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Clinical practice guidelines for the treatment of Crohn's disease in the adult population

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Abstract

Objective: Crohn's disease is an idiopathic inflammatory disorder of unknown origin, influenced by genetic, immunological, and environmental factors. The incidence and prevalence of Crohn's disease have increased in Colombia. The treatment of these patients is not easy and has improved in recent years. Therefore, it is necessary to develop the Colombian Clinical Practice Guideline to guide the treatment of this complex disease and unify criteria. **Materials and methods:** The present guideline was carried out by a multidisciplinary team with support from the Asociación Colombiana de Gastroenterología, the Cochrane ITS Team, and the Clinical Research Institute of the Universidad Nacional de Colombia. Clinical questions regarding this disease were developed, and national and international guidelines were searched in specialized databases. The existing guidelines were evaluated in terms of quality and applicability. The Cochrane Group conducted a systematic search of the existing literature. Evidence tables were elaborated, and recommendations were made using the GRADE methodology. **Results:** An evidence-based clinical practice guideline was developed for the medical and surgical treatment of Crohn's disease in the adult population in Colombia. Treatment algorithms were designed, taking into account the activity, behavior, and location of the disease. **Conclusions:** It was established that proper clinical, endoscopic, and imaging assessment, as well as individual risk stratification, are important for treatment. Also, the indications for adequate medical and surgical treatment of these patients were specified.

Keywords

Crohn's disease, behavior, extension, mucosal healing, biological therapy, perianal Crohn's, postoperative Crohn's.

RATIONALE AND THEORETICAL FRAMEWORK

Inflammatory bowel disease (IBD) is a term used to describe two rare chronic inflammatory conditions of the gastrointestinal tract that mainly affect the colon and the small intestine: *Crohn's disease* (CD) and *ulcerative colitis* (UC). IBD is characterized by multiple relapses; besides, an increased frequency of occurrence has been detected worldwide in recent years. (1, 2) Its etiology is unknown, but it results from a complex interaction between the host's genotype, intestinal microbiota and environmental factors, which trigger an alteration in the intestinal immune system response (3). Despite CD has traditionally been considered an autoimmune disease, it does not meet the criteria

to be considered as such (4) and, therefore, some authors think it is actually an autoinflammatory disease (5, 6).

Historically, studies reporting the highest prevalence rates of IBD have been conducted in Scandinavian countries, the United Kingdom, and North America. IBD affects approximately 5 million people worldwide, including 1.4 million in the United States and about 3 million in Europe (7). In this regard, a systematic review of epidemiological studies about IBD found a CD prevalence of 0.6-322, 16.7-318.5, and 0.88-67.9 cases per 100,000 people in Europe, North America, and Asia, respectively. Also, an increase in its incidence over time has been described in 75% of CD studies (8). In addition, a recent systematic review that included 147 studies reported high prevalence rates of CD in Europe (where the highest prevalence was found in Germany with 322 cases per 100,000 people) and North America (being the highest prevalence found in Canada with 319 cases per 100,000 people), which have remained stable (9). However, population-based studies conducted since 1990 have shown an increase in the incidence and prevalence of CD in developing countries from Asia and South America such as Brazil, Mexico, and Colombia (9-13).

In Colombia, CD has been found to be less frequent than UC: in 1991, in one of the first studies published in the country about this topic, and that included 108 patients diagnosed with IBD (98 with UC and 10 with CD) between 1968 and 1990 in Bogota (Colombia), a UC/CD ratio of 9.8:1 was described (14). Then, in 2010, a study conducted at the Hospital Pablo Tobón Uribe in Medellín (Colombia) found that out of 202 patients diagnosed with IBD between 2001-2009, only 15.8% were CD cases, while 80.7% had UC (classifying the type of IBD was not possible in 3.5% of the study population), that is, a UC/CD ratio of 5.1:1 (15). In addition, in a recent work conducted at the same hospital, a UC/CD ratio of 3.0:1 was found, since out of 649 patients with IBD, 478 had UC (73.7%), 159 had CD (24.5%). and in 12 (1.8%) it was not possible to determine the form of IBD; besides, in said study, CD was predominant in men (13). Other case series carried out in Colombia have also described a higher frequency of UC cases compared to CD cases (16, 17). These data show that in Colombia, more and more patients are diagnosed with CD in the context of IBD, which is a similar situation to what has been reported in developed countries (18).

Because of its low prevalence, CD, unlike UC, meets the criteria to be considered an *orphan disease.* In Colombia, an orphan disease is defined as a severe, chronic debilitating and life-threatening disease with a prevalence (the number of individuals affected by a disease within a particular period of time) of less than 1 case per 5000 people (Law 1392 of 2010/Law 1438 of 2011) (19).

CD usually occurs between the second and fourth decade of life, with a small additional peak in people aged 50-60 years (20). Its diagnosis is based on the simultaneous evaluation of, on the one hand, clinical signs and symptoms and, on the other, alterations in endoscopic or radiological and biochemical and histopathological studies. Isolated alterations in the histopathology report are not enough to reach a CD diagnosis. In fact, the European Crohn's and Colitis Organisation, in their recently published guidelines on CD, has confirmed that there is not a "gold standard" for the diagnosis of CD, and that genetic or serological tests should not be used for diagnosing it (21, 22). Clinically, CD is a chronic inflammatory disorder of the gastrointestinal tract that mainly affects the colon and the small intestine; however, it can affect any part of the gastrointestinal tract from the mouth to the perianal area. It can also affect organs outside the gastrointestinal tract, and its clinical course is variable with alternating periods of activity and remission of symptoms. CD produces a segmental, asymmetric and transmural inflammation, and, from a clinical perspective, is a heterogeneous, insidious and progressive disorder. Depending on the severity, location and behavior of CD, the most common symptoms and clinical signs are abdominal pain, diarrhea, gastrointestinal bleeding, and weight loss (1). Smoking, living in urban areas, exposure to antibiotics, and oral contraceptive use have been described as risk factors for CD (23).

When performing a physical examination in these patients, signs of systemic toxicity, dehydration, malnutrition, anemia and malabsorption, as well as abdominal pain or palpable abdominal masses must be looked for. Physical examination of the perianal area is mandatory since perianal involvement occurs in up to one third of patients (1). The most frequent laboratory findings are anemia, thrombocytosis, hypoalbuminemia, and high C-reactive protein (CRP) levels; however, the latter does not correlate well with endoscopic findings and in one third of patients, CPR levels never increase (21, 24). Fecal biomarkers such as calprotectin have been correlated with inflammatory activity by neutrophils in the intestine and are being used as a screening test with high sensitivity and specificity for the diagnosis of IBD (25). In this regard, it has been reported that patients with irritable bowel syndrome (IBS) symptoms and with a fecal calprotectin concentration <40 μg/g, have a 1% chance of having IBD (26). On the other hand, between 60% and 70% of patients with CD may have elevated antimicrobial antibody levels, being *anti-Saccharomyces cerevisiae* antibodies (ASCA) the most prevalent; somehow, the sensitivity and specificity of these antibodies are too low to reach a CD diagnosis (27).

Endoscopic findings reported by means of ileocolonoscopy are key to the diagnosis of CD. Typical findings

include the presence of multiple inflammatory aphthous ulcers with segmental involvement, associated with longitudinal and serpentiginous ulcers. Additionally, the presence of perianal involvement, fistulas, ileitis, and strictures supports the diagnosis of CD (22, 28). In case of negative results in the ileocolonoscopy, but clinical suspicion of CD, small bowel capsule endoscopy is indicated in the absence of obstructive symptoms or known stenosis (21). Histologically, inflammatory involvement is chronic, focal, discontinuous, and transmural. Epithelioid granuloma is the histological marker of CD, but it is only found in 15% of mucosal biopsies and 70% of surgical specimens (1, 29). Imaging studies such as magnetic resonance (MR) enterography and Computed tomography (CT) enterography are useful to reach a CD diagnosis, as well as to determine its extent and rule out complications such as strictures and fistulas; furthermore, they can be useful for follow-up purposes, since they can be used to measure the activity of the disease and the patient's response to treatment (30). It should be noted that MR enterography is preferred due to the lower radiation exposure it involves compared to CT enterography. Finally, the use of pelvic MRI is recommended for the study of perianal and fistulizing CD (30).

Once the diagnosis has been reached, patients with CD should be phenotyped according to the Montreal classification (31) in order to determine its location and clinical behavior. The location of the disease tends to be stable, but its behavior usually changes over time (32).

Age at diagnosis (A)	A1: under the age of 16 years A2: between 17 and 40 years A3: older than 40 years
Location (L)	L1: ileum L2: colon L3: ileum and colon L4: isolated segment of the upper gastrointestinal tract
Behavior (B)	B1: non-stenosing, and non-penetrating CD B2: stenosing CD B3: penetrating P: perianal CD

A systematic review that included population-based studies found that the risk of surgery in patients with CD was 16.3%, 33.3%, and 46.6% at 1, 5, and 10 years of follow-up, respectively (33). Unfortunately, CD cannot be cured with surgery: 50% of patients report clinical recurrence, 80%, endoscopic recurrence, and 30% require additional surgical management (34). In addition, patients with CD are classified based on the risk of developing complications (35). On the other hand, conditions that are associated with a poor prognosis in these patients include isolated location in the ileum or location in the ileum and colon, severe involvement of the small bowel or extensive involvement of the upper gastrointestinal tract, perianal lesions, severe rectal involvement, deep ulcers on colonoscopy, history of intestinal surgical resections, stenosing and penetrating behavior of the disease, the need for steroid use at the time of diagnosis, young age at diagnosis (<30 years) and being a smoker (35, 36).

The current objective of CD treatment is to induce and maintain the clinical and endoscopic remission of its symptoms in order to prevent its progression (37, 38). In the past, the goal was to control CD symptoms; however, they do not correlate with the inflammatory activity of the involved areas. Therefore, the lack of this correlation has shifted the treatment goals to achieve a "deep remission", which includes both, clinical remission, and endoscopic healing (1, 39). When "deep remission" is achieved, there are fewer relapses, fewer surgeries, and less intestinal damage (38). Considering that deep remission is the current goal of treatment for CD, therapeutic targets ("Treat to Target") have been identified (40), and recent studies suggest that this strategy, besides being cost-effective, should have an impact on CD progression and improve outcomes in these patients (41).

Drugs used in the treatment of CD aim to attenuate or reduce the chronic abnormal inflammatory activity by acting on the immune pathways of the disease (1). It should be noted that none of the available treatment cures CD. Drugs used to treat CD include 5-aminosalicylates (5-ASA); systemic (prednisone, prednisolone) or topical (budesonide) steroids; immunomodulators (azathioprine, 6-mercaptopurine, methotrexate); biological therapy (tumor necrosis factor-alpha [TNF-α] inhibitors): infliximab, adalimumab, and certolizumab pegol; anti-integrins: natalizumab, vedolizumab, anti-L12/23 p40 subunit, ustekinumab; probiotics, and antibiotics (ciprofloxacin, metronidazole). Surgical treatment is also available. Furthermore, the expiration of the patent of infliximab has allowed the introduction of its biosimilar (37, 42-44).

Given the complexity of CD, management by a multidisciplinary team is necessary, which, in addition to the gastroenterologist, includes the fundamental participation of a colon and rectal surgeon expert in the disease, as well as a nurse, a radiologist, a pathologist, a nutritionist and a psychologist, among others (45).

The standard of care includes the education of patients and their families, the absolute prohibition of smoking and the vaccination of patients (46-49).

Once the CD diagnosis has been established, ruling out the presence of diseases that may recur or be exacerbated when starting immunosuppressive treatment (steroids, immunomodulators or biological therapy) is essential (50). Therefore, performing some tests is required, including tuberculin test; chest x-rays; hepatitis B virus panel: hepati-

tis B surface antigen, HBsAb (hepatitis B surface antibody), anti-HBc or HBcAb (hepatitis B core antibody); HCV antibody (anti-HCV test); human immunodeficiency virus (HIV), varicella zoster, and Epstein-Barr virus tests (51). On the other hand, a concern when using biological therapy is the risk of infection, serious infection, and opportunistic infection. A serious infection occurs when the patient requires hospitalization or intravenous administration of antibiotics, and an opportunistic infection is caused by the weakening of the immune system, since it does not occur in immunocompetent individuals. Some examples of this type of infection include those caused by *Clostridium difficile*, mycobacterium, candida, cytomegalovirus, and varicella zoster (50). Per se, CD activity also increases the risk of infections: when the disease is moderate-severe, the risk of serious disease increases twofold. For every 100 points of activity, the risk of serious infection and opportunistic infections increases by 39% and 31%, respectively (51).

CD treatment involves an induction pharmacological regimen and then a maintenance pharmacological regimen. The choice of medication depends on the severity of the disease, the use of the medication in any previous treatment, and the presence of risk factors for developing complications (35, 37, 52, 53).

Currently, there are several pharmacological therapies and surgical interventions to treat CD; however, and despite there are multiple randomized studies, some clinical conditions related to CD are still managed based on clinical judgment and experts' opinion, which has been reflected in the existing conceptual differences regarding the treatment of these patients. Taking this into account, and the fact that CD is a chronic disease that mostly affects young people, as well as the resulting social and economic implications, the development by multidisciplinary groups of a clinical practice guideline (CPG) for the treatment of this disease based on the best and more recent available evidence is necessary to unify the criteria for the successful management of CD in Colombia. The wide variety of clinical scenarios and the diverse individual and social circumstances of these patients difficult the provision of medical care to them, which is one of the justifications for developing this GPC with the aim of reducing the unjustified variability of criteria for treating patients with CD. Although the concepts presented here are based on the best published scientific evidence, this CPG provides recommendations that shall be used according to the clinical judgment of the treating physician.

OBJECTIVES

This CPG was developed taking into account the following objectives:

- To make evidence-informed recommendations for the treatment of patients with CD.
- To contribute to the timely and safe treatment of patients with CD, considering the minimization of the need for hospitalization and sequelae.
- To support decision makers in the development of policies for the proper management of CD.

POPULATION

Population groups to be considered

Patients older than 16 years diagnosed with CD, regardless of the time of progression and the clinical stage of the disease, nor the health care insurance plan they are enrolled in.

Population groups that are not considered

- Patients with ulcerative colitis.
- Patients with indeterminate inflammatory bowel disease.
- Patients with extraintestinal manifestations of CD.
- Patients with side and/or adverse effects resulting from CD treatment.
- Pregnant women or nursing mothers with CD.
- Patients with infectious colitis.

USERS OF THE CLINICAL PRACTICE GUIDELINE

This CPG is intended for health care workers such as gastroenterologists, colorectal surgeons (coloproctologists), gastrointestinal surgeons, internal medicine specialists, family medicine specialists, general practitioners, as well as for patients and other health care professionals interested in the management of CD.

FUNDING OF THE CLINICAL PRACTICE GUIDELINE

The development of this GPC was funded by the Colombian Association of Gastroenterology.

EDITORIAL INDEPENDENCE STATEMENT

The funding organization provided support to the group in charge of the development of the guidelines (GDG) during its development, thus guaranteeing that its contents are transferable and applicable in the Colombian context. The scientific research work, as well as the recommendations included in this document were carried out independently by the GDC. The funding organization did not have any influence on the contents of the CPG.

SCOPE

This CPG is directly intended for health care professionals who provide medical care to patients with CD, but it is also indirectly intended for health care decision makers in the context of health care provision, and health insurance companies, health care payers, and health care policy makers. This CPG is intended to establish guidelines for the treatment of CD, and its scope is limited to the target population.

Health care provision setting

This CPG aims to help medical care providers treating patients older than 16 years with CD in any level of care. It should be noted that the management of very specific conditions by health care professionals involved in the care of patients with CD requires specific recommendations, which are beyond the scope of this guideline.

This CPG provides recommendations for all levels of care in which patients with CD are treated. It also provides health care professionals with enough information to provide guidelines for the proper management of CD.

Main clinical aspects

Clinical aspects addressed by the CPG:

- The CPG will address the medical and surgical treatment of CD and poor prognostic factors in patients older than 16 years.
- Aspects related to the diagnosis of the disease or the rehabilitation of these patients will not be addressed since, due to their length and complexity, these should be addressed in separate CPGs to be developed *de novo* (NICE, 2010).

GUIDELINE AUDIT SUPPORT

Review criteria and assessment indicators have been included in the development of the CPG.

UPDATING THE CLINICAL PRACTICE GUIDELINE

Recommendations made in this guideline must be updated within the next three (3) years or sooner if new evidence modifying said recommendations becomes available. This process should be carried out by creating an expert panel responsible for making the necessary changes.

LEVEL OF EVIDENCE AND STRENGTH (GRADE) OF RECOMMENDATIONS

Level of evidence

Overall quality of evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system

Grade	Judgment	Characteristics
A	High ⊕⊕⊕⊕	Further research is unlikely to change confidence in the estimate of the effect.
B	Moderate ⊕⊕⊕O	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
C	Low ⊕⊕OO	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
D	Very low ⊕OOO	Any estimate of effect is very uncertain

Grade of recommendation

Strength of recommendations according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system

Strength of recommendation	Meaning
Strong in favor	Desirable consequences clearly outweigh undesirable consequences. **Following the recommendation is recommended.**
Weak in favor	Desirable consequences are likely to outweigh undesirable consequences. **Following the recommendation is suggested.**
Weak against	Undesirable consequences clearly outweigh desirable consequences. **Following the recommendation is not suggested.**
Strong against	**Following the recommendation is not recommended.**
Good practice point	Recommended practice based on the clinical practice of the group in charge of the development of the guideline

GLOSSARY

- Active disease: CD is clinically classified as *mild*, *moderate,* and *severe*. The severity of the disease is determined using the Crohn's Disease Activity Index (CDAI). In most clinical trials, CD is classified depending on the score as follows: mild: 150-220; moderate: 220-450, and severe: >450.
- Steroid-dependent Crohn's disease:
  - patients in which reducing the steroid dose below the equivalent of prednisone 10 mg/day (budesonide 3 mg/day) within the first 3 months after being administered the steroids is not possible without experiencing disease recurrence; or
  - patients who relapse within the first 3 months after steroids are suspended.
  - total length of steroid therapy should not exceed 3 months.
- Extensive disease: intestinal involvement >100 cm, regardless of CD location. The sum of inflammation areas alternating with non-involvement areas is included.
- Localized disease: intestinal involvement of less than 30 cm.
- Steroid refractory disease: patients with CD activity despite the administration of up to 1 mg/kg/day prednisone for 4 weeks.
- Relapse: exacerbation of symptoms in a patient with CD who was in clinical remission, either if it occurs spontaneously or after medical treatment; a 70-point increase in the CDAI. Confirming the relapse with laboratory, endoscopic or imaging studies in the clinical practice is suggested.
- Early relapse: exacerbation of symptoms in less than 3 months in a patient with CD in clinical remission and undergoing medical treatment.
- Recurrence: recurrence of endoscopic lesions after undergoing surgical resection.
- Clinical recurrence: recurrence of symptoms after performing the complete macroscopic resection of the disease, and after confirming the recurrence of endoscopic lesions. Confirming the presence of lesions is important, since there are conditions with symptoms that can mimic those of CD (bile salts malabsorption, motility disorders, bacterial overgrowth, among others).
- Morphological recurrence: appearance of new CD lesions after performing the macroscopic resection of the disease, usually in the *neo-terminal ileal stricture* or in the *anastomosis*; it is usually detected through endoscopy, imaging studies or surgery. Endoscopic recurrence is classified according to the RUTGEERTS score: 0: no evident lesions. 1: less than 5 anastomotic aphthous lesions. 2: more than 5 apthous lesions with normal mucosa between the lesions. 3: diffuse aphthous ileitis with diffusely inflamed mucosa. 4: ileitis with ulcers, nodules, and/or strictures.
- Clinical remission: CDAI <150 points. Confirming clinical remission by means of objective parameters based on laboratory (fecal calprotectin, CRP), endoscopic or imaging studies in the clinical practice is suggested.
- Response to treatment: a change in the CDAI score, a ≥100 points decrease in the CDAI score.

METHODOLOGY

This section has been adapted from the Pan American Health Organization (PAHO) template available in the *Strengthening national evidence-informed guideline programs. A tool for adapting and implementing guidelines in the Americas* document, published in 2018.

Composition of the group

The GDG was composed by experts in gastroenterology, colorectal surgery, gynecology, epidemiology, pharmaceutical chemistry, and public health. In addition, cooperation by the Colombian Cochrane STI (Sexually Transmitted Infections) Group was received by the GDG. The Cochrane STI Group performed the systematic search of the relevant literature, retrieved the full text of the studies and created the GRADE tables.

CONFLICTS OF INTEREST STATEMENT

Those who took part and are responsible for the making of the recommendations presented in this CPG shall state in writing and in advance any conflicts of interest regarding said recommendations.

An analysis of the conflicts of interest was carried out and, based on the conflict or conflicts stated, partial or full participation was decided. Two experts were excluded from the formulation process of recommendations related to biological drugs for they are speakers for several pharmaceutical companies on the use of these drugs for treating CD. This analysis is available in **Annex 1**.

Definition of the scope and objectives of the clinical practice guideline

The scope and objectives of this CPG were defined by the Colombian Association of Gastroenterology with the purpose of supporting health professionals that provide medical care to patients with CD, so that they can provide high quality, equitable, efficient, and homogeneous medical care to these patients. After conducting a literature review on CD, the GDG wrote a document considering the heterogeneity in clinical practice,

the availability of new evidence, the existence of new therapeutic alternatives, the inadequate use of resources, and the quality problems found in clinical practice resulting from the health care provision system. The topics that were addressed and those who were not addressed, as well as the target population and main clinical aspects of the CPG were also defined.

