level as the dose before the one that caused relapse. In severe cases, inpatients may be given 100 mg IV hydrocortisone every 6 or 8 hours, followed by oral prednisone (without exceeding 60 mg/day) as soon as the patient is able to take it.

Corticosteroids usually induce clinical remission (70%-90% of cases after 4-6 weeks of treatment). However, they do not induce endoscopic and histologic remission in the same proportion as clinical remission (endoscopic and histologic remission approximately 30%)[46, 61]. In CD the frequency of corticosteroid-resistant (insensitive) and corticosteroid-dependent cases is high ranging from 8%-20% and from 15%-36%, respectively[62]. In UC frequency of corticosteroid -resistance (29%) is usually higher than corticosteroid-dependence (<10%)[43].

Corticosteroids side effects are well known, mainly when used for prolonged periods of time, even at low doses: appetite stimulation and increase in bodyweight, edema, insomnia, emotional lability, psychosis, acne, Cushing syndrome, osteoporosis, osteonecrosis, growth stunt, hypothalamus-hypofisis-adrenal axis suppression, infections, myopathies, cataract, skin atrophy, striations, ecchymosis, fatty liver, diabetes, hypertension, glaucoma and acute pancreatitis[85]. Due to these side effects new corticosteroids have been developed in an attempt to reduce such effects. The most widely studied corticosteroid is budesonide which is metabolized fast (approximately 90%) in inactive products after its first passage through the liver. It is commercialized as an enema (2 mg/100 mL) and eudragit-L(3 mg) coated pills.

Oral budesonide side effects (9 mg/day) were similar to those in the placebo group, except for the "moon face", more common in the budesonide group in comparison with the placebo (budesonide = 7%; placebo = 2%, $P$ = 0.001) [32]. When compared to prednisone, budesonide's side effects concerning corticosteroid therapy were less frequent in the budesonide group (33% of patients in the budesonide group and 55% in the prednisolone group ($P$ = 0.003)[76]. Moreover, the hypothalamus-hypofisis-adrenal axis was less suppressed with the use of budesonide.

Corticosteroids should not be used as maintenance drugs. However, budesonide can be used for more prolonged periods of time (up to 6 months) when necessary. As soon as the patient presents signs of corticosteroid dependence (corticosteroid is necessary to maintain remission) or of insensitivity (nonresponsive to a corticosteroid dose of 0.75-1 mg/kg/day prednisone for 4-6 weeks), other alternatives (e.g. immunosuppressors such as azathioprine or 6-mercaptopurine) must be instituted.

## Immunosuppressors

Azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX) and cyclosporine are included in this group of drugs.

## Azathioprine (AZA) and 6-mercaptopurine

The exact mechanism of action of AZA and its metabolite, 6-MP has not been fully elucidated. What is known is that thioguanine nucleotides resulting from the drug metabolization prevent DNA and RNA formation. More recently, AZA and 6-MP have been shown to act via Rac1[70, 92] blocking CD-28 signaling molecules reducing Bcl-x synthesis and favoring CD4 lymphocytes apoptosis.

Immunosuppressors are effective to maintain remission in CD and UC and at the same time are useful at promoting corticosteroid withdrawal in corticosteroid-dependent patients[4, 68].

AZA and 6-MP are first choice immunosuppressors followed by metotrexate (MTX) being indicated for CD in the following situations: a) resistance (insensitivity) or corticosteroid-dependence; b) for patients who need more than 2 courses of corticosteroids a year; c) for patients with early relapse after corticosteroid withdrawal (weaning) (<3 months); d) for patients submitted to bowel resection with remaining disease; e) for patients with fistulizing disease (penetrating); and f) for patients with extensive disease in the small bowel. In the case of UC immunosuppressors are indicated for patients: a) corticosteroid-dependent or -resistant; b) who need more than two courses of corticosteroids a year; and c) disease insensitive to the usual clinical treatment.

AZA and 6-MP dose is 2-3 mg/kg/day and 1-1.5 mg/kg/day, respectively. Both drugs have delayed action effects, thus a period of at least 3 months is required before the treatment can be considered as a therapeutic failure[79].

AZA and 6-MP side effects are related to bone marrow suppression which may occur in 3% of treated patients/year. Mielotoxicity depends on the dose used and the individual's own ability to metabolize AZA and 6-MP adequately and it can be controlled with drug reduction or withdrawal. Leucopenia

is its more common manifestation. Mielotoxicity may occur in any phase of the treatment, but the initial dose adjustment requires closer attention[30].

During this phase, hemogram, AST, ALT and amylase exams should be performed more frequently (every 15-30 days) and later every 3 or 4 months during the whole period of treatment.

Among other AZA and 6-MP complications, acute pancreatitis occurs in 1.6% of all treated patients, is not dose-dependent and occurs mainly in the first 3 or 4 weeks of treatment. Such complications are usually mild and improve with drug discontinuation. However they occur again almost universally in case the drug is reintroduced[7].

Besides the side effects above mentioned, nausea, vomits, abdominal pains, allergic reactions such as fever, rash, myalgia and articulation pains may also occur.

Approximately 10%-15% of patients are intolerant to AZA or 6-MP. In this case they should be given an alternate drug (e.g., MTX). However, some AZA- intolerant patients may tolerate 6-MP and vice-versa.

Several drugs may interact with 6-MP metabolism such as 5-ASA (mesalazine), allopurinol, acetyl salicylic acid (ASS) and furosemide. Although aminosalicylates enhance the concentration of the active metabolite, in clinical practice they do not seem to interfere significantly in the management of AZA and 6-MP. Allopurinol on the other hand must be used with caution as it inhibits the drug metabolism main pathway.

In the long run, an increase in lymphoma risk becomes the major concern with the use of immunosuppressors. Nevertheless, despite the increased risk with the prolonged ASA and 6-MP use, an analysis using the Markov models to evaluate therapy impact over survival and life quality showed a gain in life expectancy and quality similar to that recommended for the use of rubella and hepatitis B vaccination and platelet antiaggregant in patients with high risk for cerebral vascular accident[50]. Such benefit is higher in young patients since lymphoma risk in lower in this group and life expectancy higher, but it progressively decreases with age[50].

AZA and 6-MP must be used over an undetermined period of time if the patient reacts well and if there are no complications. Their discontinuation is not necessary for patients to undergo elective surgeries[47].

### Metotrexate (MTX)

Metotrexate is a folate antagonist and it interferes in DNA synthesis. It acts over cytokines and inflammatory mediators, blocking IL-1 binding to its receptor thus reducing IL-2, IL-6, IL-8, interferon-gamma and leukotriene $B_4$ synthesis. MTX is indicated for patients with CD who need immunosuppressors and are azathioprine- or 6-MP-intolerant. Induction weekly doses are 25 mg intramuscularly, reducing to 15 mg/week after 3 to 4 months[20, 21]. In the initial phase, a monthly control of hemogram, AST, ALT, ALF and GGT is required. Later the control must be done every 3 months during all the treatment, while the patient's response is good and no complications occur[89]. MTX adverse reactions occur in 10% to 25% of patients: nausea, diarrhea, stomatitis, leucopenia, hair loss, increase in transaminases, hypersensitivity pneumonia and hepatic fibrosis. Hepatic routine biopsy is not recommended and must be carried out in case of hepatoxicity evidences. MTX is a teratogen and may induce miscarriage thus being contraindicated to women who wish to get pregnant.

### Cyclosporine

Cyclosporine acts by reducing interleukine-2 (IL-2) production by T-helper cells. It has been effective as a "rescue treatment" of severe unresponsive UC after 5-10 days of intravenous corticotherapy. The current recommended dose is 2 mg/kg/day[97] IV, with continuous infusion for 1 to 2 weeks, followed by the oral administration of another maintenance drug. At short-term results are favorable ranging from 60% to 80%. At medium and long term, however, the drug does not elict good results unless an immunosuppressor such as AZA or 6-MP is introduced. The major drawbacks to cyclosporine therapy are: need for serum levels monitoring, interaction with other drugs and mainly its toxicity. Plasma levels between 150-300 ng/mL measured by radioimmunoassay with monoclonal antibody or HPLC (high-performance liquid chromatography) are considered safe. Cyclosporine is metabolized in the liver cytochrome P-450 and therefore drugs that induce it (such as cimetidine, rifampicin, trimetropim, carbamazepine, phenobarbital, phenytoin, octreotide) may decrease cyclosporine blood concentration and the ones that inhibit it (e.g., verapamil, fluconazole, cetoconazole, claritromicine, erythromicine, corticosteroids, metoclopramide, choloroquine) may enhance it. Side effects occur frequently and may reach 50%. Listed in order of frequency they are: paraesthesia, blood hypertension, hypertrichosis, kidney failure, cephalea, opportunist infections, gingival hyperplasia, dizziness and anaphylaxis. Grand mal seizures may occur in patients with low plasma levels of cholesterol (<120 mg/ dL).

### Biological therapy

This new approach is generically called biological therapy as it acts on mediators and natural and physiological phenomena.

Many biological therapies are still being tested[69]. However, results with the anti-TNF antibody (antibody against tumoral necrosis) therapy are widely known. Drugs already commercialized in Brazil such as infliximab (chimeric anti-TNF, 75% human) and adalimumab (anti-TNF 100% human) are included in this category.

Biological therapy has been increasingly used to treat UC and CD, however it must be applied to moderate and severe cases or when the patient is insensitive to other treatments. Extraintestinal manifestations insensitive to other treatments may also be treated with anti-TNF even without signals of bowel inflammatory activity. Likewise, situations in which life quality is severely compromised such as in the case of anal and/ or perianal fistulae can be treated early with biological therapy.

Anti-TNF side effects usually occur in less than 10% of cases and in some trials it was not higher than that observed in the placebo group[23, 52]. The most commonly anti-TNF side effects mentioned are: infusion reactions, upper respiratory tract infections, bronchitis, pharyngitis, fever, cephalea,

nausea, abdominal pain; less frequently: dizziness, thoracic pain, arthralgia, delayed sensitivity reactions (abdominal or perianal), pneumonia furunculosis, bowel obstruction, hemolytic anemia, cardiac dysfunction, drug-induced lupus (positive anti-DNA), and increased risk of lymphoma.

Tuberculosis reactivation may occur post anti-TNF use thus PPD and chest X-ray are mandatory prior to the infusion[101]. Patients with PPD >5 mm and normal chest X-ray must take isoniazide for 6 months and anti-TNF may be started after the 1st month of this treatment. If chest X-ray indicates active disease, treatment with triple scheme is recommended before the infusion. Similarly, the drug must be avoided in patients with functional class III/IV heart failure. There is no formal contraindication of anti-TNF use for patients with bowel stenosis[67].

Something vital that has been described about biological therapy is that it can promote endoscopic and histologic improvement, which in the future may be translated as a positive impact over the disease natural history.

Infliximab recommended dose is 5 mg/kg at 0, 2 and 6 weeks, IV followed by a maintenance dose every 8 weeks[33]. If the patient loses response during maintenance treatment, dose may be increased to 10 mg/kg or the interval between infusions may be reduced (every 4-6 weeks)[42]. Approximately 30% of patients using infliximab for 3 years will require a dose increment or to decrease interval between infusions.

Adalimumab induction dose regimen is 160 mg via subcutaneous injection, followed by 80 mg after 2 weeks[36]. During the maintenance regimen, drug must be used at 40 mg every 2 weeks[14, 80].

The mechanism of anti-TNF action is complex and requires more than one phase. The anti-TNFs bind to the circulating soluble TNF, preventing it from playing its pro-inflammatory role. They also neutralize TNF receptors, resulting in the signaling block of this cytokine, thus reducing the inflammatory process. Moreover, anti-TNFs bind to the TNFs bound to producing membrane cells (transmembrane TNF) and produce reverse signaling which inhibits TNF production and induces apoptosis of cells producing TNF. When anti-TNF binds to receptors or transmembrane TNF, it facilitates complement activation and fagocitosis of the immuncomplex[69].

Presently the best time to use anti-TNF therapy has been widely discussed. D'Haens et al.[18] advocate the early use of infliximab, when diagnosis is made, as they consider that this early intervention may reduce the future complications caused by the disease. However, although their study reports that this therapeutic option induces increased clinical remission in the first year and endoscopic one in 2 years of follow-up when compared with conventional strategies, their study lacks long-term data showing that this more aggressive therapy indeed causes a great impact on CD natural history. Therefore the present consensus guidelines recommend that until more data are available addressing this issue biological therapy be used for insensitive cases of CD and UC.