Decision on the development or adaptation of the clinical practice guideline

The GDG conducted a systematic search of the literature in order to identify all Colombian and international CPGs addressing the management of patients with CD and that had a similar scope and objective to those proposed for this CPG. The quality of the CPGs retrieved was evaluated using the AGREE II tool (54) and each document was graded independently by two raters in order to determine the overall quality of each guideline. According to the guidelines proposed by international CPG developers, once the grading process was completed, discrepancy levels for each guideline were assessed to identify the domains that required to be reviewed. This discrepancy was evaluated using the rating system proposed by the AGREE group (54).

Once the overall quality of each guideline was determined and the domains that needed to be reviewed were identified, informal consensus meetings were held to establish the possibility of adapting or developing *de novo* the CPG. Bearing this in mind, the GDG used the criteria included in the CPG adaptation or *de novo* development decision matrix as input (55).

The following aspects are considered in the decision matrix:

- The scope and objective of the retrieved CPGs must be related to the scope and objectives of the CPG to be developed.
- The CPGs retrieved were developed using evidence-based methodologies, have evidence tables and are less than 5 years old.
- The CPGs must have a have an adequate score in terms of methodological quality and editorial independence when evaluated using the AGREE II tool.
- The CPGs must be recommended by both raters.

Based on the results of the decision matrix, the GDG considered that none of the eligible CPGs met all the necessary criteria to be adapted, so the *de novo* development of the CPG was started.

Formulation of the clinical questions of the clinical practice guideline

The GDG reviewed the relevant clinical aspects to be included in the CPG and, based on them, formulated basic questions which were then restructured according to the PICO (population, intervention, comparison, and outcome) framework. The resulting questions can be found in **Annex 2**.

Identification and grading of the clinical practice guideline outcomes

Literature search for the de novo development

The first step for the *de novo* development was conducting a search of systematic reviews in the following databases: MEDLINE (via Ovid) EMBASE (via embase.com) and Cochrane Library, which in turn includes the *Health Technology Assessment* (HTA) database, the *Database of Abstracts of Reviews of Effects* (DARE) and the *NHS Economic Evaluation Database* (NHS EED).

Search strategies were developed and performed by the search coordinator of the Cochrane STI Group; the GDG contributed to this process too. For this purpose, identification forms of words related to the clinical questions were used to select controlled language and free language terms, which in turn allowed creating the search syntaxes for each database (**Annex 4**). No publication date or language restrictions were applied in the search. Classic and relevant studies about CD proposed by experts were also included for full analysis. Clinical questions that were not addressed by systematic reviews were answered by including primary studies.

Grading of the evidence

Evidence was graded according to the type of evidence. The systematic reviews (SR) that were retrieved were assessed using the AMSTAR checklist (56); besides, the contents, quality and clinical relevance of each SR were evaluated to identify those with the highest methodological quality, which were finally included in the GPC. When there were no high-quality systematic reviews, primary studies were assessed using the risk of bias tool recommended by Cochrane (57).

Evidence profiles were created using the www.guidelinedevelopment.org website to summarize the evidence found, and the levels of evidence were graded according to the GRADE classification, which grades the quality of the evidence in four levels (58).

Judgment	Characteristics
High ⊕⊕⊕⊕	Further research is unlikely to change confidence in the estimate of the effect.
Moderate ⊕⊕⊕O	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low ⊕⊕OO	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low ⊕OOO	Any estimate of effect is very uncertain

Grading the strength of the recommendations

Recommendations were formulated in two steps. First, the GDG made the preliminary recommendations considering the risk-benefit balance, the preferences of patients, and the Colombian context. Then, the recommendations were discussed and adjusted in an expert panel with the representatives of users and patients. The strength of each recommendation was determined based on the level of evidence and other additional considerations that were fully reviewed by the GDG, the managing body of the CPG, and the expert panel taking into account the different scenarios of the Colombian context.

The GRADE methodology grades the strength of a recommendation as "Strong" or "Weak". Once the risk-benefit balance, the quality of evidence, the values and preferences of patients, and the Colombian context were considered, the strength of each recommendation was determined using the following structure:

Strength of recommendation	Meaning
Strong in favor	Desirable consequences clearly outweigh undesirable consequences. **Following the recommendation is recommended.**
Weak in favor	Desirable consequences probably outweigh undesirable consequences. **Following the recommendation is suggested.**
Weak against	Undesirable consequences probably outweigh desirable consequences. **Following the recommendation is not suggested.**
Strong against	Undesirable consequences clearly outweigh desirable consequences. **Following the recommendation is not recommended.**

Finally, expert panel agreement with the recommendations that were suggested and the inclusion of the participants' perspective in them was verified. All recommendations and their grades were voted on.

Good practices

Good practices are operational suggestions based on the experience of the GDG and the GRADE working groups where different stakeholders participated; although they are not evidence-based, they are part of the good diagnosis, treatment, or follow-up practices of patients. Good practices are intended to support the recommendations made in the CPG.

Inclusion of costs and preferences of patients

A cost-effectiveness assessment was not performed in the development of this CPG. The preferences of patients were identified through a systematic review, where the values and treatment preferences of patients and their perception of CD were assessed, which in turn helped strengthen the recommendations.

Cost-related considerations were not included in the development of this CPG given the variability of the Latin American context, so they are not included in the value judgment table of the recommendations. In addition, cost-influenced recommendations were not identified. Regarding preferences and values of patients, a search was performed, but it yielded only one study. However, given the disease, the management strategy and the target population, there are few recommendations that can be influenced by the preferences of parents or caregivers.

Formulation of questions by expert consensus

In the case of clinical questions in which no evidence was found or where evidence was controversial, the GDG made clinical practice recommendations based on their professional experience and good practices; these recommendations were submitted to formal consensus in the GRADE working groups.

CLINICAL QUESTIONS

QUESTION N° 1. WHAT ARE THE PREDICTORS OF RELAPSE OF CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation	N°	Summary
Strong in favor		Measuring C-reactive protein (CRP) levels and using erythrocyte sedimentation rate (ESR) to predict relapse in patients with Crohn's disease is recommended. **Very low quality of evidence ⊕OOO**
Weak against		Measuring ASCA (Anti-*Saccharomyces* cerevisiae antibodies) to predict relapse in patients with Crohn's disease is not suggested. **Very low quality of evidence ⊕OOO**
Weak in favor		Measuring fecal calprotectin levels to predict relapse in patients with Crohn's disease is suggested. **Very low quality of evidence ⊕OOO**

Good practice point	Fecal calprotectin must be measured every 3 to 6 months.
Good practice point	Taking the first stool sample of the day is suggested when measuring fecal calprotectin levels; also, a cutoff point of 250 µg/g is the most reliable value to differentiate mucosal healing from inflammation caused by Crohn's disease. A cutoff point of 100 µg/g is considered a predictor value of post-operative recurrence of Crohn's disease.
Good practice point	In patients with Crohn's disease on infliximab treatment, serum levels of the drug can be measured to predict clinical and endoscopic remission.
Weak in favor	Using magnetic resonance imaging as a radiology exam to predict deep remission in patients with perianal fistulizing Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Implementing mucosal healing as a therapeutic goal in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Using capsule endoscopy to determine small bowel mucosal healing is suggested.

Summary of evidence

C-reactive protein, erythrocyte sedimentation rate, and ASCA

A systematic review (AMSTAR score 8/11) assessed the predictive ability of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ASCA in patients with CD who were in remission. The outcome of interest was the occurrence t of relapse, defined as having a CDAI score >150; the prognostic value was expressed using hazard ratios (HR) or risk ratios (RR) (59).

There was heterogeneity among studies included in the review regarding the reporting of outcomes and the cut-off points assessed; thus, summarizing the evidence using meta-analysis techniques was not possible.

C-reactive protein: a cohort study performed a relapse prediction model based on the biological parameters of 101 patients with fistulizing, inflammatory or stenosing, intestinal or extraintestinal CD. Based on this model, it was established that, during the first year of follow-up, a CRP level greater than 10 mg/L substantially increases the probability of relapse (HR: 1.5; 95% confidence interval [CI]: 1.1-1.9) within the next 92 days. The model was adjusted by fistulizing CD, presence of colitis, and level of stress (60).

A second cohort study assessed the prognostic value of CRP in 71 patients with ileal, ileocolonic or colonic CD, using a cutoff value of 20 mg/L. According to this study, a positive result in the CRP test markedly increases the risk of relapse (RR: 10.5; 95% CI: 2.3-48.1) within the next 6 weeks (61). Finally, a third study analyzed the role of CRP together with other serological tests as predictive markers in 53 patients with colonic CD. In said study, when the model was adjusted by calprotectin levels, gender, presence of smoking, extent of the disease, and azathioprine consumption, no significant differences in the risk of recurrence were found when CRP levels exceeded 9 mg/L (HR: 9.1; 95% CI: 0.5-53.3) (62).

In addition, in a meta-analysis that was already described above (24), a CPR sensitivity of 49% (95% CI: 0.34-0.64) and specificity of 92% (95% CI: 0.72-0.96) for the detection of endoscopic disease activity in patients with inflammatory bowel disease was found.

Erythrocyte sedimentation rate (ESR): a cohort study analyzed the predictive value of several biological tests in 101 patients with fistulizing, inflammatory or stenosing, intestinal or extraintestinal CD; in the bivariate analysis, no association between ESR values and subsequent risk of relapse was found (HR: 1.3; 95% CI: 1.0-1.7) (60). On the other hand, another cohort study conducted in 71 participants determined the prognostic usefulness of ESR in patients with ileal, ileocolonic or colonic CD, reporting that when ESR exceeded 15 mm, the risk of relapse increased during the next 6 weeks (RR: 6.1; 95% CI: 1.9-18.9). Finally, according to the same study, high levels of CRP (>20 mg/L) and ESR (>15 mm) were significantly associated with recurrence of active Crohn's disease within the next 6 weeks (RR: 9.9; 95% CI: 3.3-29.7) (61).

Anti-*Saccharomyces* cerevisiae antibodies (ASCA): only one cohort study, conducted in 101 patients with fistulizing, inflammatory or stenosing, intestinal or extraintestinal CD, determined the role of this biomarker as a predictor of relapse in CD patients. The analysis of this study failed to show an association between positivity for this marker and the subsequent development of active CD (HR: 1.2; 95% CI: 0.54-2.5) (60).

Quality of evidence: very low ⊕OOO

Fecal calprotectin

A systematic review and meta-analysis (63) (AMSTAR score 8/11) evaluated the diagnostic accuracy of fecal calprotectin to predict relapse of CD. The presence of active Crohn's disease, defined as having a CDAI score >150 or a Harvey-Bradshaw index score greater than 4 was determined as the standard of reference, and diagnostic accuracy was reported in terms of sensitivity, specificity, positive and negative likelihood ratios (LR+, LR-) and area under the curve values.

Based on the information provided by the six studies included in the systematic review, it was found that a

positive value in fecal calprotectin levels (positivity range from 130 µg/g to 340 µg/g) acceptably predicts the development of recurrence of CD (sensitivity, 75%; 95% CI: 64%-84%; specificity, 71%; 95% CI: 64%-76%; LR+, 2.37; 95% CI: 1.56-3.61; LR-, 0.41; 95% CI: 0.27-0.61), with an area under the curve (AUC) of 0.79 (95% CI: 0.74-0.64). Besides, the test performance was quite similar in the case of patients with colonic CD (sensitivity, 76%; 95% CI, 59%-88%; specificity, 77%; 95% CI, 69%-83%; LR+, 3.26; 95% CI, 1.89-5.25; LR-, 0.34; 95% CI, 0.19-0.60), with an AUC of 0.81 (95% CI, 0.76-0.86) (63).

In the case of post-operative endoscopic recurrence of CD, sensitivity and specificity were 0.90 and 0.36, respectively, for a fecal calprotectin cutoff point of 50 µg/g; 0.81 and 0.57, for a cutoff point of 100 µg/g; 0.70 and 0.69, for a cutoff point of 150 µg/g; and 0.55 and 0.71, for a cutoff point of 200 µg/g. In patients with a small bowel CD diagnosis confirmed by capsule endoscopy, the sensitivity and specificity values were 0.83 and 0.53, for a cutoff point of 50 µg/g, and 0.42 and 0.94, for a cutoff point of 200 µg/g, respectively (64).

The recently published CALM study combined the use of fecal calprotectin and CRP levels, reporting a mucosal healing rate in 79% of patients with calprotectin and CRP levels <250 µg/g and <5 mg/L, respectively (65).

Quality of evidence: very low ⊕○○○

Serum levels of infliximab

A systematic review and meta-analysis (66) (AMSTAR score 8/11) assessed the prognostic utility of serum levels of infliximab in patients with inflammatory bowel disease. The primary outcome was the frequency of clinical remission, while secondary outcomes included the proportion of patients with endoscopic remission and the need for colectomy. The review retrieved 22 observational studies, of which 11 were conducted exclusively in patients with CD, 4 in patients with ulcerative colitis, and 7 in individuals with indeterminate inflammatory bowel disease. Based on the findings of this systematic review, when infliximab levels exceeded 2 µg/mL at 14 weeks, patients with inflammatory bowel disease were more likely to achieve remission (RR: 2.91; 95% CI: 1.79-4.73) and intestinal mucosal healing (RR: 3.04; 95% CI: 1.42-6.51). Finally, the presence of undetectable serum levels of infliximab increased the probability of requiring colectomy compared to patients with detectable levels of this drug (RR: 5.4; 95% CI: 3.10-9.30) (66).

Quality of evidence: very low ⊕○○○

Using Magnetic resonance imaging to predict deep remission

A prospective cohort study (67) assessed the usefulness of MRI in predicting deep remission in patients with perianal fistulizing CD. The outcomes of interest were the presence of remission and deep remission (which was determined using the Van Assche index, which evaluates the complexity, extension, and location of the fistula), contrast medium uptake, rectal mucosa involvement, and the presence of abscesses; the assessment was performed independently by two radiologists with expertise in gastrointestinal tract imaging studies and who were not informed on the clinical signs and symptoms of the patients.

The cohort consisted of 49 patients who were undergoing anti-tumor necrosis factor (TNF)-α therapy and concomitant use of immunosuppressants to induce or maintain remission of the disease. According to this study, factors associated with the presence of remission were absence of rectal involvement on the MRI (OR: 4.7; 95% CI: 1.21-49.0) and absence of switch of anti-TNF-α (OR: 7.7; 95% CI: not reported; p<0.05). Regarding deep remission, absence of rectal involvement on the MRI was strongly associated with absence of ulcers in the anal canal (OR: 4.6; 95% CI: 1.03-20.5) (67).

A meta-analysis that included 12 studies on the performance of magnetic resonance enterography using a new technique based on diffusion-weighted imaging (DWI), which, unlike the conventional technique, is faster and does not require the intravenous administration of a contrast medium, reported a sensitivity of 92.9% (95% CI: 85.8%-96.6%) and a specificity of 91% (95% CI: 79.7%-96.3%) for detecting inflammation; however, there was heterogeneity among the studies retrieved, and authors concluded that there may be an overestimation of the results (68). In addition, a recent systematic review considers this new technique a valid alternative to the conventional technique that is less invasive, faster, and does not require fasting or bowel preparation (69).

Quality of evidence: very low ⊕○○○

Use of capsule endoscopy to determine small bowel mucosal healing

In a systematic review and meta-analysis of 5 observational studies that included a total of 142 patients with CD who met the inclusion criteria, an association between a capsule endoscopy mucosal healing marker (Niv or Lewis score) and clinical remission at 12 weeks and 24 months of follow-up was found (odds ratio [OR]: 11.06; 95% CI: 3.74-32.73; p<0.001) (70).

Mucosal healing

A systematic review (38) (AMSTAR score 8/11) evaluated the prognostic value of intestinal mucosal healing in the occurrence of favorable clinical outcomes in CD

patients. The following outcomes were considered: the frequency of long-term clinical remission (CDAI <150), the need for surgical treatment, and the rate of long-term mucosal healing.

The review retrieved 12 observational studies conducted in patients with stenosing or fistulizing, perianal, small bowel, ileocolonic, or colonic CD. According to this systematic review, the presence of healthy mucosa increases the likelihood of remaining in clinical remission for at least 50 weeks (OR: 2.7; 95% CI: 1.82-3.99; 304 patients), regardless of the type of treatment (biological therapy [OR: 2.89; 95% CI: 1.82-4.59] or non-biological therapy [OR: 2.48; 95% CI: 1.26-4.89]). Finally, the presence of healthy mucosa was also associated with a higher frequency of long-term endoscopic remission (OR: 14.3; 95% CI: 5.57-36.74), however it was not associated with a higher or lower frequency of patients requiring surgical intervention (OR: 0.22; 95% CI: 0.86-5.69) (38).

Quality of evidence: very low ⊕○○○

From evidence to the recommendation

The expert panel stated that CRP and ESR are low-cost tests and must be ordered simultaneously. The recommendation is strong because testing should be performed as part of a proper management of the disease that seeks to obtain the best outcomes for patients with CD.

The identification of serum levels of infliximab was not formulated as a recommendation due to its cost; only evidence about one biological drug was found, and this drug is not included in the health benefits plan of the mandatory health insurance coverage system in force in Colombia.

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION N° 2. WHAT ARE THE SAFEST AND MOST EFFECTIVE NON-BIOLOGICAL INTERVENTIONS TO INDUCE REMISSION OF CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation	N°	Summary
Strong against		Using probiotics to induce remission in patients with active Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Weak against		Using antibiotics to induce remission in patients with active Crohn's disease is not suggested. **Low quality of evidence** ⊕⊕OO
Weak against		Administering azathioprine or 6-mercaptopurine as monotherapy to induce remission in patients with active Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Strong in favor		Adding azathioprine as a combination therapy to induce remission in patients with active Crohn's who are going to undergo biological therapy with infliximab is recommended. **Very low quality of evidence** ⊕OOO
Weak against		Using sulfasalazine or mesalazine to induce remission in patients with active Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Strong against		Using methotrexate to induce remission in patients with active Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Weak in favor		Using ileal release budesonide to induce remission in patients with active Crohn's disease is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		The recommended initial dosage of budesonide is 9 mg/d; at 2 months it should be decreased to 6 mg/d, and to 3 mg/d during the next 2 months, and then it must be suspended. Induction therapy must not exceed 6 months.
Good practice point		Adverse events associated with the use of systemic steroids must be monitored after 12 weeks of use.
Strong in favor		Using systemic steroids to induce remission in patients with active Crohn's disease is recommended. **Low quality of evidence** ⊕⊕OO
Good practice point		Systemic steroid therapy is the first-line treatment for moderate to severe ileocolonic and colonic Crohn's disease or in patients with extensive small bowel involvement by Crohn's disease.
Good practice point		The recommended starting dosage of prednisolone (oral route) is 40 mg/d.
Good practice point		Steroid response must be assessed after 2 to 4 weeks of treatment. In case of therapeutic failure, the need to modify the treatment must be defined.
Weak in favor		Using oral systemic steroids as the first choice to induce remission in patients with active Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Weak in favor		Using ileal release budesonide as the first choice for the management of patients with low-risk ileal or ileocecal Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		If budesonide is not available, systemic corticosteroids such as prednisolone can be used.
Weak in favor		Using autologous stem cell transplant for the treatment of patients with Crohn's disease refractory to medical treatment is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		Stem cell transplant must be carried out in health centers with experience in performing this procedure.

Summary of evidence

Using probiotics to induce remission in patients with active Crohn's disease

A systematic review and meta-analysis (71) (AMSTAR score 8/11) evaluated the efficacy of using probiotics to induce remission in patients with CD. In said study, the assessed outcome was the frequency of patients who achieved clinical remission (defined as having a CDAI <150 or obtaining a score less than 100 points compared to the baseline score) during 3 to 24 months of follow-up. The review retrieved three controlled clinical trials with a total of 74 participants; based on the findings reported, probiotic

administration failed to increase the proportion of patients achieving remission, either when used as monotherapy (RR: 0.89; 95% CI: 0.70-1.13) or as an adjuvant in conventional treatment (RR: 0.89; 95% CI: 0.70-1.13) (71). Furthermore, in a recent Cochrane review that included 2 studies on the use of probiotics to induce remission in CD, it was concluded that available evidence about the efficacy or safety of using probiotics to induce remission in CD is very uncertain when compared to placebo (72).

Quality of evidence: very low ⊕○○○

Using antibiotics to induce remission in patients with active Crohn's disease

A systematic review (73) (AMSTAR score 7/11) assessed the efficacy of using antibiotics to induce remission in patients with active CD. All studies included in the review allowed concomitant use of other interventions (immunomodulators) and the outcome of interest was the proportion of patients who achieved clinical improvement or remission (CDAI <150 and/or a ≥70 points decrease or a >50% reduction in the number of fistulas for at least 4 weeks) during follow-up.

The review retrieved three randomized clinical trials conducted in a total of 222 participants. When compared with placebo, the use of antibiotics during the first 3 to 6 months did not increase the proportion of participants experiencing clinical improvement or remission (RR: 1.15; 95% CI: 0.56-2.36). Also, when a subgroup analysis was performed according to the type of drug used, the administration of ciprofloxacin, rifaximin and 5-nitroimidazoles showed similar results (73).

In addition, a recent Cochrane review of 13 studies suggests a modest benefit of using antibiotics in patients with active CD, and that their benefit for maintenance of remission is uncertain; therefore, according to this review, no solid conclusions regarding the efficacy of antibiotics in CD can be reached (74).

Quality of evidence: low ⊕⊕○○

Using azathioprine or 6-mercaptopurine to induce remission in patients with active CD

A systematic review and meta-analysis (75) (AMSTAR score 10/11) evaluated the efficacy and safety of using azathioprine or 6-mercaptopurine for induction of remission in CD. The outcomes assessed in this study were the proportion of patients who achieved remission or clinical improvement (defined as a CDAI <150 points or a HBI <3), the proportion of patients in which steroid dose reduction was possible (assessed with prednisone at doses <10 mg/d) and who experienced improvement or fistula closure (complete lesion healing or decreased discharge) and, finally, the proportion of patients who experienced serious adverse events, and the frequency of withdrawal.