It is not possible to establish a definite and consensual conduct concerning the use or not of immunosuppressors associated with infliximab in adults using current data[98]. Thus the physician must consider the patient's clinical history and decide on a suitable conduct in each case.

## 5. CLINICAL TREATMENT FOR CD ACCORDING TO LOCATION AND SEVERITY OF DISEASE

### Mild ileocecal CD

Acute phase treatment must be carried out preferably with oral budesonide, 9 mg/day (Grade A), as it is superior to placebo[32, 66, 84] and mesalazine[90, 91] and as it presents fewer side effects despite being less effective than prednisone[66, 84].

Oral mesalazine, 4 g/day, reduces CDAI, but clinical benefit is debatable since reduction is very small[34]. Doses lower than 4 g/day do not present any benefit.

After remission, patients may remain without maintenance treatment and be given only symptomatic drugs. Mesalazine maintenance treatment is not superior to placebo[1, 26] and cannot be recommended (Grade B).

### Moderate ileocecal CD

Oral treatment with budesonide may be attempted in some cases, but oral prednisone, 0.75-1 mb/kg/day (not exceeding 60 mg/day) has superior efficacy[66] (Grade A).

### Severe ileocecal CD

Initial treatment must be made with systemic corticosteroid either via oral or parenteral, considering the patient's previous history. Patients with early relapse or those in need of more than two courses of corticosteroids a year must be given immunosuppressors (AZA or 6-MP). For those who relapse even when the correct dose of immunosuppressors is administered, anti-TNF must be considered. Surgical treatment may be required mainly for patients with stenosing disease behavior or other complications (e.g. abscesses) (Grade C).

### CD of the colon

Treatment with sulphassalazine (>3 g/day) is superior to placebo and may be used for mild cases, with colon injury[56, 86] (Grade A). More severe cases must be treated with systemic corticosteroid such as prednisone. Use for immunosuppressors and anti-TNF is similar to that previously discussed. Patients with colon lesions respond better to therapy with anti-TNF (Grade C).

Patients with distal lesion may receive topical therapy such as enema and suppositories, associated with the oral therapy (Grade C).

Oral antibiotics (oral metronidazol, 750-1000 mg/day and oral ciprofloxacin, 1 mg/day)[71, 87] induce response superior to placebo and are a useful alternative for patients at high risk of complications with the use of corticosteroid, such as diabetic and hypertensive patients (Grade B).

### Extensive small bowel CD (>100 cm)

Extensive small bowel CD must be treated with systemic corticosteroids in the acute phase and treatment with oral immunosuppressors (AZA or 6-MP) must have been already initiated. Most of these patients are severely malnourished and will benefit from adjuvant treatment with parenteral

or enteral nutrition. Anti-TNF treatment is a worthwhile alternative and may be indicated more liberally for patients with severely compromised nutritional status. Patients with multiple stenoses, insensitive to the initial clinical treatment must undergo surgical procedures, preferably by means of stenoplasties thus avoiding extensive resection of the small bowel and the risk of short bowel (Grade C).

### CD of the upper gastrointestinal tract

Patients with esophagus and stomach lesions must be given high doses of proton pump inhibitors (e.g., omeprazol, 80-160 mg/day) associated or not with systemic corticosteroids during acute phase. Long-term treatment must be done with immunosuppressors or biological therapy. Stenoses might be approached through endoscopic dilations (Grade C).

### Anal and/or perianal CD

Patients with fistulizing (penetrating) CD are considered more critical irrespective of luminal inflammatory activity and require specific evaluation and approach. Perianal fistula examination must be carried out under narcosis and using imaging methodologies (preferably nuclear magnetic resonance) which allow the evaluation of the fistulous trajectory and the exclusion of adjacent collections or in the fistula trajectory. If collections are present, they must be surgically approached with drainage and seton placement before anti-TNF treatment is started (Grade C).

Initial treatment includes the use of antibiotics (ciprofloxacin and/or metronidazol) in the above mentioned doses, associated with immunosuppressors for a prolonged time[3, 16]. Anti-TNF is efficient and is indicated for the treatment of complex fistulae or those unresponsive to the initial treatment[22, 100]. Moreover, it is currently the most efficient treatment for anal and/or perianal fistulae with 70%-80% rates of clinical remission and 40%-60% rates of full sealing of fistula(e)[51] (Grade A). Entero-vesical, entero-cutaneous and rectum-vaginal fistulae do not present a good response to anti-TNF therapy like the anal and/or perianal fistulae (Grade C).

## 6. CLINICAL TREATMENT FOR UC ACCORDING TO SEVERITY AND EXTENSION OF DISEASE

UC choice treatment is with aminosalicylates[88] and the choice for the best formulation depends mainly on the extension of the disease, whereas need for drug titration will depend on the severity of disease (Grade A).

### Distal UC (proctitis and proctosigmoiditis)

Choice treatment for acute proctitis is done with suppositories 1 g/day[57] for 4-6 weeks. Mesalazine suppositories are more efficient than topical treatments with corticosteroids[27], which must be limited to patients intolerant or insensitive to mesalazine[73]. Mesalazine enema when well applied may reach the splenic angle and is the favorite drug to treat proctosigmoiditis, but it promotes a lower concentration of 5-ASA in the rectum when compared with suppositories. Non responsive patients may be prescribed a treatment regimen associated with oral aminosalicylates or even systemic corticosteroids[78] (Grade B).

Maintenance treatment may be carried out with mesalazine suppositories 3 g/week (1 g, 3 times a week)[59] and may be discontinued after 1 year without relapses[58]. Risk of developing neoplasia is similar to the general population (Grade B).