The review retrieved nine studies evaluating the effect of this intervention compared to placebo in 506 participants in total. According to this systematic review, in patients who were administered azathioprine or 6-mercaptopurine higher frequencies of clinical improvement (RR: 1.53; 95% CI: 1.05-2.22) and of lower steroid doses (RR: 1.34; 95% CI: 1.02-1.77) were observed, without this being reflected in a higher frequency of patients who achieved clinical remission criteria (RR: 1.23; 95% CI: 0.97-1.55) or who experienced clinical improvement or fistula closure (RR: 2.00; 95% CI: 0.67-5.93). However, the use of azathioprine or 6-mercaptopurine did not increase the risk of withdrawal (RR: 1.70; 95% CI: 0.94-3.08) or the frequency of adverse events (RR: 2.57; 95% CI: 0.92-7.13) (75).

In a second analysis carried out in the same review, the efficacy and safety of azathioprine or 6-mercaptopurine administration versus any other pharmacological intervention to induce remission in patients with CD were compared. When compared with methotrexate, the use of azathioprine or 6-mercaptopurine did not increase the proportion of patients who had steroid-free remission (RR: 1.13; 95% CI: 0.85-1.49; 2 studies, 143 participants) or the frequency of withdrawal (RR: 0.78; 95% CI: 0.23-2.71; 2 studies, 85 participants). Likewise, when patients in the control group were administered 5-aminosalicylates or sulfasalazine, no statistically significant differences were found between groups (steroid-free remission [RR: 1.24; 95% CI: 0.80-1.91] and withdrawal [RR: 0.98; 95% CI: 0.38-2.54]; 2 studies, 156 patients) (75).

However, when azathioprine administration was compared with infliximab use (1 study, 339 participants), azathioprine was associated with a lower frequency of patients achieving clinical remission (RR: 0.66; 95% CI: 0.51-0.87), steroid-free remission (RR: 0.68; 95% CI: 0.51-0.90) or presenting healthy looking mucosa on endoscopic evaluation (RR: 0.55; 95% CI: 0.33-0.94); however, there were no significant differences regarding the frequency of adverse events between groups (RR: 1.47; 95% CI: 0.96-2.23). Finally, when combination therapy with azathioprine plus infliximab was compared with infliximab monotherapy, the use of combination therapy increased the proportion of patients who achieved clinical remission (RR: 1.26; 95% CI: 1.03-1.54), steroid-free remission (RR: 1.23; 95% CI: 1.02-1.47) or who had healthy-looking mucosa on endoscopic evaluation (RR: 1.50; 95% CI: 1.02-2.19), without increasing the frequency of adverse events (RR: 1.16; 95% CI: 0.75-1.80) (75).

Quality of evidence: very low ⊕○○○

Using 5-aminosalicylates to induce remission in patients with active Crohn's disease

A systematic review (76) (AMSTAR score 10/11) evaluated the safety and efficacy of using sulfasalazine to induce remission in patients with mild to moderate CD. This review reported findings on the following outcomes: the proportion of patients who achieved clinical improvement or remission (CDAI <150 or a >25% decrease in the VHI), the frequency of serious adverse events, and withdrawal due to undesirable effects.

This review retrieved three controlled clinical trials comparing the use of this intervention versus placebo in 289 participants. Based on the results of the retrieved studies, it was found that sulfasalazine administration increased the frequency of remission (RR: 1.38; 95% CI: 1.01-1.90) but did not increase that of clinical improvement (RR: 1.52; 95% CI: 0.95-2.43), yet neither did it increase the incidence of serious adverse events (RR: 0.35; 95% CI: 0.01-8.38) or withdrawal (RR: 1.00; 95% CI: 0.26-8.83). In addition, in a second analysis, the efficacy and safety of sulfasalazine administration versus any other pharmacological intervention were compared. When compared with steroid therapy, the use of sulfasalazine was associated with a lower frequency of serious adverse events (RR: 0.43, 95% CI: 0.22-0.82; 2 studies, 159 participants) at the cost of a lower proportion of patients achieving remission (RR: 0.68, 95% CI: 0.51-0.91; 2 studies, 260 patients). No significant differences were found between groups regarding the rate of withdrawal (RR: 0.72; 95% CI: 0.33-1.59; 2 studies, 260 patients) (76).

On the other hand, when 5-aminosalicylates monotherapy was compared with sulfasalazine-steroid combination therapy, sulfasalazine monotherapy was associated with a lower frequency of participants achieving clinical remission (RR: 0.64, 95% CI: 0.47-0.86; 1 study, 110 patients) and there was no statistically significant evidence regarding the rate of withdrawal (RR: 0.52, 95% CI: 0.05-5.55; 1 trial, 110 participants). Finally, a subgroup analysis based on the type of 5-aminosalicylates was performed in this review. When mesalazine was compared with sulfasalazine, no differences were found between groups in terms of efficacy (induction of remission [RR: 1.02; 95% CI: 0.84-1.24]) or safety ([serious adverse events: RR: 0.35; 95% CI: 0.11-1.09]) (76).

Quality of evidence: very low ⊕○○○

Using methotrexate to induce remission in patients with active Crohn's disease

A systematic review (77) (AMSTAR 8/11) assessing the safety and efficacy of using methotrexate for inducing remission in patients with CD was retrieved. The review included three studies conducted in a total of 226 participants. When compared to placebo, patients in the methotrexate arm did not experience a higher frequency of clinical remission (RR: 1.02; 95% CI: 0.60-1.73), but they did experience a higher frequency of withdrawal (RR: 6.97; 95% CI: 1.61-30.10) (77).

Quality of evidence: very low ⊕○○○

Using budesonide to induce remission in patients with active Crohn's disease

A systematic review and meta-analysis (78) (AMSTAR score 10/11) evaluated the efficacy and safety of using budesonide to induce remission in patients with CD. Outcomes assessed in this study were the proportion of patients achieving remission (defined as a CDAI <150 points) and clinical improvement (a >100 points decrease in CDAI score or total CDAI<150 points), and the proportion of patients withdrawing due to serious adverse events. A comparison of the effect of this intervention with that of place was performed in three studies (379 patients in total). According to the findings of this systematic review, in the budesonide administration group higher proportions of remission (RR: 1.93, 95% CI: 1.37-2.73, at 9 mg dose; RR: 2.25, 95% CI: 1.35-3.76, at 15 mg dose) and clinical improvement (RR: 1.46, 95% CI: 1.03-2.07, at 9 mg dose; RR: 2.34, 95% CI: 0.83-6.63, at 15 mg dose) were observed, without increasing the proportion of patients who withdrew due to adverse events (RR: 1.14, 95% CI: 0.46-2.79, at 9 mg dose; RR: 1.55, 95% CI: 0.45-5.34, at 15 mg dose).

Also, in a second analysis, this review compared the efficacy and safety of budesonide administration for induction of remission in CD versus any other pharmacological intervention. When compared with mesalazine administration, budesonide use at a dose of 9 mg increased the number of patients who achieved remission at 12 weeks (RR: 1.59, 95% CI: 1.17-2.15; 1 study, 182 participants) and 16 weeks (RR: 1.79; 95% CI: 1.28-2.50; 1 study, 182 participants), but it did not increase the frequency of clinical improvement (RR: 1.18; 95% CI: 0.99-1.42; 2 studies, 489 patients) or withdrawal (RR: 0.43; 95% CI: 0.18-1.03; 2 studies, 489 patients). On the other hand, when participants in the control group were administered traditional steroids, patients in the budesonide 9 mg arm experienced a lower frequency of remission in the medium term (RR: 0.85, 95% CI: 0.75-0.97; for 8 weeks), but not in the long term (RR: 1.02, 95% CI: 0.81-1.30; for 12 weeks). Finally, patients who were administered budesonide reported a lower frequency of adverse events (RR: 0.64; 95% CI: 0.54-0.76), yet this was not reflected in a higher or lower frequency of withdrawal (RR: 0.57; 95% CI: 0.18-1.84) (78).

Quality of evidence: low ⊕⊕○○

Oral or intravenous administration of corticosteroids to induce remission in patients with active CD

A systematic review (79) (AMSTAR score 8/11) assessed the efficacy and safety of using corticosteroids (orally or intravenously) to induce remission in patients with CD. The outcomes reported in this study were the proportion of patients who achieved remission (defined as a CDAI <150 points) and the frequency of withdrawal due to serious adverse events. The effect of this intervention was compared with the effect of placebo in two studies (267 participants). According to the findings of the review, in the corticosteroid administration group, a higher frequency of remission was observed (RR: 1.99; 95% CI: 1.51-2.64), and the proportion of patients who withdrew did not increase (RR: 4.57; 95% CI: 0.75-27.83). On the other hand, a second analysis carried a comparison between the administration of steroids and 5-aminosalicylates use. Compared to the use of 5-aminosalicylates, corticosteroids were also associated with a higher frequency of remission (RR: 1.65, 95% CI: 1.33-2.03; 2 studies, 332 participants), without resulting in a higher frequency of withdrawal (RR: 1.18, 95% CI: 0.61-2.29; 6 trials, 478 patients) (79).

Quality of evidence: low ⊕⊕○○

Safety and efficacy of using mesalazine, sulfasalazine, corticosteroids, and budesonide to induce remission in patients with active Crohn's disease. Results of a network meta-analysis

A systematic review and network meta-analysis (80) (AMSTAR score 8/11) evaluated the efficacy and safety of different pharmacological strategies for the induction of remission in CD. The review included studies conducted in patients with active Crohn's disease (CDAI score between 150 and 400 points) located in the ileum, colon, cecum, or rectum. Studies that allowed the use of combination therapy or included individuals with postoperative recurrence of CD were excluded. The following interventions were assessed: administration of mesalazine, sulfasalazine, corticosteroids or budesonide, and the following outcomes were reported: induction of remission (CDAI score ≤150 points or as defined by the author) and withdrawal due to adverse events (assessed according to clinical judgment).

The review retrieved 24 randomized clinical trials. When compared with the placebo group, the administration of high doses of corticosteroids (OR: 3.86; 95% CI: 2.51-6.06), budesonide (OR: 3.18; 95% CI: 2.11-4.30; higher than 6 mg/d) or mesalazine (OR: 2.11; 95% CI: 1.39-3.31; higher than 2.4 g/d) had a significantly better performance than placebo in inducing remission. However, sulfasalazine therapy did not show a clear benefit when compared to placebo (OR: 1.56; 95% CI: 0.83-2.88). On the other hand, when determining which intervention could be the best therapeutic option, corticosteroids ranked first, followed by budesonide at doses >6 mg/d, mesalazine at doses >2.4 g/d and, finally, with a similar probability, low-dose budesonide, and sulfasalazine (80).

Steroids and high-dose budesonide were significantly superior to mesalazine, sulfasalazine, or low-dose budesonide. Corticosteroids were superior to high-dose mesalazine (OR: 1.83; 95% CI: 1.16-2.88), but their efficacy was similar to that of high-dose budesonide therapy (OR: 1.21; 95% CI: 0.84-1.76). Finally, the frequency of withdrawal in all interventions was similar to that of placebo: low-dose mesalazine (OR: 1.74; 95% CI: 0.33-8.99) and high-dose mesalazine (OR: 1.07; 95% CI: 0.36-3.43), sulfasalazine (OR: 0.79; 95% CI: 0.01-14.36), low-dose budesonide (OR: 0.35; 95% CI: 0.03-2.45) and high-dose budesonide (OR: 0.94; 95% CI: 0.36-2.81) and, finally, corticosteroids (OR: 2.19; 95% CI: 0.59-8.70). Somehow, in the corticosteroids group the likelihood of withdrawal due to adverse events was 93% and 90% higher when compared with budesonide or high-dose mesalazine therapy, respectively (80).

Quality of evidence: very low ⊕○○○

Stem cell therapy

A systematic review that included a meta-analysis of proportions (81) (AMSTAR score 10/11) assessed the efficacy and safety of stem cell therapy in patients with active CD. The interventions considered in the review were the use of bone marrow mesenchymal stem cells, adipose tissue or hematopoietic stem cells, and the outcomes reported were their clinical efficacy, defined as clinical response or remission, and the frequency of adverse events, endoscopic remission, and clinical recurrence. A total of 20 prospective experimental studies (563 patients combined) were retrieved. The overall frequencies of clinical response, endoscopic remission, and recurrence were 56% (95% CI: 33%-76%), 15% (95% CI: 0%-50%), and 16% (95% CI: 4%-34%), respectively. The overall frequency of adverse events was 12% (95% CI: 0.06-0.23).

In addition, when a subgroup analysis was performed according to the route of administration, the frequencies of clinical response and clinical remission in patients who underwent systemic therapy were 66% (95% CI: 39%-86%) and clinical 46% (95% CI: 25%-69%), respectively, (81).

Quality of evidence: very low ⊕○○○

From evidence to the recommendation

The expert panel highlighted that this group of recommendations updates the guidelines of international agencies, and the importance this entails. In general, methotrexate,

sulfasalazine and azathioprine are not recommended drugs to induce remission. The periods of time in which steroids should be used are reported as a good practice in order to use them adequately, thus minimizing side effects.

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION N° 3. WHAT ARE THE SAFEST AND MOST EFFECTIVE NON-BIOLOGICAL INTERVENTIONS TO MAINTAIN REMISSION OF CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS WITH?

List of recommendations

Recommendation	N°	Summary
Strong against		Using mesalazine to maintain remission in patients with Crohn's disease is not recommended. **Low quality of evidence** ⊕⊕OO
Weak in favor		Using azathioprine or 6-mercaptopurine to maintain remission in patients with Crohn's disease in whom remission was induced through systemic steroids is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		Azathioprine and 6-mercaptopurine recommended doses are 2.0 to 2.5 mg/kg/d and 0.75 to 1.5 mg/kg/d, respectively.
Good practice point		Thiopurine methyltransferase (TPMT) enzyme activity can be measured prior to starting the administration of thiopurines, since this allows the identification of patients who may develop severe immunosuppression if these drugs are used.
Weak against		Using budesonide to maintain remission in patients with Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Weak in favor		Using methotrexate to maintain remission in patients with Crohn's disease who achieved remission with steroids is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		Patients with steroid-dependent Crohn's disease should be treated initially with thiopurines or methotrexate as steroid "sparing" drugs
Good practice point		Methotrexate should be considered instead of thiopurines in young male patients (<35 years) because of the risk of hepatosplenic T-cell lymphoma, as well as in individuals with thiopurines intolerance or who experience adverse effects when using them.
Good practice point		The recommended dose of methotrexate for maintenance of remission is 25 mg/week intramuscularly.
Strong against		Using elemental nutrition (also elemental diet, a type of enteral nutrition) to maintain remission in patients with Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Strong against		Using probiotics to maintain remission in patients with Crohn's disease is not recommended. **Low quality of evidence** ⊕⊕OO
Strong against		Using systemic steroids to maintain remission in patients with Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO

Summary of evidence: General considerations

Using 5-aminosalicylates for maintenance of remission in Crohn's disease

A systematic review (82) (AMSTAR score 9/11) evaluated the safety and efficacy of using 5-aminosalicylates for maintenance of remission in CD. This review assessed the following outcomes: clinical or endoscopic recurrence at 12 or 24 months of follow-up (defined as having a CDAI >150 or a >60 points increase or a HBI >4) and the proportion of patients who experienced serious adverse events or who withdrew due to adverse events and serious adverse events.

The systematic review retrieved 11 randomized clinical trials conducted in a total of 2014 participants. When compared with placebo, the use of 5-aminosalicylates was not associated with lower clinical or endoscopic recurrence in the medium term (RR: 0.98, 95% CI: 0.91-1.07; 12 months) or the long term (RR: 0.99; 95% CI: 0.80-1.23; 24 months), nor with a higher frequency of serious adverse events (RR: 1.43; 95% CI: 0.24-8.44) or withdrawal due to adverse events (RR: 1.11; 95% CI: 0.88-1.38) (82).

Quality of evidence: low ⊕⊕OO

Using azathioprine or 6-mercaptopurine to maintain remission in patients with Crohn's disease

A systematic review (83) (AMSTAR score 9/11) assessed the safety and efficacy of using azathioprine or 6-mercaptopurine for maintenance of remission in CD. The following outcomes were reported: the proportion of patients who remained in remission (defines as having a CDAI <150), steroid sparing, and the frequency of serious adverse events or the frequency of withdrawals due to adverse events.

The review retrieved eight controlled clinical trials comparing this intervention versus placebo in 532 participants.

Based on the evidence retrieved, the use of azathioprine or 6-mercaptopurine increased the proportion of patients who were in remission at study enpoint (RR: 1.25; 95% CI: 1.11-1.42) at the expense of a higher frequency of serious adverse events (RR: 2.45; 95% CI: 1.22-4. 90) or withdrawal due to adverse events (RR: 3.12; 95% CI: 1.59-6.09), without modifying the proportion of patients in which reducing the steroid dose was feasible (RR: 1.59; 95% CI: 0.97-2.61) (83).

Furthermore, a second analysis was carried out to compare the administration of azathioprine or 6-mercaptopurine with mesalazine or sulfasalazine therapy. When compared with 5-aminosalicylates therapy, azathioprine or 6-mercaptopurine therapy was not associated with a higher or lower frequency of patients who remained in remission (RR: 1.09; 95% CI: 0.88-1.34) or who withdrew due to adverse events (RR: 1.86; 95% CI: 0.87-3.97), but it was associated with a higher incidence of serious adverse events (RR: 9.37; 95% CI: 1.84-47.72). Finally, in the last study retrieved in the review a comparison between combination therapy with azathioprine plus infliximab and monotherapy with infliximab was made. Combination therapy was not superior to infliximab in increasing the proportion of patients who remained in remission (RR: 1.02; 95% CI: 0.74-1.40). However, it did not increase the frequency of serious adverse events either (RR: 2.42; 95% CI: 0.10-56.46), nor of withdrawal (RR: 2.42; 95% CI: 0.10-56.46) (83).

Quality of evidence: very low ⊕○○○

Using budesonide for maintenance of remission in Crohn's disease

A systematic review (84) (AMSTAR score 10/11) evaluated the safety and efficacy of budesonide administration for maintenance of remission in CD. With this in mind, the following outcomes were assessed: proportion of patients who remained in remission (defined as having a CDAI <150), mean change in CDAI score compared to the baseline score, mean time to the first relapse episode (measured in days), and the frequency of withdrawal due to an adverse event.

Five randomized clinical trials comparing the use of this intervention with the use of placebo in 420 patients combined were retrieved. Based on the evidence found, the use of budesonide at a dose of 6 mg/d did not increase the frequency of patients who remained in remission in the medium or the long term (RR: 1.15, 95% CI: 0.95-1.39; and RR: 1.13, 95% CI: 0.94-1.35; 6 and 12 months, respectively), although it did slightly decrease disease activity in the medium and the long term (MD CDAI score at 6 months: -24.30; 95% CI: -2.29 to -46.31; and CDAI score at 12 months: -23.49; 95% CI: -0.32 to -46.65) and slightly increased mean time to the first episode of relapse (MD: 59.93 days; 95% CI: 19.02-100.84 days), without significantly increasing the proportion of patients who withdrew due to adverse events (RR: 1.08; 95% CI: 0.60-1.95) (84).

Also, when a subgroup analysis according to budesonide dose was performed, the increased dose of budesonide (9 mg versus 6 mg) did not increase the rate of remission (RR: 1.07; 95% CI: 0.91-1.26) or improve disease activity indices (MD CDAI score: -18; 95% CI: -41.06-5.06), but neither did it increase the frequency of withdrawal due to adverse events (RR: 0.31; 95% CI: 0.03-2.94). Finally, when budesonide therapy and the use of prednisolone 40 mg/d were compared, no significant differences were found between both groups regarding remission rate at 6 months (RR: 0.79; 95% CI: 0.56-1.12) or 12 months (RR: 0.79; 95% CI: 0.55-1.13) and the frequency of withdrawal due to adverse events (RR: 8.62; 95% CI: 0.48-155.52) (84).

Quality of evidence: very low ⊕○○○

Using methotrexate to maintain remission in patients with Crohn's disease

A systematic review and meta-analysis (85) (AMSTAR score 8/11) evaluated the efficacy of methotrexate therapy for maintenance of remission in CD. The outcome assessed was the proportion of patients who remained in remission in a follow-up time ranging from 30 to 76 weeks (remission was defined as having a CDAI <150). Seven controlled clinical trials (306 participants in total) comparing methotrexate therapy with any other pharmacological intervention were retrieved. When placebo and methotrexate administration were compared, the latter increased the proportion of patients who remained in remission (RR: 1.57; 95% CI: 1.10-2.23); however, this finding was not consistent when methotrexate therapy was compared with 6-mercaptopurine (RR: 1.36; 95% CI: 0.92-2.00), 5-aminosalicylates (RR: 2.62; 95% CI: 0.23-29.79) or combination therapy with infliximab (RR: 1.02; 95% CI: 0.76-1.38) (85).

Quality of evidence: very low ⊕○○○

Using elemental nutrition (also elemental diet, a type o enteral nutrition) to maintain remission in patients with Crohn's disease

A systematic review (86) (AMSTAR score 7/11) evaluated the efficacy of elemental nutrition for the maintenance of remission in CD by assessing the following outcomes: maintenance of remission (CDAI score ≤150 alone or Rutgeerts score <2), relapse (CDAI score ≥200 or a 100 points increase, or an IOIBD score ≥2, or increasing the steroid dose), need for surgical intervention, withdrawal from steroids, and health-related quality of life (assessed with the Inflammatory Bowel Disease Questionnaire [IBDQ]).