### Left-sided hemicolon UC

In this case treatment may be done only via the rectum using enema mesalazine, but many patients will require treatment with oral aminosalicylates (>2-3 g/day). The association of oral and topical mesalazine is superior to the treatment with mesalazine administered only orally or only topically[73]. Meta-analysis studies showed that an increase in mesalazine doses improves response and decreases the length of bleeding period (Grade B). Prednisone in its usual dose must be started if bleeding continues for more than 2 weeks with the suitable use of aminosalicylates. Every patient must receive maintenance treatment with aminosalicylates over an undetermined period of time (SSZ or mesalazine) via oral doses higher than 2.4 g/day[35, 73] (Grade A). Besides decreasing number of relapse episodes, maintenance treatment reduces risk of colorectal cancer

### Pancolitis

Patients with inflammation extending up to the proximal transverse colon or beyond are considered as suffering from pancolitis (universal or extensive colitis). Generally, such patients are more critical and require oral treatment associated with topical treatment[41, 60]. Similarly to patients with left-sided colitis, treatment with prednisone at the usual dose must be started if bleeding persists for more than 2 weeks after the beginning of treatment with aminosalicylates (>2-3 g/day)[49, 94] (Grade A). If the patient is already using an aminosalicylate (mesalazine or SSZ) or an immunosuppressor, corticosteroids must be started initially. All patients must receive maintenance treatment with aminosalicylates at doses higher than 2.4 g/day.

### Severe and fulminant UC

These patients face a real risk of death and should be admitted to hospital to undergo intensive treatment[38]. The choice treatment is parenteral corticosteroids (e.g., hydrocortisone, 100 mg IV, 3-4 times/day)[95]. Corticosteroid response assessment must be done between 3 and 7 days[96] and rescue or surgical treatment is indicated in case of therapeutic failure (Grade B).

Besides corticosteroid treatment it is important to: a) correct hydroelectrolytic disturbances, specially potassium and magnesium[25]: b) research *C. difficile* toxin; c) institute enteral diet[31]; d) suspend any anti-inflammatory, anticholinergic, antidiarrheic or opiate drug that the patient might be taking[25]; e) carry out blood transfusion if hemoglobin is lower than 10 g/dL; f) start prophylactic subcutaneous heparin[37] (Grade B).

Rectosigmoidoscopy without prior bowel preparation in such cases is safe and not only does it make it possible to confirm inflammation but also to rule out cytomegalovirus infection.

Fulminat cases with or without toxic megacolon must be clinically and radiologically evaluated and be supervised by a coloproctologist. In such cases, rescue therapy must be carried

out with cyclosporine IV[54, 97], or infliximab[39, 77] (Grade A). Both are efficient and have advantages and disadvantages. Cyclosporine acts more quickly but has a higher number of side effects, some of them severe and irreversible. On the other hand, infliximab therapy has fewer side effects but time to respond seems to be longer. However, there are no studies directly comparing cyclosporine rescue therapy vs anti-TNF thus precluding a choice based on scientific evidences. Taking into consideration current experience with infliximab and cyclosporine side effects this consensus guidelines recommend that the initial rescue therapy be done with infliximab and that colectomy be indicated in case rescue treatment with one of these drugs fails. Indication for colectomy must be evaluated in 24-72 h; however many times very critical patients who cannot wait for the drugs to act must be initially treated with colectomy.

All patients undergoing successful rescue treatment must receive an oral aminosalicylate (SSZ or mesalazine) besides an immunosuppressor and/or infliximab. However, the long-term possibility to preserve the colon is not promising (Grade C).

## 7. SPECIAL SITUATIONS AND CONSIDERATIONS

### Refractory proctitis

A small percentage of patients with non-specific proctitis show unproportional severity to the macroscopic extension of the disease and will require oral drugs, including aminosalicylates, systemic corticosteroids, immunosuppressors or even biological therapy. In this case it is important to review symptoms, the UC diagnosis itself, previous treatments and its adherence to it and to have a recent colonoscopy with serial biopsies. If symptoms persist for more than 4-8 weeks despite adequate therapeutic conduct, the treatment must follow the established guidelines for extensive or severe UC (Grade C).

### Early recurrence of IBD

Therapeutic decision is different for the patients with the first "acutization" crisis and the other subsequent crises. Previous treatments, interval between relapses and their frequency must be considered. Therefore patients relapsing in less than 3 months after corticosteroid weaning must be submitted again to treatment induction and be given oral immunosuppressors (AZA or 6-MP) as an attempt to avoid future relapses[4] (Grade B).

### Corticosteroid-dependant IBD patients

We consider corticosteroid-dependent all patients responding to corticosteroid treatment in the acute phase but relapsing during corticosteroid withdrawal. So, as to maintain disease in remission or at low activity levels, such patients need variable corticosteroid doses and usually have complications due to the prolonged use of corticosteroids. For this group of patients, treatment with immunosuppressors[2, 4, 68] or anti-TNF[14, 48, 77, 80, 81] is indicated to assist in the corticosteroid withdrawal (Grade A). Patients not using immunosuppressors must take AZA/6-MP or MTX, whereas for those who already use these drugs or are intolerant to them, anti-TNF therapy is indicated.

### Corticosteroid-refractory IBD patients

We consider corticosteroid-refractory patients those who do not respond to the adequate systemic corticosteroid treatment–dose (0.75-1 mg/kg/day) and period (4-6 weeks) and after other complicating factors have been excluded (e.g., abscesses, cytomegaloviruses, *C. difficile,* etc). For the therapeutic approach of corticosteroid-refractory patients, the severity of disease must be considered. Also it is important to bear in mind that immunosuppressor's time of action is longer (3-4 months). On the other hand, anti-TNF acts more quickly and is the choice treatment for these patients. Patients already using an immunosuppressor must take anti-TNF as well and in case of UC surgery must be considered. Many patients benefit from adjuvant nutritional therapy preferably via an enteral feeding tube (Grade C).

### Extraintestinal manifestations[5]

Gangrenous pyoderma may be treated with systemic corticosteroids, immunosuppressors or anti-TNF at the doses usually prescribed for underlying diseases. Metastic CD sometimes is more severe than the underlying disease and may be treated with systemic drugs such as immunosuppressors or biological therapy. Articular manifestations must be treated concomitantly with the underlying disease, using titration as necessary. Many times extraintestinal manifestations are as important or more than the intestinal manifestations and must be treated with the same drugs including biological therapy regardless of luminal inflammatory activity such as in the case of axial arthritis (sacroileitis, ankylosing spondilitis) (Grade C).

### Pregnant women

The present consensus guidelines consider disease remission during pregnancy the most important isolated factor for a complication-free pregnancy for the mother and for the unborn child. It is equally important that the patient get pregnant during a remission period. IBD patients have a higher prevalence of pre-term births with an increased risk for miscarriages and low birth weight babies regardless of the used drugs[15, 55] (Grade B). Remission patients using sulphasalazine, mesalazine, azathioprine or anti–TNF are regarded as safe patients and should remain so during all the pregnancy. MTX is contraindicated during pregnancy. Ciprofloxacin must be avoided as well, but metronidazol may be used for a short period but must be avoided before the birth (3rd trimester) (Grade C). Corticosteroids may be used when necessary as well, but physicians must take extra care with the possible onset of diabetes.

Vaginal birth should be the first choice, except in face of ileoanal pouch or active perianal disease. An episiotomy may be performed.

### Nutritional aspects in IBD

As many as 80%-90% of inpatients with CD and up to 60%-70% of inpatients with UC have any kind of nutritional deficit. These percentages drop to 50%-60% in CD and 40%-50% in UC in the case of outpatients. Enteral nutrition should be the preferred route while parenteral nutrition should be limited to

patients who cannot be fed by means of enteral diet (e.g., bowel obstruction). Polymeric (containing whole proteins), oligomeric (containing peptides) or monomeric (amminoacids) diets are equally effective[8, 11] (Grade A). Enteral nutrition therapy in adults is inferior to the corticosteroid treatment in the acute phase and should be used as an adjuvant during pre- and post-operative care. It may also be considered as an alternative in case of refractory IBD, mainly CD. For children and adolescents, exclusive nutritional therapy may be used as a primary measure for CD treatment thus avoiding the use of corticosteroids.

### Probiotics in IBD

Random clinical trials do not favor the use of probiotics in CD[13, 72, 83, 99]; thus not being recommended for this disease (Grade B). Similarly, it should not be used in CD post-operative care. However, UC studies point to the benefits of using probiotics as a maintenance therapy. *E. coli* Nissle in concentrations higher than $10^9$ and VSL#3 ($10^{11}$) are superior to placebo[102] and similar to aminosalicylates to maintain remission in UC[44, 74] thus being an alternative for maintenance treatment in patients intolerant or allergic to aminosalicylates (Grade B). Probiotics are also effective for the treatment[29] and prevention of chronic pouchitis[28] after total proctocolectomy with ileoanal pouch.

### Colon cancer screening in IBD

The following are considered risk factors for the development of cancer in IBD: a) long-term disease; b) presence of associated primary sclerosing cholangitis; c) family history of colorectal cancer; d) extensive disease; e) previous history of colonic dysplasia (Grade C).

Colorectal cancer screening using colonoscopy in UC (pancolitis) is indicated after a 8-10 year progression and in left-sided colitis, after 12-15 years of illness. Screening must performed using colonoscopy every 3 years in the 2nd decade, every 2 years in the 3rd decade and yearly in the 4th decade of illness together with 4- quadrant biopsies of non-inflamed mucosal at every 10 cm of colon, in the whole colon in association with biopsies of suspected areas. Chromo colonoscopy with biopsy of suspected area is a valid alternative to multiple biopsies. Patients with primary sclerosing cholangitis have high risk of developing colorectal cancer thus needing to undergo colonoscopy associated with yearly biopsies soon after diagnosis. Patients with rectitis should be screened similarly to the normal population.

Findings of high grade dysplasia during UC remission phase, if confirmed, will imply in total proctocolectomy (Grade C).

In colon CD, despite not being fully established, screening must be also considered after 8-10 years of disease progression (Grade C).

## 8. SURGICAL TREATMENT

### Surgical recommendations for UC

Decision about surgical approach in patients suffering from IBD must be made considering the gastroenterologist's, the coloproctologist's and the patient's opinion.

In the case of UC, surgery must be limited to patients not responding clinically well to drug therapy. In addition to clinical "untreatability" other elective indications are: growth stunt in children, extraintestinal manifestations (gangrenous pyoderma) and the presence of high grade dysplasia or adenocarcinoma in the colorectal segment.

Emergency surgical indications in UC are: hemorrhage, bowel obstruction, toxic megacolon and bowel perforation.

Surgical treatment must be performed after both the gastroenterologist and the coloproctologist indicate surgery and with the patient's agreement.

The patient must be previously informed and warned that an ostomy might be performed during the surgery.

During pre-operative exams, the stomaltherapist or the coloproctologist must establish the site for ostomy placement.

A midline incision is usually best when a laparotomy is required.

Surgery technical options (advantages and disadvantages) must be clearly explained to patients with elective indication. When an ileoanal anastomosis is indicated, the patient must be warned about the possibility to develop pouchitis.

The choice procedure for patients with fulminant colitis or toxic megacolon without improvement with conventional treatment must be total colectomy with rectum burying and terminal ileostomy. An alternative to this technique is performing a terminal ileostomy and a mucosal fistula.

In presence of fecal or purulent peritonitis (pelvic sepsis) primary anastomosis must be avoided similarly to cases of severe malnutrition.

Total proctocolectomy with definitive ileostomy is indicated for pancolitis (also known as universal colitis) associated with low rectal cancer and/or fecal incontinence.

Clinical untreatability is the main indication for total rectocolectomy and an ileoanal anastomosis with reservoir (ileal pouch).

Incidence of sexual dysfunction when an ileal pouch surgery is performed is lower than in cases of rectal resection due to tumors.

The main disadvantages of total colectomy with ileorectalanastomosis are: risk of rectal cancer, high rates of relapse and need for careful outpatient follow-up.

If corticosteroids were used for 4 months before surgery, an endovenous infusion of hydrocortisone must be applied during the surgery.

Videolaparoscopy should be used in specific cases, avoiding its use with the complex ones.

Malignization risk has been increasing in patients with UC with more than 10 years of progression, mainly with pancolitis and early onset of disease.

In case of severe dysplasia, the glass slide must be reexamined and if positive, surgical treatment is recommended.

### Surgical recommendations for CD

Crohn's disease surgical treatment must take into consideration disease location, severity of symptoms (activity) and the patient's nutritional status.

Decision for a surgical procedure must be the result of a common agreement between gastroenterologist, coloproctologist and patient.

During the preoperative evaluation, the patient must be warned about risks of a possible ostomy.

Colostomy site marking must be done during preoperative evaluation by a stoma therapist or coloproctologist.

If corticosteroids were used during the 6-month period prior to the surgery, during the surgical procedure and post operative period, patients must be given this drug as a means to prevent acute adrenal insufficiency.