Two controlled clinical trials conducted in a total of 116 participants were retrieved. When compared with the no intervention group (unrestricted diet), elemental nutrition

did not significantly change the proportion of patients who remained in remission in the short (RR: 1.21; 95% CI: 0.92-1.58; at 6 months), medium (RR: 1.37; 95% CI: 0.86-2.17; at 12 months) or long term (RR: 2.06; 95% CI: 1.00-4.43; at 24 months) or the proportion of patients requiring surgical intervention (RR: 1.03; 95% CI: 0.06-15.79). However, it significantly reduced the risk the frequency of relapse episodes at 12 and 24 months of follow-up (pooled RR: 0.57; 95% CI: 0.38-0.84) and increased health-related quality of life scores during the first year of follow-up (MD IBDQ score=4.9; 95% CI: 6.3-16.1) (86).

On the other hand, another study retrieved in this systematic review compared the efficacy of elemental nutrition versus 6-mercaptopurine therapy. No significant differences between both groups were found regarding maintenance of remission in the short (RR: 1.05; 95% CI: 0.83-1.33; at 6 months), medium (RR: 0.93; 95% CI: 0.64-1.35; at 12 months) or long term (RR: 0.77; 95% CI: 0.46-1.27), the frequency of relapse episodes (RR: 1.61; 95% CI: 0.73-3.53) or the need for surgical intervention (RR: 0.93; 95% CI: 0.06-14.32). Finally, there was also no difference in the frequency of patients who withdrew from taking steroids when elemental nutrition was compared with polymeric nutrition (RR: 0.98; 95% CI: 0.44-2.19) (86).

A more recent Cochrane review comparing enteral nutrition with corticosteroids therapy in adult population reported a significant difference in favor of corticosteroids regarding remission rates in CD (45% vs. 73%) (RR: 0.65; 95% CI: 0.52-0.82); however, the quality of evidence was very low (87).

Quality of evidence: very low ⊕OOO

Using probiotics for maintenance of remission in Crohn's disease

A systematic review (88) (AMSTAR score 9/11) assessed the efficacy and safety of using probiotics for maintenance of remission in CD. The outcomes analyzed in the review were the frequency of relapse at 12-months (CDAI >220 or a CDAI 150-220 with an ≥70 points increase compared to the baseline score) and the incidence of adverse events resulting from the intervention. Four randomized clinical trials conducted in a total of 233 participants were included. Compared to placebo, the use of probiotics did not reduce the frequency of relapse episodes (RR: 1.03; 95% CI: 0.70-1.51), but neither did it increase the frequency of adverse events (RR: 1.05; 95% CI: 0.80-1.37) (88).

Quality of evidence: low ⊕⊕OO

Using corticosteroids to maintain remission in patients with Crohn's disease

A systematic review (89) (AMSTAR score 8/11) evaluated the efficacy of corticosteroid therapy for the maintenance of remission in CD. Bearing this in mind, the review reported findings on the following outcome: frequency of relapse at 6, 12, and 24 months (a CDAI score >150 together by symptoms suggestive of CD). Three randomized clinical (303 participants combine) were included. Compared to the placebo group, corticosteroid therapy did not reduce the frequency of relapse episodes in the short (RR: 0.71; 95% CI: 0.38-1.31), medium (RR: 0.82; 95% CI: 0.47-1.44) or long term (RR: 0.72; 95% CI: 0.39-1.35) (89).

Quality of evidence: very low ⊕OOO

From evidence to the recommendation

Currently, thiopurine methyltransferase (TPMT) test is not available in Colombia; however, starting its use in the country would be an ideal scenario since patients treated with thiopurines may develop immunosuppression. The future inclusion of this test in the health benefits plan of the mandatory health insurance coverage system in force in Colombia is suggested.

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION N°4. WHAT IS THE SAFETY AND EFFICACY OF USING BIOLOGICAL DRUGS TO TREAT MODERATE TO SEVERE CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation	N°	Summary
Strong in favor		Using infliximab, adalimumab, certolizumab, vedolizumab, or ustekinumab to induce and maintain remission in patients with moderate to severe luminal Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO
Good practice point		anti-TNF agents or TNF inhibitors (infliximab, adalimumab, or certolizumab pegol) should be considered as first choice medications over other biological drugs for the initial management of moderate to severe Crohn's disease.
Good practice point		Patients older than 65 years undergoing anti-TNF therapy have a higher risk of infection (90)
Good practice point		The use of combination therapy with TNF inhibitors+thiopurines is not recommended in males younger than 35 years due to the risk of hepatosplenic T-cell lymphoma, as well as in patients with a history of malignancy. In these cases, anti-TNF monotherapy must be used.
Good practice point		In patients with contraindications to anti-TNF agents (severe heart failure, demyelinating disease, among others), the use of vedolizumab or ustekinumab should be considered.
Good practice point		Patients with Crohn's disease must be assessed 12 to 14 weeks after the induction of remission with biological therapy was initiated, so that treatment response and the need for treatment modification are determined.
Weak in favor		Using anti-TNF drugs (infliximab or adalimumab) to treat patients with perianal fistulizing Crohn's disease is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		Infliximab efficacy could be increased when co-administered with thiopurines.
Weak in favor		The use of ustekinumab to induce remission in patients with moderate to severe Crohn's disease and who have experienced treatment failure after undergoing anti-TNF therapy is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		The recommended ustekinumab initial induction dose (intravenous) is 260 mg (up to 55 kg), 390 mg (between 56 and 85 kg) and 520 mg (>85 kg). In the case of treatment for maintenance of remission, subcutaneous administration of 90 mg every 8 weeks is recommended.

Weak in favor	Clinical monitoring of opportunistic infections in patients with Crohn's disease undergoing biological therapy is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	anti-TNF therapy should be contraindicated in patients with active infection.
Good practice point	Prior to initiating biological therapy, the presence of respiratory symptoms should be determined, and a chest X-ray and a Mantoux tuberculin skin should be performed, given the risk of reactivation of latent tuberculosis.
Good practice point	Prior to starting biological therapy, hepatitis B and C serologic tests and HIV testing should be ordered.
Good practice point	Patients with Crohn's disease must get vaccinated against influenza, pneumococcus, hepatitis B, varicella (at least 3 weeks prior to starting the administration of the immunosuppressant) and human papillomavirus (prior to starting the administration of immunosuppressants, steroids, thiopurines and biological drugs).
Weak in favor	Using a second TNF inhibitor is suggested when there is no primary response or a response following the secondary loss of response to a first anti-TNF agent. **Very low quality of evidence** ⊕OOO
Good practice point	Treatment modifications should be individual and based on the anti-TNF drug serum levels and the results of the antibodies tests against the anti-TNF drug.
Good practice point	Patients with adequate TNF inhibitor serum levels and (+) antibodies must be treated with another type of anti-TNF agent or another type of biological drug.
Good practice point	In individuals with sub-therapeutic levels of the TNF inhibitor and (-) antibodies, intervals between doses should be shortened or the anti-TNF agent dose should be increased.
Weak in favor	Using infliximab biosimilars to induce and maintain remission in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Patients undergoing treatment with innovator infliximab can continue treatment with the biosimilar if they have been responding to the previous one.
Good practice point	Molecules must not be switched in case of initial treatment failure with either molecule.
Good practice point	In the event of a non-medical switch between an innovator biological drug and a biosimilar, the treating physician must be informed for pharmacovigilance purposes and the patient's consent must be obtained.
Strong in favor	Using infliximab, infliximab plus azathioprine, adalimumab, or vedolizumab to induce remission in patients with Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO
Strong in favor	Using azathioprine, methotrexate, infliximab, infliximab plus azathioprine, adalimumab or vedolizumab to maintain remission in patients with Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO

Summary of evidence: General considerations

anti-TNF agents (infliximab, adalimumab or certolizumab pegol) or anti-integrins (natalizumab or vedolizumab) or IL-12/23 antagonists (ustekinumab) versus placebo for induction or maintenance of remission in moderate or severe luminal Crohn's disease

A systematic review and network meta-analysis (91) (AMSTAR score 9/11) assessed the efficacy, compared to placebo, of using anti-TNF agents (infliximab, adalimumab or certolizumab pegol) or anti-integrins (natalizumab or vedolizumab) or interleukin 12/23 (IL-12/23) antagonists (ustekinumab) for induction or maintenance of remission in patients with moderate or severe luminal colonic, ileal or ileocolonic CD. All studies included in the review allowed concomitant use of immunomodulators, corticosteroids and/or 5-aminosalicylates. The following outcomes were assessed: induction of clinical remission (a CDAI <150 or a decrease by more than 100 or 70 points) and maintenance of remission (a CDAI <150 or a decrease by more than 100 or 70 points compared to the baseline score).

The review retrieved 11 randomized clinical trials (2530 patients in total). Compared to placebo, a higher proportion of patients in the biologic drugs group achieved clinical remission (RR: 1.44; 95% CI: 1.19-1.75) and remained in remission (RR: 2.06; 95% CI: 1.73-2.45). When subgroup analysis was performed and the outcome of interest was the induction of remission, compared to placebo, the use of anti-TNF agents significantly increased the proportion of patients in which this outcome was achieved (OR: 1.63; 95% CI: 1.24-2.14), however anti-integrins (OR: 1.20; 95% CI: 0.97-1.49) or IL-12/23 antagonist ustekinumab (OR: 0.79; 95% CI: 0.44-1.39) were not significantly superior to placebo. In addition, in the network meta-analysis, inflixi-

mab (RR: 6.11; 95% CI: 2.49-18.29) and adalimumab (RR: 2.98; 95% CI: 1.12-8.18) were significantly superior to placebo in terms of induction of remission, while certolizumab pegol (RR: 1.48; 95% CI: 0.76-2.93), natalizumab (RR: 1.36; 95% CI: 0.69-2.86), vedolizumab (RR: 1.40; 95% CI: 0.63-3.28) or ustekinumab (RR: 0.61; 95% CI: 0.15-2.49) were not significantly superior to placebo. Infliximab had an 86% probability of being the most effective therapy, followed by adalimumab, with a 16% probability (91).

On the other hand, according to the subgroup analysis in which the maintenance of remission was the outcome of interest, when anti-TNF therapy (OR: 2.18; 95% CI: 1.65-2.88) or IL-12/23 antagonist ustekinumab (OR: 2.09; 95% CI: 1.49-2.92) were used, a higher proportion of patients remained in remission. These findings were not observed when anti-integrins were used (OR: 1.52; 95% CI: 0.96-2.42). Besides, in the network meta-analysis, adalimumab (RR: 5.16; 95% CI: 1.78-18.00) and infliximab (RR: 3.31; 95% CI: 0.98-14.01) were superior to placebo in terms of maintenance of remission, while certolizumab pegol (RR: 2.26; 95% CI: 0.38-13.57), natalizumab (RR: 4.26; 95% CI: 0.71-25.49), vedolizumab (RR: 2.20; 95% CI: 0.37-13.54) and ustekinumab (RR: 0.91; 95% CI: 0.31-12.31) were not. Adalimumab had a 48% probability of being the most effective therapy, followed by natalizumab and infliximab, with a 29% and 11% probability, respectively (91).

Quality of evidence: very low ⊕○○○

A recent systematic review compared the efficacy and safety of biologic drugs (infliximab, adalimumab, certolizumab, vedolizumab, and ustekinumab) as first-line ("biologic-naïve") and second-line therapy (prior exposure to anti-TNF agents) in patients with moderate to severe CD. In total, 23 studies (randomized clinical trials; RCTs) were included: 8 using biologics as first-line agents, 6 using biologics as second-line agents, and 9 using them for maintenance of remission. Also, no head-to-head comparative studies were retrieved. In this review, the surface under the cumulative ranking curve (SUCRA), which represents the percentage of efficacy or safety achieved by an agent compared to an imaginary agent that is always the best choice and without uncertainty (i.e., SUCRA = 100%), for each biologic was determined. Infliximab (SUCRA, 0.93) and adalimumab (SUCRA, 0.75) had the highest SUCRA score for the induction of clinical remission in CD patients (moderate quality of evidence). On the other hand, in patients with prior exposure to anti-TNF agents (second-line therapy), adalimumab (SUCRA, 0.91) and ustekinumab (SUCRA, 0.71) achieved the highest rating for induction of remission (low quality of evidence). Adalimumab (SUCRA, 0.97) and infliximab (SUCRA, 0.68) had the highest scores for maintenance of remission, and Ustekinumab had the lowest risk of adverse events (SUCRA, 0.72) and infection (SUCRA, 0.71) (92).

Efficacy of using a second anti-TNF agent in patients with inflammatory bowel disease and treatment failure or intolerance to a first biologic

A systematic review (93) (AMSTAR score 8/11) evaluated the efficacy of using a second anti-TNF agent in patients with inflammatory bowel disease and primary or secondary failure or intolerance to a first anti-TNF agent therapy. Patients included in the studies retrieved were characterized by having luminal or fistulizing Crohn's disease with CDAI score ranging from 220 to 450 points or a HBI ≥7 or by having "moderate to severe Crohn's disease" or "steroid-dependent" disease or having experienced "failure to treatment with immunomodulators". Out of all the studies identified, 32 evaluated switching from infliximab to adalimumab therapy: 4, from infliximab to certolizumab, and 1, from adalimumab to infliximab. The outcomes assessed were the overall rates of remission or response after primary failure and switching from infliximab to adalimumab, and from infliximab to adalimumab or certolizumab pegol, and, finally, the overall rate of remission or secondary response in case of intolerance to infliximab. According to this meta-analysis, the percentage of remission in the short, medium and long term was 18%, 30% and 28%, respectively; also, the short-, medium- and long-term response rates after primary failure to infliximab and switching to adalimubab were, 35%, 67% and 42%, respectively (93).

In the case of primary failure to infliximab and switching to adalimumab or certolizumab, the remission rates in the short, medium and long term were 41%, 38% and 60%, and the response rates in the medium and long term were 66% and 42%, respectively. Finally, remission rates in the short, medium and long term were 50%, 60% and 83%, respectively, and response rates in the medium and long term were 70% and 77%, when infliximab therapy was switched to adalimumab therapy due to intolerance. The frequency of adverse events was not reported in this meta-analysis (93).

Quality of evidence: very low ⊕○○○

TNF inhibitors (infliximab or adalimumab) versus placebo in patients with fistulizing Crohn's disease

A systematic review (94) (AMSTAR score 8/11) evaluated the efficacy of using anti-TNF drugs (infliximab or adalimumab) to treat patients with CD and perianal or enterocutaneous or enteroenteral fistulas. Participants were administered infliximab 5 mg/kg or adalimumab 40 mg to 80 mg, and the outcomes assessed were complete or partial closure of the fistula. The review retrieved four randomized clinical trials conducted in 288 patients in total; when compared with patients in the placebo group, those in the

anti-TNF therapy arm had a higher frequency of complete fistula closure (RR; 2.40, 95% CI: 1.36-4.22), but not of partial closure (RR: 1.27, 95% CI: 0.51-3.14) (94).

Quality of evidence: very low ⊕○○○

anti-IL-12/23p40 antibodies versus placebo for induction of remission in moderate to severe Crohn's disease

A systematic review (95) (AMSTAR score 9/11) evaluated the safety and efficacy, compared to placebo, of using anti-IL-12/23p40 antibodies for induction of remission in CD. Patients included in the ustekinumab or briakinumab therapy group had moderate to severe CD and prior failure to induce remission with anti-TNF agents or corticosteroids or immunosuppressants therapy. The following outcomes were assessed: failure to induce clinical remission (CDAI score <150) or clinical improvement (clinical response) (a ≥100 points decrease in CDAI score) and the frequency of serious adverse events or the frequency of withdrawal due to serious adverse events.

The review retrieved four randomized clinical trials (2023 participants in total). When compared with placebo, briakinumab was not associated with a lower frequency of failure to induce remission (RR: 0.92; 95% CI: 0.83-1.03). However, it was associated with a lower frequency of failure to induce clinical improvement (RR: 0.82; 95% CI: 0.67-0.99). There were no statistical differences between groups regarding the frequency of serious adverse events (RR: 0.64; 95% CI: 0.26-1.56) or of withdrawal due to adverse events (RR: 0.47; 95% CI: 0.15-1.53) (95).

In addition, when compared with the placebo group, patients undergoing ustekinumab therapy had a lower frequency of failure to induce clinical remission (RR: 0.91; 95% CI: 0.86-0.95) or of failure to induce clinical improvement (RR: 0.73; 95% CI: 0.66-0.81). On the other hand, no significant differences were found between groups regarding the presence of serious adverse events (RR: 0.83; 95% CI: 0.58-1.20) or withdrawal due to adverse events (RR: 0.44; 95% CI: 0.18-1.05) (95).

Quality of evidence: very low ⊕○○○

A recent Cochrane systematic review evaluated the efficacy and safety of anti-IL-12/23p40 antibodies for maintenance of remission in CD. Three randomized controlled trials (646 participants) met the inclusion criteria, and all were assessed as having a low risk of bias. Two trials assessed the efficacy of ustekinumab (542 participants), while the other (n=145) compared subcutaneous administration of ustekinumab (90 mg) at 8 and 16 weeks with placebo. Failure to maintain remission at 22 weeks was reported in 58% (42/72) of the patients in the ustekinumab group and in 73% (53/73) of those in the placebo group (RR: 0.80; 95% CI: 0.63-1.02; moderate-certainty). A second study (n=388) compared subcutaneous administration of ustekinumab (90 mg) every 8 or 12 weeks for 44 weeks with placebo use, finding that 49% (126/257) of the participants in the ustekinumab group failed to maintain clinical remission at 44 weeks in comparison with 64% (84/131) in the placebo group (RR: 0.76; 95% CI: 0.64-0.91; moderate-certainty evidence). Moderate-certainty evidence means that, when compared to placebo, ustekinumab is likely to be effective for the maintenance of clinical remission and clinical response in patients with moderate to severe CD, without increasing the risk of adverse events (high-certainty evidence) or serious adverse events (moderate-certainty evidence) (96).

Safety of biological therapy in patients with moderate to severe inflammatory bowel disease

A systematic review (97) (AMSTAR score 10/11) assessed the risk of developing infections or malignancies in CD patients undergoing biologic therapy with adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, or vedolizumab. The outcomes reported in the study were the frequency of serious infections (i.e. those requiring hospitalization, use of intravenous antibiotics or resulting in death), opportunistic infections (presence of *Mycobacterium tuberculosis*; *Nocardia*, cytomegalovirus or Epstein-Barr infection; oral or esophageal candida infection; varicella-zoster or herpes zoster infection; *Pneumocystis jirovecii* or *Histoplasma capsulatum* infection or pneumonia caused by any species of *Legionella* bacteria, or herpes simplex infection, or any unspecified opportunistic infection), any type of infection, as well as the development of tuberculosis (confirmed diagnosis, TB reactivation, miliary or cavitary pulmonary TB or TB affecting any other organ) or malignancy.

This systematic review included 47 observational studies (14,440 participants), and based on the findings retrieved, the use of biologic drugs increased the frequency of opportunistic infections (OR: 1.90; 95% CI: 1.21-3.01) and of any other type of infection (OR: 1.19; 95% CI: 1.10-1.29), but did not increase the risk of serious infections (OR: 0.89; 95% CI: 0.71-1.12), tuberculosis (OR: 2.04; 95% CI: 0.71-5.89) or malignancy (OR: 0.90; 95% CI: 0.54-1.50). In addition, when subgroup analysis according to drug type was performed, no differences were found between anti-TNF agents and anti-integrins in the frequency of serious infections (anti-TNF: OR: 0.90; 95% CI: 0.69-1.17; vs. anti-integrin: OR: 0.87; 95% CI: 0.54-1.39; p-value for subgroup difference=0.89), opportunistic infections (anti-TNF: OR: 1.89; 95% CI: 1.15-3.12; vs. anti-integrin: OR: 1.99; 95% CI: 0.64-6.18; p-value for subgroup diffe-

rence=0.94) or any other type of infection (anti-TNF: OR: 1.21; 95% CI: 1.10-1.33; vs. anti-integrin: OR: 1.14; 95% CI: 0.99-1.32; p-value for subgroup difference=0.49) (97).

Quality of evidence: very low ⊕○○○

A systematic review that included 15 observational studies evaluated the risk of infection in patients with inflammatory bowel disease treated with biologics and immunosuppressive agents. According to the findings of this study, compared with anti-TNF monotherapy, the risk of infection increased with the combination of anti-TNF therapy and immunosuppressants (RR: 1.19; 95% CI: 1.03-1.37; 6 cohorts), with the combination of anti-TNF therapy and steroids (RR: 1.64; 95% CI: 1.33-2.03; 4 cohorts) and with the combination of the three drugs (RR: 1.35; 95% CI: 1.04-1.77; 2 cohorts). On the contrary, the risk of infection was lower in patients undergoing monotherapy with an immunosuppressive agent than in those undergoing anti-TNF monotherapy (RR: 0.61; 95% CI: 0.44-0.84; 7 cohorts) or a combination therapy with an anti-TNF agent plus an immunosuppressant (RR: 0.56; 95% CI: 0.39-0.81) (98).

Safety and efficacy of using CT-P13 (a biosimilar of infliximab) in patients with moderate to severe Crohn's disease

A systematic review and meta-analysis (99) (AMSTAR score 9/11) evaluated the safety and efficacy of using CT-P13 (a biosimilar of infliximab) in patients with CD located in the terminal ileum, the colon, the ileum and colon, or the upper gastrointestinal tract. None of the studies retrieved in the review performed a head-to-head comparison between the biosimilar and infliximab, and in all of them, patients were first treated with infliximab and then were administered the biosimilar. The following outcomes were reported: rates of clinical response (defined as a ≥25% decrease in the CDAI score or a ≥70 points decrease compared to the baseline score or, in case of fistulizing CD, a ≥50% decrease in the number or size of fistulas), and clinical remission (defined as having a CDAI <150 or, in case of fistulizing CD, complete fistula closure or a HBI <5 and absence of active fistulas), and, finally, the frequency of adverse events (assessed with infusion reactions, latent tuberculosis or development of infections) (99).

The review retrieved seven observational cohort studies (225 patients combined). Regarding the clinical response rate outcome, 79% (95% CI: 65%-88%) patients with nonfistulizing CD and 67% (95% CI: 27%-92%) with fistulizing CD remained in remission in the short term (follow-up: 8-14 weeks). In the medium term (follow-up: 24-30 weeks), clinical response rates were 77% (95% CI: 63%-86%) and 67% (95% CI: 27%-92%) in participants with fistulizing and nonfistulazing CD, respectively. Finally, the long-term clinical response rate (follow-up: 48 to 63 weeks) was 75% (95% CI: 44%-92%) in patients with nonfistulizing CD; no information was retrieved for the fistulizing CD group (99).

On the other hand, the clinical remission rates in the short (follow-up: 8 to 14 weeks) and the medium term (follow-up: 24-30 weeks) in nonfistulizing and fistulizing CD patients were 66% (95% CI: 53%-77%) and 33% (95% CI: 8%-73%), and 60% (95% CI: 49%-70%) and 50% (95% CI: 17%-83%), respectively. No information on clinical remission rates in the long term was retrieved. Finally, the overall frequency of adverse events was 10% (95% CI: 2%-31%) (99).

Quality of evidence: very low ⊕○○○

Safety and efficacy of different strategies to induce and maintain remission in patients with Crohn's disease. Results of a network meta-analysis

A systematic review and network meta-analysis (100) (AMSTAR score 7/11) evaluated the efficacy and safety of different strategies to induce and maintain remission in patients with CD. Patients included were characterized as having active disease (CDAI score between 150 and 450 points or HBI >7) or refractory or steroid-dependent disease, or refractory to azathioprine disease. The following interventions were assessed: the administration of azathioprine/6-mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab and vedolizumab as monotherapy or as part of combination therapy. Natalizumab was not included because the available studies recruited patients who had experienced failure to induce remission using TNF inhibitors. The outcomes assessed were induction of remission (CDAI l ≤150 points or as defined by the author of each study), maintenance of remission (CDAI ≤150 or as defined by the author of each study), and withdrawals due to adverse events (assessed according to clinical judgment) (100).

The review retrieved 24 randomized clinical trials (4694 participants in total). When compared to placebo, azathioprine/6-mercaptopurine or methotrexate use did not increase the probability of inducing remission (OR: 1.2, 95% CI: 0.76-2.1; OR: 1.5, 95% CI: 0.72-3.2, respectively) in patients with CD. On the other hand, infliximab monotherapy (OR: 2.8; 95% CI: 1.4-7.2), infliximab plus azathioprine (OR: 4.3; 95% CI: 2.0-9.8), adalimumab monotherapy (OR: 2.9; 95% CI: 1.6-5.5) and vedolizumab monotherapy (OR: 2.0; 95% CI: 1.2-3.3) increased the proportion of patients in whom clinical remission was achieved. The likelihood of these interventions being superior to placebo was >99% (100).

Regarding the maintenance of remission, all interventions were superior to placebo: azathioprine/6-mercaptopurine

(OR: 1.7; 95% CI: 1.3-2.6), methotrexate monotherapy (OR: 2.4; 95% CI: 1.1-4.8), infliximab monotherapy (OR: 2.8; 95% CI: 1.8-4.5), certolizumab monotherapy (OR: 2.0; 95% CI: 1.4-3.0), infliximab plus azathioprine (OR: 5.2; 95% CI: 2.8-11.0), adalimumab monotherapy (OR: 5.1; 95% CI: 3.3-8.1) and vedolizumab monotherapy (OR: 2.2; 95% CI: 1.3-3.7). The likelihood of these interventions being superior to placebo was >99% (100).

Finally, the frequency of adverse events was higher in the following interventions: azathioprine/6-mercaptopurine (OR: 3.9; 95% CI: 2.4-6.4), methotrexate monotherapy (OR: 13; 95% CI: 3.2-109), infliximab monotherapy (OR: 2.7; 95% CI: 1.6-4.7), and infliximab plus azathioprine (OR: 3.2; 95% CI: 1.6-6.1). None of the other options, either used as monotherapy or as part of combination therapy, were associated with a higher or lower frequency of adverse events when compared to placebo (100).

Quality of evidence: very low ⊕OOO

From evidence to the recommendation

The expert panel expressed the need for appropriate use of biologics, since they must be used taking into account the preferences of patients and their medical record, as well as the monitoring of potential adverse events through clinical surveillance. The use of biosimilars will allow easier access to treatment.

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION N° 5. WHAT ARE THE SAFEST AND MOST EFFECTIVE INTERVENTIONS TO TREAT PERIANAL CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation N°	Summary
Weak in favor	Using ciprofloxacin as adjunctive therapy in Crohn's disease patients with perianal fistulas treated with surgery or immunosuppressant drugs is suggested. **Low quality of evidence ⊕⊕OO**
Good practice point	Using antibiotics, together with surgery and biological therapy, is recommended to attempt perianal fistulas closure.
Good practice point	Pelvic MRI or rectal endosonography should be performed prior to drainage.
Good practice point	Symptomatic patients with simple perianal fistulas must be treated with fistulotomy or seton placement and antibiotic management (ciprofloxacin 500 mg, every 12 hours, and/ or metronidazole 500 mg, every 8 hours, for 6-8 weeks).
Good practice point	Perianal fistulas must be classified into: • simple: superficial or low intersphincteric or low transsphincteric fistula with a single external orifice; • complex: high intersphincteric, high transsphincteric or suprasphincteric, rectovaginal fistulas with perianal abscess, inflammatory activity in the rectal mucosa or anorectal stenosis.
Good practice point	Pelvic MRI or rectal endosonography should be performed in suspected perianal Crohn's disease cases for diagnosis and follow-up purposes.
Weak in favor	Using infliximab for maintenance of remission of complex perianal fistulas in patients with Crohn's disease is suggested. **Very low quality of evidence ⊕OOO**
Good practice point	Infliximab administration must always be initiated in combination therapy with thiopurines unless the latter is contraindicated.
Good practice point	Administration of ciprofloxacin 500 mg every 12 hours must be added during 12 weeks to anti-TNF therapy in order to improve short-term outcomes in patients with complex perianal fistulas.
Strong in favor	The use of combination therapy with TNF inhibitors plus seton placement in the treatment of complex perianal fistulizing Crohn's disease is recommended to increase complete fistula closure. **Very low quality of evidence ⊕OOO**
Good practice point	In complex fistulas cases, surgical drainage of abscesses must be performed before initiating medical treatment with anti-TNF drugs.
Good practice point	Once the infection is controlled, the drainage seton must be removed to allow closure of the perianal fistula.
Good practice point	Patients with perianal Crohn's disease require multidisciplinary management with the coloproctology service.
Weak in favor	Use of tacrolimus is suggested to treat fistulizing Crohn's disease in patients who are refractory to biologic therapy and antibiotics. **Very low quality of evidence ⊕OOO**
Strong against	Using fibrin glues in the treatment of patients with perianal Crohn's disease is not recommended. **Very low quality of evidence ⊕OOO**
Weak in favor	Transrectal or transvaginal advancement flap is suggested for achieving rectovaginal fistulas closure in patients with Crohn's disease. **Very low quality of evidence ⊕OOO**
Good practice point	Transrectal advancement flap approach must be chosen as the first alternative for achieving rectovaginal fistulas closure.
Good practice point	There must be no endoscopic activity in the rectum for at least two years before surgical closure of the fistula is considered.
Weak in favor	Using fecal diversion as salvage therapy in patients with perianal Crohn's disease who have experienced failure to conventional medical and surgical management is suggested. **Very low quality of evidence ⊕OOO**
Weak in favor	Local stem cell therapy is suggested for the management of patients with perianal Crohn's disease refractory to medical treatment. **Very low quality of evidence ⊕OOO**

Summary of evidence: General considerations

Use of antibiotics

A systematic review (73) (AMSTAR score 7/11) assessed the efficacy of using antibiotics to induce remission in patients with perianal fistulas secondary to CD. All the studies included in the review allowed concomitant use of other interventions (immunomodulators) and compared antibiotics use with either placebo, immunomodulatory monotherapy, or immunomodulatory therapy plus placebo. The efficacy outcome reported was the proportion of patients who achieved clinical improvement or remission (CDAI <150 and/or a ≥70 points decrease in CDAI score or a >50% reduction in the number of fistulas for at least 4 weeks) during follow-up. The review retrieved 15 randomized clinical trials conducted in 1407 participants altogether. In the perianal fistula subgroup, ciprofloxacin use was associated with short-term lesion improvement (RR: 1.64, 95% CI: 1.16-2.32; 3 studies, 63 patients) (73).

Quality of evidence: low ⊕⊕OO

Monotherapy with biologics

The ACCENT II (A Crohn's Disease) double-blind, randomized, placebo-controlled clinical trial (101) evaluated the efficacy and safety of using infliximab compared to placebo in patients with fistulizing CD who had not been previously treated with infliximab. Participants were divided into two groups: those who had a response to the initial treatment and those who did not; in turn, in each group, participants were randomly assigned to receive an infusion of either placebo or infliximab 5 mg/kg every 8 weeks during 32 weeks. Efficacy outcomes were measured taking into account the Crohn's disease activity index (CDAI), the period of time with complete absence of draining fistulas, and the quality of life (measured with the Inflammatory Bowel Disease Questionnaire), while safety was established based on the frequency of adverse events. Follow-up time was 54 weeks after initiation of therapy.

As a result, 282 patients were randomized with a similar frequency of fistulizing perianal CD between groups (82% to 87%). In the group of participants who achieved remission at 14 weeks, infliximab maintenance therapy increased the period of time with complete absence of draining fistulas (40 weeks vs. 14 weeks; p<0.001) and the quality-of-life score (infliximab maintenance therapy median increase 14 vs. placebo median increase 4; p=0.002) and reduced the probability of experiencing relapses (estimated RR: 0.66; 95% CI: 0.5-0.88) (101).

On the other hand, in the group of patients who had no response, continuing infliximab therapy was not associated with an increased probability of achieving clinical remission (estimated RR: 1.31; 95% CI: 0.53-3.21). Finally, there were no differences between groups in the frequency of serious adverse events (estimated RR: 0.6; 95% CI: 0.35-1) and the proportion of patients who withdrew (estimated RR: 0.43; 95% CI: 0.15-1.2) (101).

Quality of evidence: very low ⊕OOO

Combination therapy with an anti-TNF agent plus seton drainage versus monotherapy in patients with perianal fistulas and Crohn's disease

A systematic review (94) (AMSTAR score 8/11) evaluated the efficacy of using combination therapy with anti-TNF drugs plus seton drainage for the treatment of patients with perianal fistulas and CD. The anti-TNF drug administered was infliximab and three of the four studies allowed the concomitant use of other medical therapies. The following outcomes were assessed in the review: complete or partial fistula closure and frequency of fistula recurrence, with a follow-up range of 4 months to 30 months.

The review retrieved three observational studies (293 participants in total). According to the findings of this systematic review, 45% to 100% of the patients in the combination therapy group had a complete closure of the fistula, in contrast with 17% to 70% and 63% to 82% in the seton drainage monotherapy and the anti-TNF monotherapy groups, respectively. On the other hand, regarding partial closure, the effect range in patients exposed to combination therapy was 14% to 88% versus 20% to 72% and 18% to 44% in those who underwent monotherapy with seton drainage and anti-TNF monotherapy, respectively. Finally, fistula recurrence was reported in 18% to 44% of patients who underwent combination therapy, in 42% to 78% of those who underwent anti-TNF monotherapy, and in 42% of those in the seton drainage monotherapy group (94).

Quality of evidence: very low ⊕OOO

Tacrolimus

A systematic review (102) (AMSTAR score 7/11) evaluated the efficacy of using tacrolimus in patients with luminal or perianal CD. Studies addressing the intervention of interest, namely, oral, intravenous or topical administration of tracolimus were included, and subgroup analyses according to the location of CD were performed. Clinical improvement (defined as at least 50% closure of the fistula), remission (defined as complete closure of the fistula), and frequency of adverse events were reported as outcomes.

Regarding perianal CD, a randomized clinical trial comparing oral administration of tacrolimus with placebo was identified (103). In this trial, differences in favor of tacrolimus use regarding the frequency of clinical improvement were found (adjusted OR: 7.74; 95% CI: 1.28-46.8); however, no diffe-

rences in the frequency of remission (calculated RR: 1.19; 95% CI: 0.18-7.74) or serious adverse events (tacrolimus 5% vs. placebo 0%; p=0.46) were found (102, 103).

Quality of evidence: very low ⊕○○○

Fibrin glue versus surgical treatment

A systematic review and meta-analysis (104) (AMSTAR score 7/11) evaluated the efficacy of using fibrin glue for the treatment of patients with perianal CD. Patients included in the review were characterized by having simple, complex and transsphincteric anal fistulas; no additional information on their clinical characteristics was reported. The following interventions were included: fibrin glue injections (81 patients in total) versus any other surgical intervention (fistulotomy, seton drainage, advancement flaps). On the other hand, the outcomes reported were fistula recurrence and anal incontinence. The review included 3 studies (2 clinical trials and 1 non-randomized control group study) conducted in a total of 311 participants. No statistically significant differences were found between groups in terms of fistula recurrence (OR: 0.33; 95% CI: 0.03-3.66) or frequency of fecal incontinence (OR: 1.00; 95% CI: 0.43-2.34) (104).

Quality of evidence: very low ⊕○○○

Rectovaginal advancement flaps in patients with perianal fistulas

A systematic review and meta-analysis (105) (AMSTAR score 7/11) evaluated the efficacy and safety of transrectal advancement flap compared to transvaginal advancement flap approach for treating rectovaginal fistulas in patients with CD; no further specifications are informed by the authors of the study. The following outcomes were reported: primary fistula closure, secondary closure, and fistula recurrence. The review included 11 nonrandomized studies for a total of 224 procedures. No significant differences were found between both approaches in relation to the rates of primary closure (estimated OR: 1.02; 95% CI: 0.33-3.21), overall closure (estimated OR: 1.14; 95% CI: 0.45-2.91) or recurrence (estimated OR: 0.36; 95% CI: 0.03-3.84) (105).

Quality of evidence: very low ⊕○○○

Fecal diversion in patients with refractory perianal Crohn's disease

A systematic review and meta-analysis of proportions (106) (AMSTAR score 9/11) determined the efficacy of temporary fecal diversion in patients with perianal CD. Adult and pediatric patients with perianal CD and with or without colonic disease were included. The proportion of successful restoration of bowel continuity was considered as the primary outcome, while early clinical improvement and the need for additional surgery, as secondary outcomes. The review retrieved 15 non-randomized studies. Of the patients who underwent temporary fecal diversion, 63.8% (95% CI: 54%-73%; 373 patients) had an early clinical response; 16.6% experienced successful bowel continuity restoration after the procedure (95% CI: 11.8%-22.9%; 15 studies, 545 patients); 26.5% required a re-diversion (without proctectomy) (95% CI: 14.1%-44.2%); and 41.6% needed to undergo a proctectomy after the procedure (95% CI: 32.6%-51.2%) (106).

Quality of evidence: very low ⊕○○○

Stem cell therapy

Use of adipose mesenchymal stem cells, bone marrow-derived mesenchymal stem cells, and hematopoietic stem cells

A systematic review and meta-analysis of proportions (81) (AMSTAR score 10/11) evaluated the efficacy and safety of stem cell therapy in patients with active CD. The use of bone marrow-derived mesenchymal stem cells, adipose mesenchymal stem cells, or hematopoietic stem cells were considered as interventions; on the other hand, clinical efficacy (defined as clinical response or clinical remission), fistula healing, and the frequency of adverse events, endoscopic remission and clinical recurrence were considered as outcomes.

The review retrieved 13 prospective experimental studies reporting data on the efficacy of stem cell therapy for treating perianal CD. In the subgroup analysis performed according to the stem cell type used, the clinical response rate in patients who received bone marrow-derived mesenchymal stem cells was 59% (95% CI: 34%-80%; 6 studies), with a 60% probability of fistula closure (95% CI: 44%-75%). On the other hand, the clinical response rate in participants treated with adipose-derived stems cells was 56% (95% CI 13%-88%), with a 23% clinical remission rate (95% CI 7%-54%; 4 studies). Finally, in the group of patients who underwent hematopoietic cells therapy, a 73% clinical remission rate (95% CI: 36%-93%; 4 studies) and a 35% rate of adverse events (95% CI: 5%-86%) were found (81).

Regarding the analysis of the route of administration, the fistula healing rate in patients who received systemic stem cell therapy was 29% (95% CI: 3%-85%), whereas in those who received local injection of stem cells, it was 60% (95% CI: 47%-72%) (81).

Mesenchymal stromal cells versus placebo for the treatment of fistulas in Crohn's disease

A systematic review and meta-analysis (107) (AMSTAR score 7/11) evaluated the efficacy, compared to placebo, of using mesenchymal stem cells to treat fistulas associated with CD. The review included comparative studies conduc-

ted in patients with active disease (mean CDAI score <450 with presence of fistulas) and the outcome assessed was the frequency of fistula healing; safety outcomes were not considered. The review included 14 studies (477 patients in total). According to the findings reported in this systematic review, a lower proportion of persistent fistulas was found in the group of patients who underwent stem cell therapy (OR: 0.21; 95% CI: 0.09-0.32) (107).

Quality of evidence: very low ⊕○○○

In addition, a second systematic review that retrieved 11 studies that met the inclusion criteria and included only 3 studies with a control group in the meta-analysis, reports that mesenchymal stem cell therapy was associated with increased clinical healing of perianal fistulas when compared with controls at 6 and 24 weeks (OR: 3.06; 95% CI: 1.05-8.90; p = 0.04) and at 24 and 52 weeks (OR: 2.37; 95% CI: 0.90-6.25; p = 0.08). Also, there was no an increased frequency of adverse events (OR: 1.07; 95% CI: 0.61-1.89; p = 0.81) and serious adverse events (OR: 0.53; 95% CI: 0.28-0.98; p = 0.04) in patients treated with mesenchymal stem cells (108).

Efficacy of medical therapy for the management of fistulizing Crohn's disease

A systematic review that included 21 studies conducted in patients with fistulizing CD found moderate-quality of evidence supporting the efficacy of anti-TNF therapy (RR: 2.01; 95% CI: 1.36-2.97), particularly infliximab, ustekinumab (RR, 1.77; 95% CI: 0.93-3.37), and mesenchymal stem cell therapy (RR: 1.31; 95% CI: 0.98-1.73) for inducing fistula remission, and low-quality of evidence supporting the efficacy of vedolizumab and immunosuppressants. Regarding maintenance of fistula remission, moderate quality of evidence supporting the efficacy of anti-TNF therapy compared to placebo was found (RR: 1.94; 95% CI: 1.25-3.02; p = 0.003) (109).

From evidence to recommendation

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION N° 6. WHAT ARE THE SAFEST AND MOST EFFECTIVE SURGICAL AND ENDOSCOPIC INTERVENTIONS TO TREAT CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation	N°	Summary
Weak in favor		Surgical procedure should not be contraindicated in patients with Crohn's disease undergoing biological therapy. **Very low quality of evidence** ⊕OOO
Weak in favor		Continuing the administration of azathioprine prior to performing the surgical procedure in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		If the procedure can be deferred, surgery should be performed prior to starting the next dose of biological therapy.
Good practice point		The possibility of postoperative infections should be monitored.
Weak in favor		Surgical treatment is suggested in patients with intra-abdominal abscesses associated with Crohn's disease only in case they fail to respond to initial medical and/or interventional radiology treatment. **Very low quality of evidence** ⊕OOO
Good practice point		Abscesses smaller than 3 cm must be treated only with antibiotics. Patients with abscesses larger than 3 cm additionally require image-guided percutaneous drainage.
Good practice point		In case of no response to medical treatment or that abscesses cannot be drained (partitioned or difficult to access), surgical treatment must be implemented.
Strong in favor		Pneumatic balloon dilation is recommended in patients with strictures associated with Crohn's disease. **Very low quality of evidence** ⊕OOO
Good practice point		Pneumatic dilation should be performed in the case of: • stricture length less than 4 cm; • presence of strictures in the terminal ileum or ileocolic anastomosis; • single strictures.
Good practice point		The presence of fistulas or abscesses in the area of the stricture implies a contraindication for pneumatic dilation.
Good practice point		Diagnostic imaging studies should be used to try determining whether the component of the stricture is fibrotic or inflammatory.
Strong in favor		Strictureplasty is recommended in patients with small bowel stenosing Crohn's disease. **Very low quality of evidence** ⊕OOO
Good practice point		Strictureplasty is highly recommended in patients with multiple strictures (smaller than 10 cm) to avoid extensive small bowel resections and reduce the risk of short bowel syndrome. It should be performed by specialists experienced in treating this condition.
Weak in favor		Performing laparoscopy or open surgery is suggested for surgical treatment of patients with Crohn's disease. The selection of the surgical technique shall be made according to local experience. **Very low quality of evidence** ⊕OOO
Good practice point		Whenever feasible, minimally invasive surgery should be preferred due to the lower risk of adhesions and better cosmetic outcomes.
Good practice point		Minimally invasive surgery should be performed in experienced centers with adequate patient volume.
Strong in favor		Performing side-to-side anastomosis in patients with Crohn's disease undergoing surgical resection is recommended. **Very low quality of evidence** ⊕OOO
Weak in favor		Segmental resection is suggested in patients with colonic Crohn's disease (<30 cm). **Very low quality of evidence** ⊕OOO

Summary of evidence: General considerations

Biologic drugs and frequency of postoperative complications in patients with inflammatory bowel disease

A systematic review (110) (AMSTAR score 9/11) assessed the frequency of postoperative complications in patients with CD who underwent open or laparoscopic surgery and who received anti-TNF therapy within the three months prior to the procedure. Of the studies included in the review, 11 recruited only patients with CD, and 3, patients with any type of inflammatory bowel disease (CD, ulcerative colitis, or indeterminate colitis). The outcomes reported in this review were the frequency of anastomosis-related complications (presence of dehiscence, fistula, intra-abdominal abscess or occurrence of enteric fistula), the proportion of patients who experienced a major medical complication (defined as life-threatening complication or a complication requiring hospitalization, including thrombotic, renal or cardiovascular diseases) or a minor complication (surgical site infection, prolonged ileus, adhesions, gastric bleeding

or wound dehiscence), the need for reoperation and, finally, associated mortality.