Corticosteroids in high doses and for over a prolonged period of time are the only drug that can negatively interfere with the surgery outcome.

Ponderal loss higher than 15% of bodyweight in 3 months and hypoalbuminemia (<2.5 g/dL) are risk factors for surgical complications.

The median incision must the choice for patients requiring a laparotomy both in elective and emergency settings.

Videolaparoscopic resection should not be performed in presence of very complex diseases and previous surgeries. It should be limited to specific cases.

Main indications for elective surgeries are: clinical "untreatability", growth stunt, extraintestinal manifestations, high grade dysplasia, presence of adenocarcinoma, intestinal obstruction, refractory intestinal suboclusion, internal and external fistulae, palpable abdominal mass and perianal disease.

CD intestinal resections must be limited to the macroscopically compromised area (economical resection).

Enteroplasty or economical resection should be the chosen techniques when the disease is located in the small bowel.

When the small bowel has multiple stenoses located in a short section, primary resection is the best therapeutic alternative.

Manual or mechanical latero-lateral anastomosis should be preferred as it presents lower rates of symptomatic relapse than the termino-terminal one.

Surgical drains must be avoided in CD surgery.

In case of ileal or ileocecal CD with intestinal obstruction, resection must be performed using mechanical latero-lateral anastomosis, whereas enteroplasty may be used in specific cases of anular segmentar stenosis.

Freezing biopsies is not necessary when an enteroplasty is performed.

Dehiscence rates with enteroplasty are not higher than intestinal resection with mechanical latero-lateral anastomosis.

Resection with mechanical latero-lateral with ascending-ileum is recommended in case of severe acute ileitis (with stenosis, mesentiritis, panniculitis).

In presence of acute ileitis with a discrete inflammatory process associated with appendicitis, an appendicectomy must be performed. If the appendix is normal, no resection should be performed. However appendicectomy is recommended for patients who cannot undergo follow-up.

In case of an intraperitoneal abscess, whenever possible a diagnostic emptying image-guided puncture should be performed in association with antibiotic therapy. Surgery must be performed at a later time.

In presence of an internal (entero-vesical or colonvesical) or external (enterocutaneous or colocutaneous) abdominal fistula, the choice conduct is a laparotomy with resection of the compromised section.

A loop ileostomy without resection (as an isolated surgery) must be avoided for the treatment of Crohn's pancolitis and perianal disease.

A partial colostomy must be the choice treatment in case of segmental diseases located in the colon (<1/3 or 1/4 of compromised colon) without concomitant perianal disease.

Total colectomy with ileo-rectal anastomosis is the best therapeutic alternative when two segments separated from the colon are affected by active CD and in absence of concomitant perianal disease.

Total colectomy is the suitable treatment for severe left-sided colitis.

Primary anastomosis must be avoided both in case of pelvic and peritoneal sepsis and in presence of severe malnutrition

Stenoplasties must be avoided in the colon.

Ileal pouch should not be recommended as a rule in CD – only in specific cases (severe pancolitis in young individuals who refuse to undergo ostomy and do not present perianal disease).

Recommendations for emergency surgery in CD are: acute obstructed abdomen, severe and persistent hemorrhage, intestinal perforation, toxic megacolon and acute ileitis.

In the cases of toxic megacolon refractory to conventional measures (hydrocortisone, cyclosporine and biological therapy) total colectomy without anastomosis is the recommended surgery. Reconstruction should be performed with the burying of rectum or mucous fistula and a terminal ileostomy should be performed.

Endoscopic dilations of stenoses can be used in CD, although they might be associated with complications.

Anal and perianal disease should only be treated with surgery when symptomatic.

In case of severe ano-rectal perianal CD, hyperbaric oxygen therapy is a useful alternative, and it may be associated with antibiotics, immunosuppressors and anti–TNF.

Ano-rectal perianal surgery in CD must be conservative performed with abscess drainage and seton placement, always associated with clinical measures. Sphincterotomies should be avoided. Severe perianal disease should not be treated only with ostomy.

### Prevention of postoperative relapse in CD

Main risk factors for postoperative relapse are: smoking, pancolitis, small bowel extensive disease, fistulizing perianal disease and absence of complementary drug therapy.

Patients must be strongly advised to discontinue smoking early and they should be helped to reach this objective.

During terminal ileum CD postoperative a colonoscopy is recommended between 6 and 12 months post surgery and the Rutgers score[75] must be used as a guideline for therapeutic conduct as follows: i0 – absence of ileal lesions; i1 – fewer than five aphthous ulcers less than 5 mm in length; i2 – more than five aphthous ulcers with normal mucosa between the lesions

**OR** larger focal lesions **OR** lesions confined to the ileocolonic anastomosis less than 1 cm in length; i3 diffuse aphthous ileitis with diffusely inflamed mucosa; i4 – diffuse inflammation with larger ulcers, nodules and/or narrowing. CD patients referred to ileocolic surgery presenting **HIGH** risk for postoperative recurrence (e.g. older than 30 years of age, smokers, with penetrating disease, previous resection(s), resections more than 100 cm in length, use of corticosteroids during the last 3 months, short-lasting disease) should take metronidazol together with AZA or 6-MP at regular doses. AZA or 6-MP may be started approximately 2 weeks after surgery. A colonoscopy must be done 6-12 months post surgery and the Rutgers score must be applied: from cases i0 to i2, it is recommended to maintain AZA or 6-MP; in cases i3 or i4, biological therapy must be considered. Moreover, patients should undergo a colonoscopy every 1-2 years. Patients with **LOW** risk for postoperative recurrence (those not included in the high risk group) are recommended not to receive any drugs. A colonoscopy should be performed 6-12 months later and the Rutgers score should be applied. Cases included in the i0 to i2 groups may remain unmedicated, whereas in cases i3 or i4 the introduction of AZA or 6-MP is recommended at regular doses. Next, a control colonoscopy every 1-2 years is recommended )[10, 17, 64, 65].

### Pouchitis

Pouchitis crises usually increase during the postoperative period.

Approximately 30% to 50% of patients undergoing UC ileal pouch operation will develop pouchitis after 10 years of follow-up.

Pouchitis diagnosis must be based on clinical, endoscopy and histological evidences.

Differential diagnosis must be done based on cuffitis, pelvic sepsis and irritable pouch syndrome.