The review retrieved 13 observational studies conducted in a total of 2046 patients. In nine studies, patients were administered infliximab, while in four they were administered adalimumab or certolizumab. All participants concomitantly received steroids and immunomodulators. According to the findings of this systematic review, the administration of biologic drugs during the months prior to the intervention was not associated with a higher or lower frequency of anastomosis-related complications (OR: 0.91; 95% CI: 0.56-1.47) or reoperation (OR: 1.09; 95% CI: 0.61-1.95), but it was associated with an increased risk of major complications (OR: 1.97; 95% CI: 1.23-3.14) and minor complications (OR: 1.40; 95% CI: 1.05-1.85). However, the frequency of these adverse events was not associated with increased mortality (OR: 4.80; 95% CI: 0.66-34.82) (110).

Quality of evidence: very low ⊕○○○

In a systematic review that included 27 studies, the effect of anti-TNF agent infusion timing prior to surgery and the risk of postoperative surgical site infection were evaluated. Compared with controls, no significant differences in terms of surgical site infections, abscess formation, or anastomotic leak were found in patients with CD when an anti-TNF drug was administered at 4, 8, or 12 weeks prior to surgery (111).

Use of immunomodulators prior to bowel resection in patients with Crohn's disease and risk of complications

A systematic review (112) (AMSTAR score 7/11) evaluated the safety of using immunomodulators prior to performing bowel resection in patients with CD. In 14 of the studies included in the review, participants were administered an anti-TNF agent; in 13, corticosteroids; in 8, thiopurines; and in 6, two immunosuppressants were used concomitantly, within the 3 months prior to undergoing the surgical intervention. The outcome of interest was the proportion of patients with postoperative infection, defined as the presence of a focus of infection in soft tissues or the development of wound dehiscence, or having a diagnosis of intra-abdominal abscess, sepsis, pneumonia, peritonitis, or bacteremia.

This systematic review retrieved 21 observational cohort and case-control studies (648 patients in total). According to the findings of the review, prior use of anti-TNF drugs, as well as of corticosteroids, increased the proportion of patients who experienced postoperative infection (RR: 1.42, 95% CI: 1.05-1.92, and RR: 1.45, 95% CI: 1.01-2.08, for anti-TNF drugs and corticosteroids, respectively). However, this was not the case when thiopurines were used (RR: 1.23, 95% CI: 0.66-2.29). These findings remained constant when a subgroup analysis excluding studies that recruited patients with an inflammatory bowel disease other than CD was performed (RR: 1.31, 95% CI: 1.06-1.64, in the case of anti-TNF drugs, and RR: 1.45, 95% CI: 1.13-1.87, in the case of corticosteroids) (112).

Quality of evidence: very low ⊕○○○

Surgical management versus medical management in intra-abdominal abscesses

A systematic review and meta-analysis (113) (AMSTAR score 5/11) compared the efficacy of medical management (antibiotics or antibiotics and percutaneous drainage) with that of surgical management (laparotomy with or without bowel resection) in patients with intra-abdominal abscesses secondary to CD. The location of CD, nor the type of antibiotic or the distribution of surgical techniques that were used were not specified in this review, and the following outcomes were assessed: resolution of abscesses, time required to show improvement, number of patients requiring stomas, and hospital stay. In all studies included in the review, the follow-up period was at least 1 year, except for one study, in which follow-up time was 3 months.

The review retrieved 9 retrospective observational studies. Differences favoring surgical treatment in terms of resolution of abscesses (OR: 3.44; 95% CI: 1.8-6.58) and clinical improvement before 1 year (OR: 4.58; 95% CI: 2.02-10.36) were found. Regarding the need for stoma creation, a higher frequency was observed in the group of patients who underwent surgical management compared with the medical management group (OR: 3.35; 95% CI: 1.43-7.87). Regarding hospital stay, it is descriptively reported that hospitalization length was shorter in the medical management group (quantitative data are not provided) (113).

Quality of evidence: very low ⊕○○○

Endoscopic pneumatic dilation in Crohn's disease

A systematic review and meta-analysis of proportions (114) (AMSTAR score 8/11) evaluated the efficacy of endoscopic pneumatic dilation in adult patients with stenosing CD. The review did not report the anatomic distribution of the disease and included a total of 1089 patients, 790 strictures and 2664 dilations. The following outcomes were reported: symptomatic response, endoscopic response, and the presence of postoperative complications. The median follow-up time was 83.5 months (range: 12 to 172 months). The review retrieved 25 studies, of which 16 included symptomatic response as an outcome, with a pooled frequency of 70.2% (95% CI: 60%-78.8%); the endoscopic response pooled rate was 90.6% (95% CI: 87.8%-92.8%; 22 studies), and the perforation pooled rate was 3% (95% CI: 2.2%-4%) (114).

Quality of evidence: very low ⊕○○○

Strictureplasty versus bowel resection in patients with small bowel Crohn's disease

A systematic review and meta-analysis (115) (AMSTAR score 8/11) evaluated the efficacy and safety of strictureplasty compared with bowel resection with or without dilation in patients with small bowel CD; no further specifications are provided. Surgical and medical recurrence were assessed as efficacy outcomes, and bowel obstruction, bleeding, septic complications, and overall complications, as safety outcomes. The review retrieved seven non-randomized studies that included pediatric and adult populations. Regarding recurrence-free survival time, differences in favor of strictureplasty were found (HR: 1.08; 95% CI: 1.02-1.15), but no differences were observed in terms of frequency of overall recurrence (OR: 1.36; 95% CI: 0.96-1.93) or overall complications (OR: 0.60; 95% CI: 0.31-1.16). Also, there were no differences between groups in the following outcomes: surgical and medical recurrence (OR: 1.36; 95% CI: 0.96-1.93), bowel obstruction (OR: 0.8; 95% CI: 0.09-1.93), hemorrhage (OR: 0.51; 95% CI: 0.13-2.0), and sepsis (OR: 0.67; 95% CI: 0.27-1.67) (115).

Quality of evidence: very low ⊕○○○

Laparoscopy versus open surgery

A systematic review (116) (AMSTAR score 10/11) compared the efficacy of laparoscopy and the rates of reoperation and recurrence associated with it versus open surgery in patients with small bowel CD. The review included patients older than 16 years who underwent elective surgery with ileocolic resection and anastomosis or small bowel resection plus anastomosis or strictureplasty. Perioperative morbidity and reoperation due to disease recurrence were considered as primary outcomes, and postoperative pain, duration of postoperative ileus, postoperative hospital stay length, duration of the procedure, amount of blood loss, mortality, and conversion rates, as secondary outcomes. The median follow-up time of the studies included in the review ranged from 3 months to 10.9 years after surgery. The review found 4 randomized clinical trials conducted in a total of 120 patients. In the pooled analyses, no statistically significant differences were found between both groups regarding the rate of infections (OR: 0.25; 95% CI: 0.03-2.39), the rate of anastomotic leaks (OR: 0.97; 95% CI: 0.13-6.98), the rate of intra-abdominal abscesses (OR: 0.19; 95% CI: 0.11-74.12), and the rates of reoperation within the first 30 days (OR: 0.57; 95% CI: 0.07-4.46) or in the long term (OR: 0.85; 95% CI. 0,32-2,27). Also, there were no differences in hospital stay duration (OR: 0.7; 95% CI: 0.28-1.73), duration of postoperative ileus (OR: 0.55; 95% CI: 0.13-2.43), and mean blood loss (surgery: 133 ± 70 mL *versus* laparoscopy: 173 ± 123 mL; p = 0.25). A conversion rate <3% was found and none of the studies reported mortality cases (116).

Quality of evidence: very low ⊕○○○

Types of anastomosis in ileocolic resection

A systematic review and meta-analysis (117) (AMSTAR score 8/11) compared the efficacy and safety of side-to-side anastomosis versus end-to-end anastomosis after ileocolic resection in patients with CD. The review included three randomized clinical trials and five non-randomized studies (821 patients in total) and the following outcomes were evaluated: frequency of complications, hospital stay, mortality, recurrence, and need for reoperation. Regarding the frequency of complications, differences in favor of side-to-side anastomosis were found (overall complications: OR: 0.54; 95% CI: 0.32-0.93), but these differences were not significant when complications were disaggregated into anastomotic leak, wound infection, pulmonary embolism, intra-abdominal abscess, and bowel obstruction or stricture. Regarding recurrence, statistically significant differences in favor of side-to-side anastomosis were found (OR: 0.20; 95% CI: 0.07-0.55), as well as regarding the frequency of reoperation (OR: 0.18; 95% CI: 0.07-0.45). No differences between both groups were found in terms of postoperative hospital stay length (weighted mean difference: -0.59; 95% CI: -1.87 to 0.68) or the risk of mortality (OR: 1.94; 95% CI: 0.30-12.48) (117).

Quality of evidence: very low ⊕○○○

Surgical resection in patients with colonic Crohn's disease

A systematic review and meta-analysis (118) (AMSTAR score 7/11) evaluated the efficacy and safety of segmental colectomy compared with subtotal or total colectomy in patients with colonic CD. Only pediatric or adult patients with a diagnosis of CD, as defined by the Price and Morson criteria, with initial colonic involvement or with active colonic CD were included. One of the studies retrieved included patients with ileocolonic CD. The review identified 6 comparative observational studies, and surgical recurrence, overall recurrence, postoperative complications, and the need for a permanent stoma were considered as the outcomes of interest. According to the findings of this systematic review, there were no significant differences between interventions in relation to surgical recurrence (OR: 1.08; 95% CI: 0.39-2.95), overall recurrence (OR: 1.01; 95% CI: 0.49-2.06), postoperative complications (OR: 1.43; 95% CI: 0.16-12.74) or the need for a permanent stoma (OR: 2.75; 95% CI: 0.78-9.71) (118).

Quality of evidence: very low ⊕○○○

From evidence to recommendation

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

QUESTION NO. 7. WHAT ARE THE SAFEST AND MOST EFFECTIVE INTERVENTIONS TO PREVENT POSTOPERATIVE RECURRENCE OF CROHN'S DISEASE IN PATIENTS OLDER THAN 16 YEARS?

List of recommendations

Recommendation	N°	Summary
Strong against		Using probiotics to prevent postoperative recurrence of Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Good practice point		The presence of risk factors for postoperative relapse must be identified in all patients with Crohn's disease undergoing surgical resection, so that preventive pharmacological interventions are implemented. • high-risk factors: age <30 years, smoking, >2 surgeries due to penetrating CD (B3); • low-risk factors: age >50 years, non-smokers, first surgery, short stenosis <10-20 cm, CD duration >10 years.
Good practice point		An ileocolonoscopy must be performed 6 to 12 months after surgery in order to identify endoscopic relapse.
Weak in favor		Using antibiotics to prevent postoperative recurrence of Crohn's disease is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		Metronidazole is the antibiotic to be used, at a dose of 15 to 20 mg/kg and for 3 months. When using this medication, tolerance and the occurrence of adverse events, especially peripheral neuropathy, should be closely monitored.
Good practice point		In low-risk patients, a 3-month metronidazole treatment is recommended, or, in case of drug intolerance, close monitoring without antibiotic use.
Good practice point		Any patient with Crohn's disease who has undergone surgery as a treatment option must avoid smoking.
Weak in favor		The use of azathioprine or 6-mercaptopurine to prevent postoperative recurrence of Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		In patients at high risk of relapse, thiopurines can be used concomitantly with anti-TNF drugs, with or without metronidazole, for the first 3 months. Drug tolerance should be monitored.
Weak in favor		Using 5-ASA to prevent postoperative clinical recurrence of Crohn's disease is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		Use of mesalazine should be considered only in patients with a low risk of postoperative relapse or in those in which thiopurines or TNF inhibitors are absolutely or relatively contraindicated.
Weak against		Using budesonide to prevent postoperative recurrence of Crohn's disease is not suggested. **Low quality of evidence** ⊕⊕OO
Weak in favor		Using anti-TNF agents as first-line therapy to prevent endoscopic recurrence of Crohn's disease after surgery is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		Starting a 6-month treatment with anti-FNT agents ± thiopurines, if there are no contraindications, whether associated or not to metronidazole therapy (3 months), in patients at a high risk of recurrence is recommended.
Strong in favor		Using anti-TNF drugs to treat postoperative relapses of Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO
Good practice point		Initial use of thiopurines ± metronidazole (the latter for 3 months) is recommended in patients with low-risk postoperative recurrence; in case they fail to respond to the treatment, it must be managed with anti-TNF therapy.
Strong in favor		Providing Crohn's disease patients with clear information about the management of the disease and treatment options, as well as their risks and benefits, is recommended. **Very low quality of evidence** ⊕OOO
Strong in favor		Assessing the presence of signs of depression or worsened quality of life and, if necessary, referring the patient to support groups and specialized help groups is recommended. **Very low quality of evidence** ⊕OOO

Summary of evidence: General considerations

Using probiotics to prevent postoperative recurrence of Crohn's disease

A systematic review (71) (AMSTAR score 9/11) evaluated the efficacy and safety of using probiotics for maintenance of remission in CD. In this case, the following outcomes

were analyzed: frequency of clinical relapse (CDAI >150 or a ≥70 points increase compared to the baseline score) or endoscopic relapse (Rutgeerts score >2) at 12 months. Compared to placebo, the administration of probiotics did not reduce the incidence of clinical relapse (RR: 1.06; 95% CI: 0.59-1.92) or endoscopic relapse (RR: 1.04; 95% CI: 0.82-1.31). It should be noted that this review did not assess the frequency of adverse events in this population (patients with CD).

Another systematic review (88) (AMSTAR score 8/11) also assessed the efficacy of using probiotics in maintaining remission in patients with CD after undergoing surgical treatment. The outcome reported by this review was the incidence of endoscopic relapse (Rutgeerts score) with a follow-up time ranging from 3 to 24 months. Three studies comparing the use of this intervention versus placebo in 200 patients in total were included. No statistically significant differences were found between groups (RR: 1.08; 95% CI: 0.67-1.74).

Quality of evidence: very low ⊕OOO

Using antibiotics to prevent postoperative recurrence of Crohn's disease

A systematic review (73) (AMSTAR score 7/11) assessed the efficacy of using antibiotics to induce remission in patients with postoperative recurrence of CD. All studies included in the review allowed concomitant use of other interventions (immunomodulators) and the outcome reported was the proportion of patients who achieved clinical improvement or remission (CDAI score <150 and/or a ≥70 points decrease in CDAI score or a >50% reduction in the number of fistulas for at least 4 weeks) during follow-up. The review retrieved one randomized clinical trial (33 participants). Compared to placebo, antibiotic administration did not increase the frequency of patients in which remission was maintained during the first 3 to 6 months (RR: 1.13; 95% CI: 0.43-2.98) (53).

Quality of evidence: low ⊕⊕OO

A second systematic review (119) (AMSTAR score 9/11) included two controlled clinical trials assessing the rate of severe endoscopic recurrence (3-month follow-up and assessed with a Rutgeerts score I2 or higher) and the rate of withdrawal due to serious adverse events when using 5-nitroimidazoles. Compared to placebo, 5-nitroimidazoles use decreased the frequency of severe endoscopic recurrence (RR: 0.44; 95% CI: 0.26-0.74), at the expense of a higher adverse events rate (RR: 3.00; 95% CI: 1.37-6.58) (119).

Quality of evidence: low ⊕⊕OO

Use of azathioprine or 6-mercaptopurine to prevent postoperative recurrence of Crohn's disease

A systematic review and meta-analysis (120) (AMSTAR score 9/11) evaluated the safety and efficacy of using different interventions to maintain surgically induced remission of CD. This review assessed the following outcomes: the proportion of patients who experienced clinical relapse (defined as having a CDAI score >200 or requiring steroids or having a 60-point increase in CDAI score compared to the baseline score) or endoscopic relapse (defined as having a Rutgeerts score >2) and the frequency of withdrawal due to adverse events.

The review retrieved two controlled clinical trials (168 participants in total) comparing this intervention with placebo. According to the findings of this review, the use of azathioprine or 6-mercaptopurine reduced the incidence of clinical relapse (RR: 0.74; 95% CI: 0.58-0.94) and endoscopic relapse (RR: 0.40; 95% CI: 0.19-0.83) during the 3 to 12 months of follow-up, without increasing the frequency of withdrawal (RR: 1.33; 95% CI: 0.59-2.98). In addition, in this review, azathioprine or 6-mercaptopurine therapy was also compared with the administration of 5-aminosalicylates. In this regard, five studies conducted in 425 patients in total and comparing the safety and efficacy of these interventions were included. No differences were found between groups in terms of clinical relapse (RR: 1.14; 95% CI: 0.93-1.41) and endoscopic relapse (RR: 0.55; 95% CI: 0.23-1.32); however, a higher rate of withdrawal due to adverse events was observed in the azathioprine or 6-mercaptopurine arm (RR: 2.07; 95% CI: 1.26-33.90) (120).

Finally, a comparison between azathioprine or 6-mercaptopurine therapy and anti-TNF therapy was also made. When infliximab was used, there were no differences regarding the rate of clinical relapse (RR: 2.00; 95% CI: 0.21-18.98), the rate of endoscopic relapse (RR: 4.40; 95% CI: 0.59-33.07) or the frequency of withdrawal (RR: 3.00; 95% CI: 0.14-66.53). However, azathioprine or 6-mercaptopurine therapy significantly increased the rate of relapse, both clinical an endoscopic (RR: 5.18; 95% CI: 1.35-19.83, and RR: 10.35; 95% CI: 1.50-71.32, respectively) when compared to adalimumab. Finally, withdrawal rates were similar between groups (RR: 1.88, 95% CI: 0.19-18.80) (120).

Quality of evidence: very low ⊕OOO

Using 5-aminosalicylates to prevent postoperative recurrence of Crohn's disease

A systematic review (121) (AMSTAR score 8/11) assessing the efficacy and safety of using 5-aminosalicylates for maintenance of surgically induced remission of CD was retrieved.

This review included eight studies (1061 participants in total) and the outcomes reported were the frequency of clinical relapse during the first 24 months of follow-up (defined as a CDAI >150 or >200 or a >60 points increase compared to the baseline score) and the frequency of adverse events. Compared to placebo, the administration of 5-aminosalicylates reduced the frequency of relapse (RR: 0.71; 95% CI: 0.54-0.94) but did not reduce the frequency of adverse events (RR: 1.06; 95% CI: 0.61-1.85) (121).

Quality of evidence: low ⊕⊕OO

Use of budesonide to prevent postoperative recurrence of Crohn's disease

A meta-analysis, resulting from a systematic literature search (119) (AMSTAR score 9/11), retrieved two controlled clinical trials assessing the rate of severe endoscopic recurrence (12-month follow-up and assessed with a Rutgeerts score I2 or higher) and the frequency of withdrawal due to serious adverse events when using budesonide. Compared to placebo, this intervention did not reduce the incidence of severe endoscopic relapse (RR: 0.87; 95% CI: 0.50-1.49), but neither did it increase the frequency of withdrawal due to adverse events (RR: 1.01; 95% CI: 0.37-2.78) (119).

Quality of evidence: low ⊕⊕OO

Anti-TNF therapy versus conventional therapy to prevent postoperative recurrence of Crohn's disease

A second systematic review (122) (AMSTAR score 7/11) compared the efficacy of infliximab administration within the first 2 to 4 weeks after performing the surgical procedure to prevent histologic recurrence, which was defined according to the modified D'Haens histologic scoring system. This review retrieved a study conducted in 24 participants and in which this outcome was evaluated. When compared with the administration of mesalamine or 6-mercaptopurine, infliximab therapy increased the proportion of patients who did not experience a histologic recurrence episode during the first 54 weeks of follow-up (RR: 6.00; 95% CI: 1.02-35.37) (122).

Quality of evidence: low ⊕⊕OO

Safety and efficacy of different pharmacological strategies to prevent postoperative recurrence of Crohn's disease. Results of a network meta-analysis

A systematic review and network meta-analysis (123) (AMSTAR score 8/11) evaluated the safety and efficacy of different pharmacological interventions to prevent clinical relapse (CDAI ≥ 150) or endoscopic relapse (Rutgeerts score I2-I4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies) in patients with CD after surgery. Patients with established CD, a history of successful bowel resection with removal of macroscopically visible disease, and who had started postoperative prophylaxis for CD within the first 3 months after undergoing bowel resection were included.

According to the results of this network meta-analysis, when compared with placebo (or no intervention), the use of mesalazine (RR: 0.60; 95% CI: 0.37-0.88), antibiotics (RR: 0.26; 95% CI: 0.08-0.61), immunomodulator monotherapy (RR: 0.36; 95% CI: 0.17-0.63), combination therapy with immunomodulators plus antibiotics (RR: 0.11; 95% CI: 0.02-0.51) and anti-TNF monotherapy (RR: 0.04; 95% CI: 0.00-0.14) were effective interventions in terms of decreasing the frequency of clinical relapse episodes. However, budesonide therapy did not appear to be superior to placebo (RR: 0.93; 95% CI: 0.40-1.84). On the other hand, regarding endoscopic relapse, this meta-analysis reported that the use of antibiotics (RR: 0.41; 95% CI: 0.15-0.92), immunomodulatory monotherapy (RR: 0.33; 95% CI: 0.13-0.68), combination therapy with immunomodulators plus antibiotics (RR: 0.16; 95% CI: 0.04-0.48) and anti-TNF monotherapy (RR: 0.01; 95% CI: 0.00-0.05) were superior to placebo, however this was not the case for mesalazine (RR: 0.67; 95% CI: 0.39-1.08) or budesonide (RR: 0.86; 95% CI: 0.61-1.22) (123).

Furthermore, this systematic review conducted a second analysis to determine which of these pharmacological interventions was the most effective in preventing clinical relapse. In this regard, the network analysis showed that anti-TNF monotherapy was superior to immunomodulator monotherapy (RR: 0.11; 95% CI: 0.01-0.40). On the other hand, anti-TNF monotherapy was also superior to antibiotic use, but this estimator was based primarily on indirect evidence (RR: 0.20; 95% CI: 0.01-0.84). Also, there were no significant differences between combination therapy with immunomodulators plus antibiotics and immunomodulator monotherapy (RR: 0.34; 95% CI: 0.05-1.20) or antibiotic monotherapy (RR: 0.48; 95% CI: 0.08-1.46). Immunomodulator monotherapy was not superior to antibiotic therapy (RR: 1.92; 95% CI: 0.93-4.00) (123).

Finally, this systematic review also aimed to determine which of these pharmacological interventions might be the best in preventing endoscopic relapse. Based on the results of this network meta-analysis, anti-TNF monotherapy was superior to all other interventions: vs. mesalazine (RR: 0.02; 95% CI: 0.00-0.07), antibiotics (RR: 0.03; 95% CI: 0.00-0.15), immunomodulator monotherapy (RR: 0.04; 95% CI: 0.00-0.14), combination therapy with immunomodulators plus antibiotics (RR: 0.03; 95% CI: 0.00-0.49) and budesonide (RR: 0.005; 95% CI: 0.00-0.08). Also, there were no significant differences between combination therapy with immunomodulators plus antibiotics and immunomodulator monotherapy (RR: 0.54; 95% CI: 0.12-1.59) or antibiotic monotherapy (RR: 0.43; 95% CI: 0.10-

1.19). Additionally, there were no significant differences between immunomodulator monotherapy and antibiotic monotherapy in terms of reducing the risk of endoscopic relapse (RR: 0.97; 95% CI: 0.26-2.53) (123).

Quality of evidence: low ⊕⊕OO

A systematic review and meta-analysis that included 10 studies (751 patients in total) analyzed postoperative endoscopic recurrence of CD at 12 months of follow-up. Anti-TNF monotherapy was significantly better than placebo in preventing endoscopic recurrence (RR: 0.13; 95% CI: 0.04-0.39). The same outcome was obtained when combined with 5-ASA drugs (RR: 0.30; 95% CI: 0.12-0.75) or with nitroimidazoles (RR: 0.40; 95% CI: 0.23-0.69). Combination therapy with thiopurines plus metronidazole was also more effective than placebo (RR: 0.56; 95% CI: 0.40-0.80), as well as thiopurine monotherapy (RR: 0.84; 95% CI: 0.74-0.94). Somehow, nitroimidazoles and 5-ASA drugs were not superior to placebo in preventing endoscopic recurrence postoperatively (124).

Anti-TNF agents versus immunomodulators for the treatment of postoperative relapse of Crohn's disease

A systematic review (125) (AMSTAR score 8/11) evaluated the efficacy of administering anti-TNF drugs to treat postoperative relapse of CD. The review retrieved two clinical trials conducted in a total of 50 patients, and the outcome reported was the frequency of endoscopic remission (Rutgeerts score <2) with a follow-up time ranging from 6 to 12 months. Compared to immunomodulators, anti-TNF therapy increased the proportion of patients who achieved endoscopic remission (OR: 16.64; 95% CI: 2.51-110.27) (125).

Quality of evidence: low ⊕⊕OO

From evidence to recommendation

	Value Judgment					
Problem	No	Probably not	Probably yes	Yes	Varies	Unknown
Desirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Undesirable effects	Trivial	Small	Moderate	Large	Varies	Unknown
Confidence in the evidence	Very low	Low	Moderate	High		No evidence was found
Variability	High uncertainty	Significant variability	Non-significant variability	Absence of variability		Unknown
Balance of effects	It favors the comparison	It probably favors the comparison	It does not favor any intervention	It probably favors the intervention	It favors the intervention	Unknown
Overall quality of evidence	Very low	Low	Moderate	High		No evidence was found
Equity	Reduced	Probably reduced	It probably has no impact	Probably increased	Increased	Unknown
Users' acceptability	No	Probably not	Probably yes	Yes	Varies	Unknown
Implementation feasibility	No	Probably not	Probably yes	Yes	Varies	Unknown

VALUES AND PREFERENCES OF PATIENTS

What are the needs of patients in relation to Crohn's disease?

Summary of the recommendations

Recommendation	N°	Summary
Strong in favor		Providing Crohn's disease patients with clear information about the management of the disease and treatment options, as well as their risks and benefits, is recommended. **Very low quality of evidence ⊕OOO**
Strong in favor		Assessing the presence of signs of depression or worsened quality of life and, if necessary, referring the patient to support groups and specialized help groups is recommended. **Very low quality of evidence ⊕OOO**

Values and preferences

Inflammatory bowel disease (IBD) has a major impact on the quality of life and psychological well-being of patients. An emotional component that may affect therapeutic outcomes in these patients has been identified.

A qualitative systematic review (126) (AMSTAR 7/11) that included 36 studies conducted in adult population explored how to support improvement of these outcomes in IBD patients. According to this review, patients with psychological adaptation mechanisms to new situations (patients with a family support network and individual strength) showed faster improvement than those with psychological adaptation problems (i.e., patients who focus more on negative situations).

In addition, this review reports that, on average, 43% of IBD patients suffer some degree of depression according to specialized scales with emphasis on the "loneliness", "resilience" and "disease activity" domains. In this regard, the systematic review included a study conducted in 49 patients reporting that the degree of depression is a predictor of the positive effect of the therapy. Also, a meta-analysis based on 50 patients found that psychological therapy had an effect on the disease at 12 months, but that it did not have any effect at 6 months. A qualitative study conducted in 31 patients with severe IBD found that eating habits changes, support networks, strategies to control IBD-related situations, positive attitudinal changes toward the disease, relaxation techniques, finding distractions from the disease, and disease awareness contributed to improved well-being and symptoms alleviation. The SR concludes that IBD patients should undergo psychological therapy for achieving emotional management of the disease (126).

Values and preferences

Most patients with CD need to undergo surgery within 10 years after the initial diagnosis is made. Although it affects their quality of life, bowel resection is the surgical procedure most frequently used to treat CD.

A systematic review (127) (AMSTAR 7/11) assessed the impact of bowel resection on quality of life using the HRQoL scale and identified predictors of postoperative health-related quality of life (HRQOL) and patient satisfaction with this surgery. Nine studies conducted in a total of 1108 patients with CD who underwent bowel resection were included. Patients' median age range was between 29 and 41 years. Ileocolic resection was the most frequently performed bowel resection, and the most common indication for surgery were bowel obstruction, stenosing disease, perforation, and pharmacological therapy failure. Regarding HRQoL, it was found that all patients reported a postoperative improvement in their quality of life (at 30 days). Likewise, in general, the effect on HRQoL lasted from 2 to 5 years. Furthermore, the systematic review analyzed the predictors of HRQoL, finding that patients older than 49 years had less improvement in HRQoL at 9 months after surgery compared to younger patients. Also, a decreased improvement in HRQoL was observed in smoking patients compared to non-smokers. No differences were found in relation to gender and surgical technique. Regarding patient satisfaction, 80% of patients reported they were satisfied with the surgery and that they would undergo it again if necessary. Also, 92% expressed they preferred laparoscopic surgery (127).

Values and preferences

Perianal CD can affect quality of life involving physical, functional, and psychological aspects.

A cross-sectional study (128) determined the factors positively or negatively affecting quality of life in 69 patients with perianal Crohns' disease, as well as their impact on symptoms. Participants' mean age was 42.7 years and 62% were female. 80% of patients had undergone surgery prior to completing the questionnaire used in the study. Anal pain and discomfort were considered the most important symptoms by 41% of the patients, and 39% reported that managing sleeping difficulty, physical activity restriction, and feeling unclean were "very important to improve quality of life". Likewise, 85% of patients expressed they would accept using a stoma to improve symptoms.

In addition, anal pain was the most important symptom for women compared to men (53% vs. 19%). The presence of drainage was reported as the strongest predictor of incontinence, feeling unclean, and confidence in going outside. Finally, the study concluded that physical symptoms are the

most important symptoms for patients with perianal Crohn's disease and that drainage affects their quality of life (98).

Values and preferences

The management of CD poses challenges regarding the selection of the most appropriate therapy. Thus, patients' preferences may guide therapy selection.

A qualitative study (99) compared the preferences of 300 CD patients with those of 92 surgeons and 74 gastroenterologists in Australia. This study found that the preferences of patients differed from those of specialists. Patients were more interested in improving their quality of life given the risks and benefits of the therapies they were presented with. In this regard, 37% surgeons did not seek to perform ileocolic resection compared to 39% patients ($p<0.01$). Also, patients preferred using a permanent stoma instead of undergoing colorectal surgery (85% vs. 56%; $p>0.01$). However, when asked to choose between restorative proctocolectomy and permanent stoma, the same preference was observed in both, patients and surgeons (50%; $p>0.05$).

When the preferences of patients were compared with those of gastroenterologists, differences in surgical preferences were found. A higher proportion of patients preferred ileocolic resection. No differences were found regarding the selection of the pharmacological therapy ($p>0.05$) (129).

SUMMARY OF THE RECOMMENDATIONS

CLINICAL ASPECT: PROGNOSIS

Question N° 1. What are the predictors of relapse of Crohn's disease in patients older than 16 years?

Recommendation N°	Summary
Strong in favor	Measuring C-reactive protein (CRP) levels and using erythrocyte sedimentation rate (ESR) to predict relapse in patients with Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO
Weak against	Measuring ASCA (Anti-*Saccharomyces* cerevisiae antibodies) to predict relapse in patients with Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Measuring fecal calprotectin levels to predict relapse in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Fecal calprotectin must be measured every 3 to 6 months.
Good practice point	Taking the first stool sample of the day is suggested when measuring fecal calprotectin levels; also, a cutoff point of 250 µg/g is the most reliable value to differentiate mucosal healing from inflammation caused by Crohn's disease. A cutoff point of 100 µg/g is considered a predictor value of post-operative recurrence of Crohn's disease.
Good practice point	In patients with Crohn's disease on infliximab treatment, serum levels of the drug can be measured to predict clinical and endoscopic remission.
Weak in favor	Using magnetic resonance imaging as a radiology exam to predict deep remission in patients with perianal fistulizing Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Implementing mucosal healing as a therapeutic goal in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Using capsule endoscopy to determine small bowel mucosal healing is suggested.

Question N° 2. What are the safest and most effective non-biological interventions to induce remission of Crohn's disease in patients older than 16 years?

Recommendation N°	Summary
Strong against	Using probiotics to induce remission in patients with active Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Weak against	Using antibiotics to induce remission in patients with active Crohn's disease is not suggested. **Low quality of evidence** ⊕⊕OO
Weak against	Administering azathioprine or 6-mercaptopurine as monotherapy to induce remission in patients with active Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Strong in favor	Adding azathioprine as a combination therapy to induce remission in patients with active Crohn's who are going to undergo biological therapy with infliximab is recommended. **Very low quality of evidence** ⊕OOO
Weak against	Using sulfasalazine or mesalazine to induce remission in patients with active Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO

Strong against	Using methotrexate to induce remission in patients with active Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO
Weak in favor	Using ileal release budesonide to induce remission in patients with active Crohn's disease is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point	The recommended initial dosage of budesonide is 9 mg/d; at 2 months it should be decreased to 6 mg/d, and to 3 mg/d during the next 2 months, and then it must be suspended. Induction therapy must not exceed 6 months.
Good practice point	Adverse events associated with the use of systemic steroids must be monitored after 12 weeks of use.
Strong in favor	Using systemic steroids to induce remission in patients with active Crohn's disease is recommended. **Low quality of evidence** ⊕⊕OO
Good practice point	Systemic steroid therapy is the first-line treatment for moderate to severe ileocolonic and colonic Crohn's disease or in patients with extensive small bowel involvement by Crohn's disease.
Good practice point	The recommended starting dosage of prednisolone (oral route) is 40 mg/d.
Good practice point	Steroid response must be assessed after 2 to 4 weeks of treatment. In case of therapeutic failure, the need to modify the treatment must be defined.
Weak in favor	Using oral systemic steroids as the first choice to induce remission in patients with active Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Using ileal release budesonide as the first choice for the management of patients with low-risk ileal or ileocecal Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	If budesonide is not available, systemic corticosteroids such as prednisolone can be used.
Weak in favor	Using autologous stem cell transplant for the treatment of patients with Crohn's disease refractory to medical treatment is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Stem cell transplant must be carried out in health centers with experience in performing this procedure.

Question N° 3. What are the safest and most effective non-biological interventions to maintain remission of Crohn's disease in patients older than 16 years?

Recommendation N°	Summary
Strong against	Using mesalazine to maintain remission in patients with Crohn's disease is not recommended. **Low quality of evidence** ⊕⊕OO
Weak in favor	Using azathioprine or 6-mercaptopurine to maintain remission in patients with Crohn's disease in whom remission was induced through systemic steroids is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Azathioprine and 6-mercaptopurine recommended doses are 2.0 to 2.5 mg/kg/d and 0.75 to 1.5 mg/kg/d, respectively.
Good practice point	Thiopurine methyltransferase (TPMT) enzyme activity can be measured prior to starting the administration of thiopurines, since this allows the identification of patients who may develop severe immunosuppression if these drugs are used.
Weak against	Using budesonide to maintain remission in patients with Crohn's disease is not suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Using methotrexate to maintain remission in patients with Crohn's disease who achieved remission with steroids is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Patients with steroid-dependent Crohn's disease should be treated initially with thiopurines or methotrexate as steroid "sparing" drugs
Good practice point	Methotrexate should be considered instead of thiopurines in young male patients (<35 years) because of the risk of hepatosplenic T-cell lymphoma, as well as in individuals with thiopurines intolerance or who experience adverse effects when using them.
Good practice point	The recommended dose of methotrexate for maintenance of remission is 25 mg/week intramuscularly.
Strong against	Using elemental nutrition (also elemental diet, a type of enteral nutrition) to maintain remission in patients with Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO

Strong against	Using probiotics to maintain remission in patients with Crohn's disease is not recommended. **Low quality of evidence ⊕⊕OO**
Strong against	Using systemic steroids to maintain remission in patients with Crohn's disease is not recommended. **Very low quality of evidence ⊕OOO**

Question N°4. What is the safety and efficacy of using biological drugs to treat moderate to severe Crohn's disease in patients older than 16 years?

Recommendation N°	Summary
Strong in favor	Using infliximab, adalimumab, certolizumab, vedolizumab, or ustekinumab to induce and maintain remission in patients with moderate to severe luminal Crohn's disease is recommended. **Very low quality of evidence ⊕OOO**
Good practice point	anti-TNF agents or TNF inhibitors (infliximab, adalimumab, or certolizumab pegol) should be considered as first choice medications over other biological drugs for the initial management of moderate to severe Crohn's disease.
Good practice point	Patients older than 65 years undergoing anti-TNF therapy have a higher risk of infection (90)
Good practice point	The use of combination therapy with TNF inhibitors+thiopurines is not recommended in males younger than 35 years due to the risk of hepatosplenic T-cell lymphoma, as well as in patients with a history of malignancy. In these cases, anti-TNF monotherapy must be used.
Good practice point	In patients with contraindications to anti-TNF agents (severe heart failure, demyelinating disease, among others), the use of vedolizumab or ustekinumab should be considered.
Good practice point	Patients with Crohn's disease must be assessed 12 to 14 weeks after the induction of remission with biological therapy was initiated, so that treatment response and the need for treatment modification are determined.
Weak in favor	Using anti-TNF drugs (infliximab or adalimumab) to treat patients with perianal fistulizing Crohn's disease is suggested. **Low quality of evidence ⊕⊕OO**
Good practice point	Infliximab efficacy could be increased when co-administered with thiopurines.
Weak in favor	The use of ustekinumab to induce remission in patients with moderate to severe Crohn's disease and who have experienced treatment failure after undergoing anti-TNF therapy is suggested. **Very low quality of evidence ⊕OOO**
Good practice point	The recommended ustekinumab initial induction dose (intravenous) is 260 mg (up to 55 kg), 390 mg (between 56 and 85 kg) and 520 mg (>85 kg). In the case of treatment for maintenance of remission, subcutaneous administration of 90 mg every 8 weeks is recommended.
Weak in favor	Clinical monitoring of opportunistic infections in patients with Crohn's disease undergoing biological therapy is suggested. **Very low quality of evidence ⊕OOO**
Good practice point	anti-TNF therapy should be contraindicated in patients with active infection.
Good practice point	Prior to initiating biological therapy, the presence of respiratory symptoms should be determined, and a chest X-ray and a Mantoux tuberculin skin should be performed, given the risk of reactivation of latent tuberculosis.
Good practice point	Prior to starting biological therapy, hepatitis B and C serologic tests and HIV testing should be ordered.
Good practice point	Patients with Crohn's disease must get vaccinated against influenza, pneumococcus, hepatitis B, varicella (at least 3 weeks prior to starting the administration of the immunosuppressant) and human papillomavirus (prior to starting the administration of immunosuppressants, steroids, thiopurines and biological drugs).
Weak in favor	Using a second TNF inhibitor is suggested when there is no primary response or a response following the secondary loss of response to a first anti-TNF agent. **Very low quality of evidence ⊕OOO**
Good practice point	Treatment modifications should be individual and based on the anti-TNF drug serum levels and the results of the antibodies tests against the anti-TNF drug.
Good practice point	Patients with adequate TNF inhibitor serum levels and (+) antibodies must be treated with another type of anti-TNF agent or another type of biological drug.

Good practice point	In individuals with sub-therapeutic levels of the TNF inhibitor and (-) antibodies, intervals between doses should be shortened or the anti-TNF agent dose should be increased.
Weak in favor	Using infliximab biosimilars to induce and maintain remission in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point	Patients undergoing treatment with innovator infliximab can continue treatment with the biosimilar if they have been responding to the previous one.
Good practice point	Molecules must not be switched in case of initial treatment failure with either molecule.
Good practice point	In the event of a non-medical switch between an innovator biological drug and a biosimilar, the treating physician must be informed for pharmacovigilance purposes and the patient's consent must be obtained.
Strong in favor	Using infliximab, infliximab plus azathioprine, adalimumab, or vedolizumab to induce remission in patients with Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO
Strong in favor	Using azathioprine, methotrexate, infliximab, infliximab plus azathioprine, adalimumab or vedolizumab to maintain remission in patients with Crohn's disease is recommended. **Very low quality of evidence** ⊕OOO

Question N° 5. What are the safest and most effective interventions to treat perianal Crohn's disease in patients older than 16 years?

Recommendation	N°	Summary
Weak in favor		Using ciprofloxacin as adjunctive therapy in Crohn's disease patients with perianal fistulas treated with surgery or immunosuppressant drugs is suggested. **Low quality of evidence** ⊕⊕OO
Good practice point		Using antibiotics, together with surgery and biological therapy, is recommended to attempt perianal fistulas closure.
Good practice point		Pelvic MRI or rectal endosonography should be performed prior to drainage.
Good practice point		Symptomatic patients with simple perianal fistulas must be treated with fistulotomy or seton placement and antibiotic management (ciprofloxacin 500 mg, every 12 hours, and/or metronidazole 500 mg, every 8 hours, for 6-8 weeks).
Good practice point		Perianal fistulas must be classified into: • simple: superficial or low intersphincteric or low transsphincteric fistula with a single external orifice; • complex: high intersphincteric, high transsphincteric or suprasphincteric, rectovaginal fistulas with perianal abscess, inflammatory activity in the rectal mucosa or anorectal stenosis.
Good practice point		Pelvic MRI or rectal endosonography should be performed in suspected perianal Crohn's disease cases for diagnosis and follow-up purposes.
Weak in favor		Using infliximab for maintenance of remission of complex perianal fistulas in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		Infliximab administration must always be initiated in combination therapy with thiopurines, unless the latter is contraindicated.
Good practice point		Administration of ciprofloxacin 500 mg every 12 hours must be added during 12 weeks to anti-TNF therapy in order to improve short-term outcomes in patients with complex perianal fistulas.
Strong in favor		The use of combination therapy with TNF inhibitors plus seton placement in the treatment of complex perianal fistulizing Crohn's disease is recommended to increase complete fistula closure. **Very low quality of evidence** ⊕OOO
Good practice point		In complex fistulas cases, surgical drainage of abscesses must be performed before initiating medical treatment with anti-TNF drugs.
Good practice point		Once the infection is controlled, the drainage seton must be removed to allow closure of the perianal fistula.
Good practice point		Patients with perianal Crohn's disease require multidisciplinary management with the coloproctology service.
Weak in favor		Use of tacrolimus is suggested to treat fistulizing Crohn's disease in patients who are refractory to biologic therapy and antibiotics. **Very low quality of evidence** ⊕OOO
Strong against		Using fibrin glues in the treatment of patients with perianal Crohn's disease is not recommended. **Very low quality of evidence** ⊕OOO

Weak in favor	Transrectal or transvaginal advancement flap is suggested for achieving rectovaginal fistulas closure in patients with Crohn's disease. **Very low quality of evidence** ⊕OOO
Good practice point	Transrectal advancement flap approach must be chosen as the first alternative for achieving rectovaginal fistulas closure.
Good practice point	There must be no endoscopic activity in the rectum for at least two years before surgical closure of the fistula is considered.
Weak in favor	Using fecal diversion as salvage therapy in patients with perianal Crohn's disease who have experienced failure to conventional medical and surgical management is suggested. **Very low quality of evidence** ⊕OOO
Weak in favor	Local stem cell therapy is suggested for the management of patients with perianal Crohn's disease refractory to medical treatment. **Very low quality of evidence** ⊕OOO

Question N° 6. What are the safest and most effective surgical and endoscopic interventions to treat Crohn's disease in patients older than 16 years?