Metronidazol at 400 mg, 3 times a day for 2 weeks is the choice treatment. In case of intolerance, ciprofloxacin 500 mg, twice a day for 2 weeks should be administered.

If antibiotics prove to be ineffective, other treatments may be used.

Grupo de Estudos da Doença Inflamatória Intestinal do Brasil – GEDIIB. Consenso brasileiro sobre a doença inflamatória intestinal. Arq Gastroenterol. 2010;47(3):313-25.

**RESUMO** – Este é o primeiro Consenso Brasileiro sobre a Doença Inflamatória Intestinal, realizado pelo Grupo de Estudos sobre a Doença Inflamatória Intestinal do Brasil (GEDIIB), e aborda o tratamento da doença de Crohn e da retocolite ulcerativa durante a fase de agudização e remissão. A primeira parte do texto traz uma revisão das principais drogas utilizadas no tratamento da doença inflamatória intestinal, bem como seus mecanismos de ação e os cuidados necessários durante seu uso. Na segunda parte do trabalho, é apresentada a opinião do grupo sobre as abordagens clínicas e cirúrgicas mais recomendadas com base no grau de atividade da doença, na sua localização e no comportamento da doença. As recomendações emitidas pelo GEDDIB foram amplamente discutidas em várias reuniões científicas, com ativa participação de todos os membros do grupo e baseadas em evidências científicas da literatura.

**DESCRITORES** – Doença de Crohn. Colite ulcerativa. Consenso.

## REFERENCES

1. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane Database Syst Ver. 2005;(1):CD003715.
2. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Ver. 2005;(1):CD003459.
3. Angelberger S, Reinisch W, Dejaco C, Miehsler W, Waldhoer T, Wehkamp J, Lichtenberger C, Schaeffeler E, Vogelsang H, Schwab M, Teml A. NOD2/CARD15 gene variants are linked to failure of antibiotic treatment in perianal fistulating Crohn's disease. Am J Gastroenterol. 2008;103:1197-202.
4. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006;55:47-53.
5. Barrie A, Regueiro M. Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2007;13:1424-9.
6. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007;369:1641-57.
7. Bermejo F, Lopez-Sanroman A, Taxonera C, Gisbert JP, Pérez-Calle JL, Vera I, Menchén L, Martín-Arranz MD, Opio V, Carneros JA, Van-Domselaar M, Mendoza JL, Luna M, López P, Calvo M, Algaba A. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther. 2008;28:623-8.
8. Berni Cananni R, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, S'Armiento F, Romeo EF, Cucchiara S. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. Dig Liver Dis. 2006;38:381-7.
9. 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;70:439-44.
10. Blum E, Katz JA. Postoperative therapy for Crohn's disease. Inflamm Bowel Dis 2009;15:463-72.
11. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol. 2006;4:744-53.
12. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol. 2003;3:521-33.
13. Chermesh I, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, Gelber M, Halpern Z, Bengmark S, Eliakim R. Failure of synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. Dig Dis Sci. 2007;52:385-9.
14. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132:52-65.
15. Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut. 2007;56: 830-7.
16. Dejaco C, Harrer M, Waldhoer T, Miehsler W, Vogelsang H, Reinisch W. Antibiotics and azathioprine for the treatment of perianal fistulas in Crohn's disease. Aliment Pharmacol Ther. 2003;18:1113-20.
17. D'Haens GR, Vermeire S, Van Assche G, Noman M, Aerden I, Van Olmen G, Rutgeerts P. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology. 2008;135:1123-9.

18. D'Haens G, Baert F, Van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371:660-7.
19. Dignass AU, Bokemeyer B, Adamek H, Mross M, Vinter-Jensen L, Borner N, Silvennoinent J, Tan G, Pool MO, Stijnen T, Dietel P, Klugmann T, Vermeire S, Bhatt A, Veerman H. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. Clin Gastroenterol Hepatol. 2009;7:762-9.
20. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med. 1995;332:292-7.
21. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med. 2000;342:1627-32.
22. Felley C, Mottet C, Juillerat P, Pittet V, Froehlich F, Vader JP, Michetti P, Gonvers JJ. Fistulizing Crohn's disease. Digestion. 2007;76:109-12
23. Fidder H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, Henckaerts L, Van Assche G, Vermeire S, Rutgeerts. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut. 2009;58:501-8.
24. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology. 1998;115:182-205.
25. Gan SI, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. Am J Gastroenterol. 2003;98:2363-71.
26. Gendre JP, Mary JY, Florent C, Modigliani R, Colombel JF, Soulé JC, Galmiche JP, Lerebours E, Descos L, Viteau JM, et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). Gastroenterology. 1993;104:435-9.
27. Gionchetti P, Rizzello F, Venturi A, Brignola C, Ferretti M, Peruzzo S, Campieri M. Comparison of mesalazine suppositories in proctitis and distal proctosigmoiditis. Aliment Pharmacol Ther. 1997;11:1053-7.
28. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, Vitali B, Poggioli G, Miglioli M, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology. 2003;124:1202-9.
29. Gionchetti P, Rizzello F, Morselli C, Poggioli G, Tambasco R, Calabrese C, Brigidi P, Vitali B, Straforini G, Campieri M. High-dose probiotics for the treatment of active pouchitis. Dis Colon Rectum. 2007;50:2075-82.
30. Gisbert JP, Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. Am J Gastroenterol. 2008;103:1783-800.
31. Gonzalez-Huix F, Fernandez-Banares F, Esteve-Comas M, Abad-Lacruz A, Cabre E, Acero D, Figa M, Guilera M, Humbert P, de Léon R. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. Am J Gastroenterol. 1993;88:227-32.
32. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. N Engl J Med. 1994;331:836-41.
33. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541-9.
34. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol. 2004;2:379-88.
35. Hanauer SB, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, Regalli G, Yeh C, Smith-Hall N, Ajayi F. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. Am J Gastroenterol. 2005;100:2478-85.
36. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130:323-33.
37. Irving PM, Pasi KJ, Rampton DS. Thrombosis and inflammatory bowel disease. Clin Gastroenterol Hepatol. 2005;3:617-28.
38. Jakobovits SL, Travis SP. Management of acute severe colitis. Br Med Bull. 2006;75-76:131-44.
39. Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Gränno C, Vilien M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005;128:1805-11.
40. Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132:66-75.
41. Kane SV, Bjorkman DJ. The efficacy of oral 5-ASAs in the treatment of active ulcerative colitis: a systematic review. Rev Gastroenterol Disord. 2003;3:210-8.
42. Kaplan GG, Hur C, Korzenik J, Sands BE. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis. Aliment Pharmacol Ther. 2007;26:1509-20.
43. Kjeldsen J. Treatment of ulcerative colitis with high doses of oral prednisolone. The rate of remission, the need for surgery, and the effect of prolonging the treatment. Scand J Gastroenterol. 1993;28:821-6.
44. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. Gut. 2004;53:1617-23.
45. Lakatos PL, Fischer S, Lakatos L, Gal I, Papp J. Current concept on the pathogenesis of inflammatory bowel disease-crosstalk between genetic and microbial factors: pathogenic bacteria and altered bacterial sensing or changes in mucosal integrity take "toll"? World J Gastroenterol. 2006;12:1829-41.
46. Landi B, Anh TN, Cortot A, Soule JC, Rene E, Gendre JP, Bories P, See A, Metman EH, Florent C. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology. 1992;102: 1647-53.
47. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005;128:1812-8.
48. Lemann M, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadiot G, Picon L, Bourreille A, Sobahni I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. Gastroenterology. 2006;130:1054-61.
49. Lennard-Jones JE, Longmore AJ, Newell AC, Wilson CW, Jones FA. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. Gut. 1960;1:217-22.
50. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. Gastroenterology. 2000;118:1018-24.
51. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology. 2005;128:862-9.
52. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol. 2006;4:621-30.
53. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006;130:940-87.
54. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994;330:1841-5.
55. Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology. 2007;133:1106-12.
56. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984;86:249-66.
57. Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther. 1995;9:293-300.
58. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997;40:775-81.
59. Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. Gut. 1998;42:195-9.
60. Marteau P, Probert CS, Lindgren S, Gassul M, Tan TG, Dignass A, Befrits R, Midhagen G, Rademaker J, Foldager M. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut. 2005;54:960-5.
61. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology 1990;98:811-8.
62. Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994;35:360-2.

63. Ng SC, Kamm MA. Review article. New drug formulations, chemical entities and therapeutic approaches for the management of ulcerative colitis. Aliment Pharmacol Ther. 2008;28:815-29.
64. Ng SC, Kamm MA. Management of postoperative Crohn's disease. Am J Gastroenterol. 2008;103:1029-35.
65. Nos P, Domenech E. Postoperative Crohn's disease recurrence: a practical approach. World J Gastroenterol. 2008;14:5540-8.
66. Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Ver. 2005;(4):CD000296.
67. Pallotta N, Barberani F, Hassan NA, Guagnozzi D, Vincoli G, Corazziari E. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. World J Gastroenterol. 2008;14:1885-90.
68. Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Ver. 2000;(2):CD000067.
69. Peyrin-Biroulet L, Desreumaux P, Sandborn WJ, Colombel JF. Crohn's disease: beyond antagonists of tumour necrosis factor. Lancet. 2008;372:67-81.
70. Poppe D, Tiede I, Fritz G, Becker C, Bartsch B, Wirtz S, Strand D, Tanaka S, Galle PR, Bustelo XR, Neurath MF. Azathioprine suppresses ezrin-radixin-moesin-dependent T cell-APC conjugation through inhibition of Vav guanosine exchange activity on Rac proteins. J Immunol. 2006;176:640-51.
71. Prantera C, Zannoni F, Scribano ML, Berto E, Andreoli A, Kohn A, Luzi C. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. Am J Gastroenterol. 1996;91:328-32.
72. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002;51:405-9.
73. Regueiro M, Loftus EV Jr., Steinhart AH, Cohen RD. Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. Inflamm Bowel Dis. 2006;12:979-94.
74. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet. 1999;354:635-9.
75. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956-63.
76. Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, Danielsson A, Goebell H, Thomsen OO, Lorenz Meyer H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med. 1994;331:842-5.
77. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462-76.
78. Safdi M, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targans S, Fleishman C, Wiita B. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997;92:1867-71.
79. Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Ver. 2000;(2):CD000545.
80. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56:1232-9.
81. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3:390-407.
82. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-53.
83. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol. 2004;15:4-5.
84. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Ver. 2008;(3):CD000296.
85. Singleton JW, Law DH, Kelley ML, Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology. 1979;77:870-82.
86. Summers RW, Switz DM, Sessions JT, Jr, Becktel JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology. 1979;77:847-69.
87. Sutherland L, Singleton J, Sessions J, Hanauer S, Krawitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M. Double blind, placebo controlled trial of metronidazole in Crohn's disease. Gut. 1991;32:1071-5.
88. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Ver. 2006;(2):CD000544.
89. Te HS, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol. 2000;95:3150-6.
90. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, Vatn M, Persson T, Pettersson E. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. N Engl J Med. 1998;339:370-4.
91. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, Vatn M, Persson T, Pettersson E. Budesonide and mesalazine in active Crohn's disease: a comparison of the effects on quality of life. Am J Gastroenterol. 2002;97:649-53.
92. Tiede I, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, Lehr HA, Wirtz S, Becker C, Atreya R, Mudter J, Hildner K, Bartsch B, Holtmann M, Blumberg R, Walczak H, Iven H, Galle PR, Ahmadian MR, Neurath MF. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. J Clin Invest. 2003;111:1133-45.
93. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041-8.
94. Truelove SC, Watkinson G, Draper G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. Br Med J. 1962;2:1708-11.
95. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet. 1974;1:1067-70.
96. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007;5:103-10.
97. Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, S'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125:1025-31.
98. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, Baert F, Noman M, Vermeire S, Ternant D, Waiter H, Paintaud G, Rutgeerts P. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology. 2008;134:1861-8.
99. Van Gossum A, Dewit O, Louis E, de Hertogh G, Baert F, Fontaine F, DeVos M, Enslen M, Paintin M, Franchimont D. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. Inflamm Bowel Dis. 2007;13:135-42.
100. West RL, van der Woude CJ, Hansen BE, Felt-Bersma RJ, van Tilburg AJ, Drapers JA, Kuipers EJ. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. Aliment Pharmacol Ther. 2004;20: 1329-36.
101. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol. 2006;2:602-10.
102. Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006;23:1567-74.


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