Recommendation	N°	Summary
Weak in favor		Surgical procedure should not be contraindicated in patients with Crohn's disease undergoing biological therapy. **Very low quality of evidence** ⊕OOO
Weak in favor		Continuing the administration of azathioprine prior to performing the surgical procedure in patients with Crohn's disease is suggested. **Very low quality of evidence** ⊕OOO
Good practice point		If the procedure can be deferred, surgery should be performed prior to starting the next dose of biological therapy.
Good practice point		The possibility of postoperative infections should be monitored.
Weak in favor		Surgical treatment is suggested in patients with intra-abdominal abscesses associated with Crohn's disease only in case they fail to respond to initial medical and/or interventional radiology treatment. **Very low quality of evidence** ⊕OOO
Good practice point		Abscesses smaller than 3 cm must be treated only with antibiotics. Patients with abscesses larger than 3 cm additionally require image-guided percutaneous drainage.
Good practice point		In case of no response to medical treatment or that abscesses cannot be drained (partitioned or difficult to access), surgical treatment must be implemented.
Strong in favor		Pneumatic balloon dilation is recommended in patients with strictures associated with Crohn's disease. **Very low quality of evidence** ⊕OOO
Good practice point		Pneumatic dilation should be performed in the case of: • stricture length less than 4 cm; • presence of strictures in the terminal ileum or ileocolic anastomosis; • single strictures.
Good practice point		The presence of fistulas or abscesses in the area of the stricture implies a contraindication for pneumatic dilation.
Good practice point		Diagnostic imaging studies should be used to try determining whether the component of the stricture is fibrotic or inflammatory.
Strong in favor		Strictureplasty is recommended in patients with small bowel stenosing Crohn's disease. **Very low quality of evidence** ⊕OOO
Good practice point		Strictureplasty is highly recommended in patients with multiple strictures (smaller than 10 cm) to avoid extensive small bowel resections and reduce the risk of short bowel syndrome. It should be performed by specialists experienced in treating this condition.
Weak in favor		Performing laparoscopy or open surgery is suggested for surgical treatment of patients with Crohn's disease. The selection of the surgical technique shall be made according to local experience. **Very low quality of evidence** ⊕OOO
Good practice point		Whenever feasible, minimally invasive surgery should be preferred due to the lower risk of adhesions and better cosmetic outcomes.
Good practice point		Minimally invasive surgery should be performed in experienced centers with adequate patient volume.

Strong in favor	Performing side-to-side anastomosis in patients with Crohn's disease undergoing surgical resection is recommended. **Very low quality of evidence ⊕OOO**
Weak in favor	Segmental resection is suggested in patients with colonic Crohn's disease (<30 cm). **Very low quality of evidence ⊕OOO**

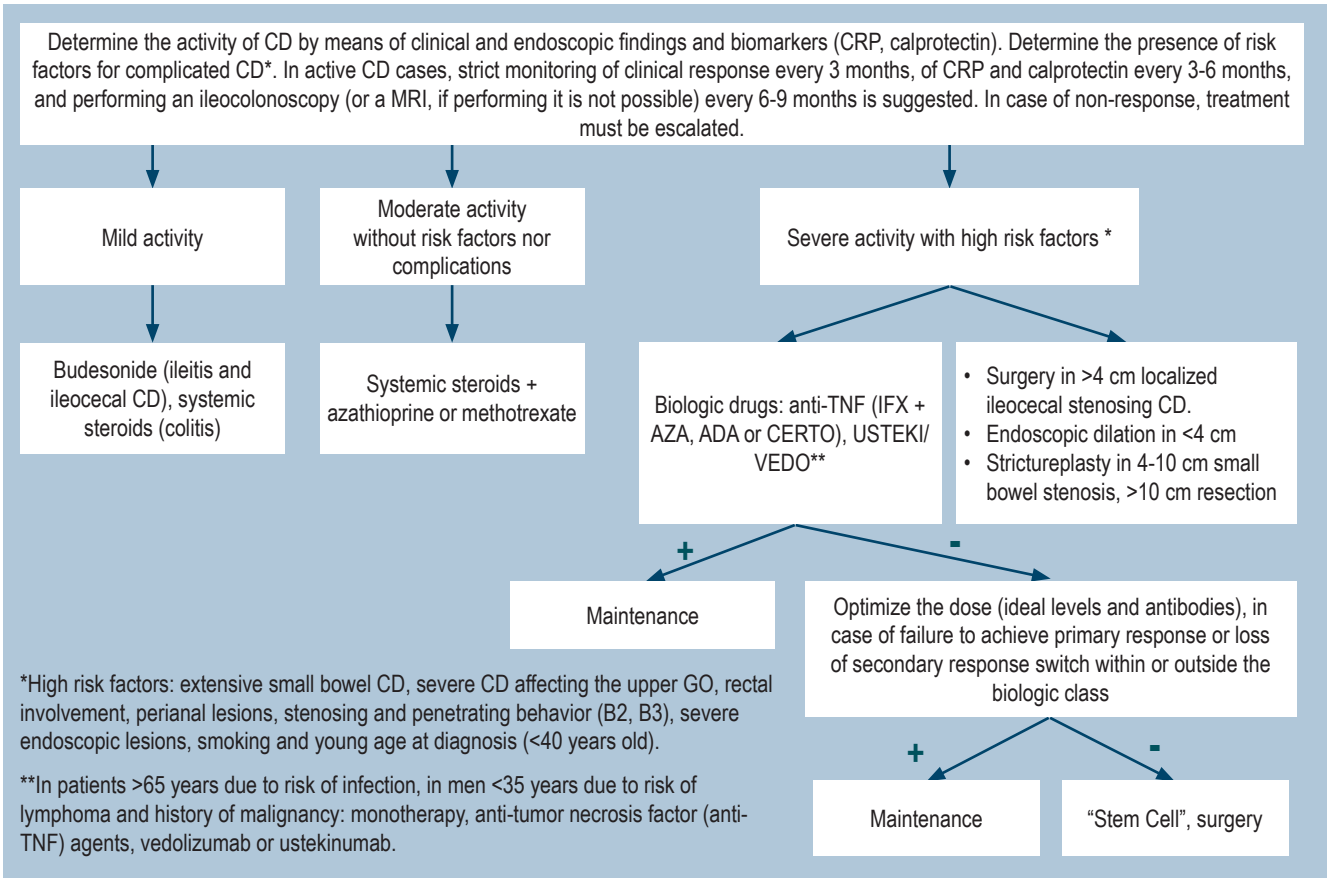
Question No. 7. What are the safest and most effective interventions to prevent postoperative recurrence of Crohn's disease in patients older than 16 years?

Recommendation	N°	Summary
Strong against		Using probiotics to prevent postoperative recurrence of Crohn's disease is not recommended. **Very low quality of evidence ⊕OOO**
Good practice point		The presence of risk factors for postoperative relapse must be identified in all patients with Crohn's disease undergoing surgical resection, so that preventive pharmacological interventions are implemented. • high-risk factors: age <30 years, smoking, >2 surgeries due to penetrating CD (B3); • low-risk factors: age >50 years, non-smokers, first surgery, short stenosis <10-20 cm, CD duration >10 years.
Good practice point		An ileocolonoscopy must be performed 6 to 12 months after surgery in order to identify endoscopic relapse.
Weak in favor		Using antibiotics to prevent postoperative recurrence of Crohn's disease is suggested. **Low quality of evidence ⊕⊕OO**
Good practice point		Metronidazole is the antibiotic to be used, at a dose of 15 to 20 mg/kg for 3 months. When using this medication, tolerance and the occurrence of adverse events, especially peripheral neuropathy, should be closely monitored.
Good practice point		In low-risk patients, a 3-month metronidazole treatment is recommended, or, in case of drug intolerance, close monitoring without antibiotic use.
Good practice point		Any patient with Crohn's disease who has undergone surgery as a treatment option must avoid smoking.
Weak in favor		The use of azathioprine or 6-mercaptopurine to prevent postoperative recurrence of Crohn's disease is suggested. **Very low quality of evidence ⊕OOO**
Good practice point		In patients at high risk of relapse, thiopurines can be used concomitantly with anti-TNF drugs, with or without metronidazole, for the first 3 months. Drug tolerance should be monitored.
Weak in favor		Using 5-ASA to prevent postoperative clinical recurrence of Crohn's disease is suggested. **Low quality of evidence ⊕⊕OO**
Good practice point		Use of mesalazine should be considered only in patients with a low risk of postoperative relapse or in those in which thiopurines or TNF inhibitors are absolutely or relatively contraindicated.
Weak against		Using budesonide to prevent postoperative recurrence of Crohn's disease is not suggested. **Low quality of evidence ⊕⊕OO**
Weak in favor		Using anti-TNF agents as first-line therapy to prevent endoscopic recurrence of Crohn's disease after surgery is suggested. **Low quality of evidence ⊕⊕OO**
Good practice point		Starting a 6-month treatment with anti-FNT agents ± thiopurines, if there are no contraindications, whether associated or not to metronidazole therapy (3 months), in patients at a high risk of recurrence is recommended.
Strong in favor		Using anti-TNF drugs to treat postoperative relapses of Crohn's disease is recommended. **Very low quality of evidence ⊕OOO**
Good practice point		Initial use of thiopurines ± metronidazole (the latter for 3 months) is recommended in patients with low-risk postoperative recurrence; in case they fail to respond to the treatment, it must be managed with anti-TNF therapy.
Strong in favor		Providing Crohn's disease patients with clear information about the management of the disease and treatment options, as well as their risks and benefits, is recommended. **Very low quality of evidence ⊕OOO**
Strong in favor		Assessing the presence of signs of depression or worsened quality of life and, if necessary, referring the patient to support groups and specialized help groups is recommended. **Very low quality of evidence ⊕OOO**

ALGORITHMS

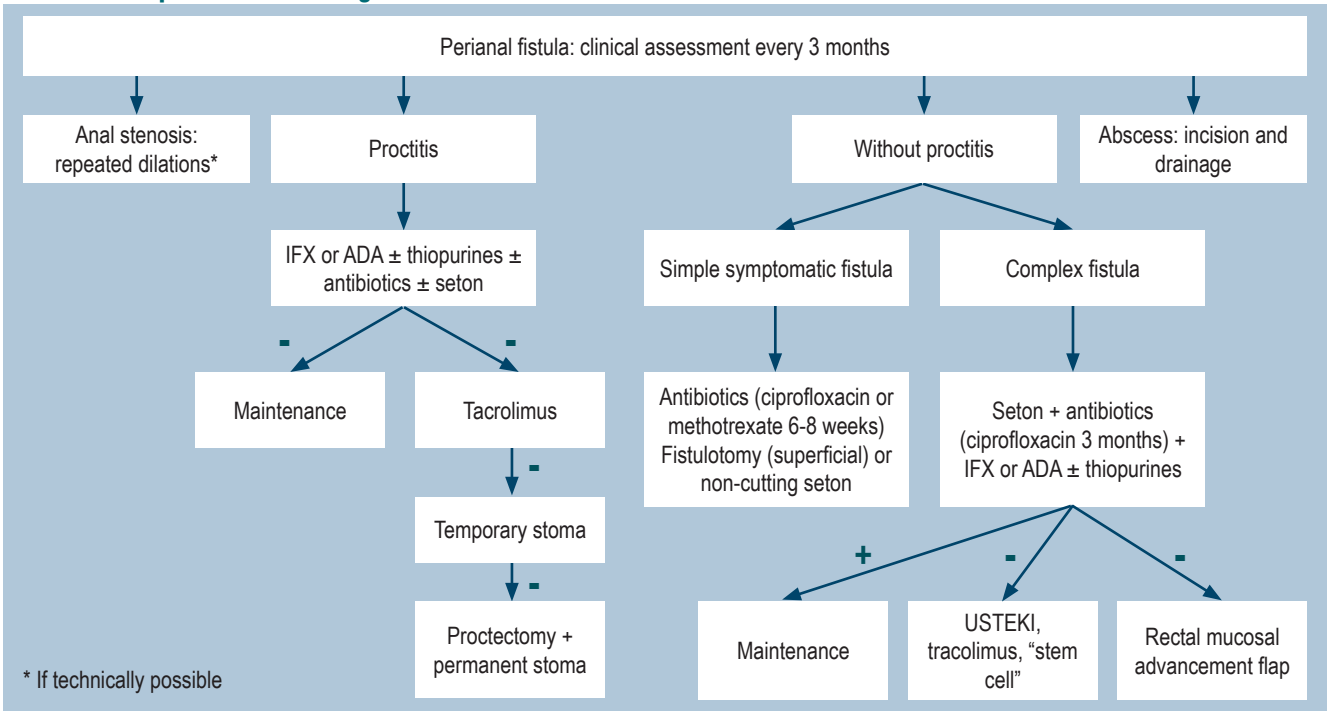
ALGORITHM N° 1

Treatment of luminal Crohn's disease



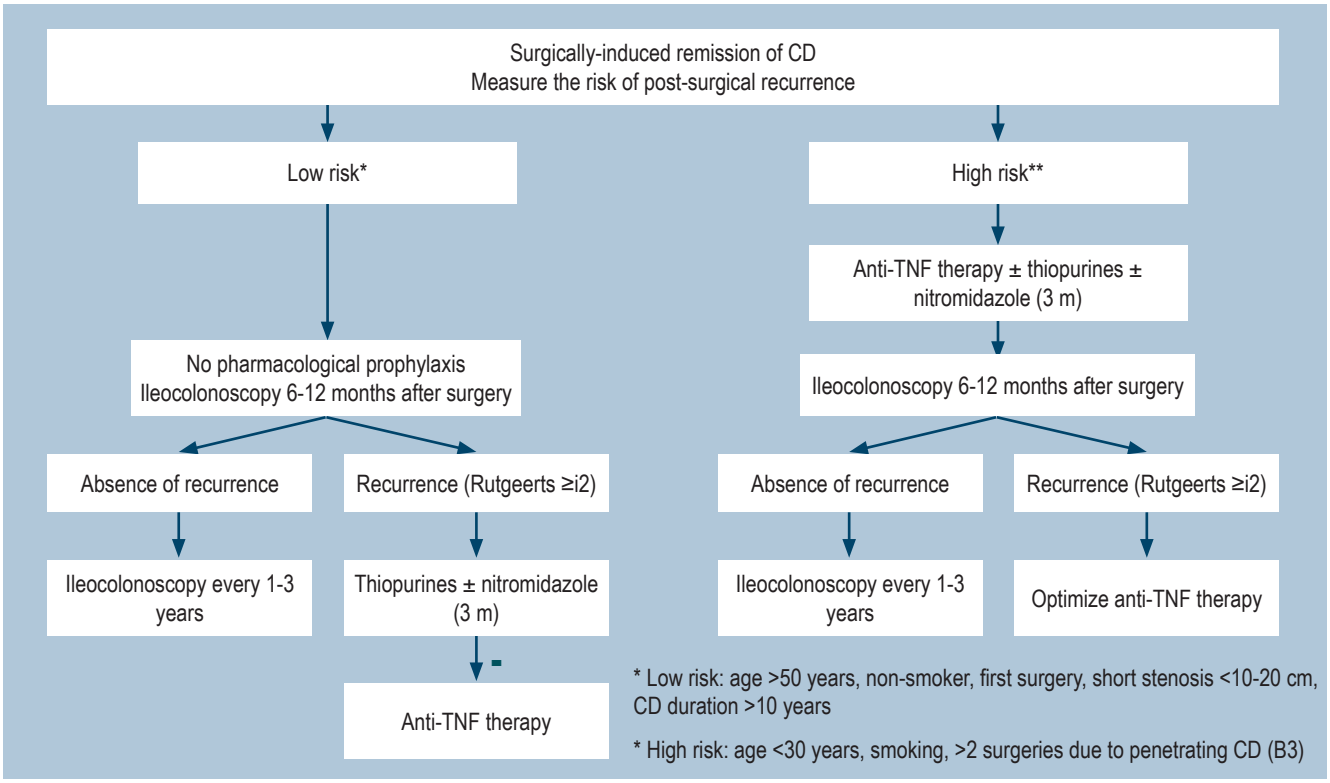
ALGORITHM N° 2

Treatment of perianal fistulizing CD



ALGORITHM N° 3

Treatment of post-surgical recurrence of CD



IMPLEMENTATION MODULE

Using the Manual for the implementation of clinical practice guidelines in the Colombian health insurance framework (MSPS, 2014) is recommended to support the implementation of this CPG.

The considerations that the different actors of the Colombian health system must take into account when implementing this CPG are presented below.

ACTORS RESPONSIBLE FOR THE IMPLEMENTATION OF THE RECOMMENDATIONS DESCRIBED IN THE CGP

It is important to identify those responsible for supporting or executing the implementation activities of the CPG at the national level or in the institutions in charge of the provision of health care (ISPSS). The main actors in the process of implementing the CPG are:

- Governmental agencies:
  - Colombian Ministry of Health and Social Protection.
  - Cuenta de Alto Costo Fondo Colombiano de Enfermedades de Alto Costo (Fund for Highly Expensive diseases)
  - Territorial bodies
  - National Superintendence of Health
- Institutions:
  - Health Promotion Entities
  - Scientific associations
  - Colombian Association of Gastroenterology
  - Institutions responsible for the provision of health care
  - Patient associations and civil society representatives.
- Users:
  - Gastroenterologists
  - Surgeons
  - Coloproctologists
  - Patients

KEY RECOMMENDATIONS FOR THE IMPLEMENTATION OF THE CPG

In order to identify the recommendations of the CPG with the greatest impact and in which implementation efforts can be prioritized, the GDG selected the following recommendations:

- Measuring C-reactive protein (CRP) levels and using erythrocyte sedimentation rate (ESR) to predict of Crohn's disease is recommended.
- Implementing mucosal healing as a therapeutic goal in patients with Crohn's disease is suggested.
- Clinical monitoring of opportunistic infections in patients with Crohn's disease undergoing biological therapy is suggested.
- Using systemic steroids for maintenance of remission in patients with Crohn's disease is not recommended.
- Using infliximab biosimilars to induce and maintain remission in patients with Crohn's disease is suggested.
- Using azathioprine, methotrexate, infliximab, infliximab plus azathioprine, adalimumab or vedolizumab to maintain remission in patients with Crohn's disease is recommended.
- The use of combination therapy with an anti-TNF drug plus seton placement in the treatment of complex perianal fistulizing Crohn's disease is recommended to increase complete fistula closure.
- Assessing the presence of signs of depression or worsened quality of life and, if necessary, referring the patient to support groups and specialized help groups is recommended.

IDENTIFICATION OF BARRIERS AND FACILITATORS

In order to facilitate the use of the CPG in the Colombian context, barriers, facilitators and implementation strategies must be identified.

Barriers	Facilitators/strategies
Lack of knowledge about the recommendations made in the CPG	• Carrying out training sessions in health care institutions, scientific and patient associations, as well as in governmental agencies. These sessions can be face-to-face or virtual in order to facilitate the training of professionals in the management of Crohn's disease. • Including reminders of the key recommendations to be implemented in each institution and in the medical records of patients diagnosed with Crohn's disease. • Including the CPG in the curricula offered by Schools of Medicine.
Limited access to the CPG	• Developing different ways of disseminating the recommendations made in the CPG, including the publication of scientific papers, the distribution of management algorithms, and the use of mobile applications. • Making the CPG available on the website of the Colombian Association of Gastroenterology. • Distributing the CPG to population groups of interest and potential users in congresses and lectures.

Perceiving that there are no support policies	• To implement policies on the provision of health care to patients with orphan diseases, such as Decree 1954 of 2012 (about reporting these diseases to information systems), Law 1392 of 2010 (about ensuring the provision of care to patients with orphan diseases), Notice 011 of 2016 issued by the Superintendence of Health (whereby instructions for the provision of treatment to patients with rare diseases by Health Benefits Plans Management Companies (EAPBs), Institutions responsible for the provision of healthcare services (IPSs), and territorial agencies, are established). • To propose policies that allow implementing the CPG at the institutional level.
Low presence of the CPG in electronic systems used to support decision making	• The CPG can be included in mobile applications, institutional electronic bulletins or in specialized websites to support quick search processes.
Absence of actors responsible for the implementation of the CPG in the Institutions responsible for the provision of healthcare services (IPSs)	• This strategy seeks to ensure that in each IPS there is a person responsible for verifying adherence to the recommendations made in the guidelines, including the CPG on the management of Crohn's disease.
Absence of administrative support in the implementation of the CPG	• The Management of each IPS should support the implementation activities of the CPG so that they can be properly carried out.
Poor adherence to the recommendations made in the CPG	• To use strategies to increase awareness of the CPG among gastroenterologists, proctologists, and patients. • To design multidisciplinary management strategies. • To improve the doctor-patient relationship. • To consider low patient adherence to the CPG according to strong predictors such as concern for adverse effects and perception of treatment, to include them in the management of the disease. • To use management algorithms.
High costs	• To include all therapeutic options in the health benefits plan

INDICATORS

The indicators of the process and outcome of the implementation of the CPG are presented below. Some indicators are part of the international consensus for the evaluation of the quality of care in Crohn's disease.

Item	Characteristic
Indicator N° 1	Proportion of patients screened for tuberculosis prior to starting anti-TNF therapy
Type of indicator	Process, international healthcare quality indicator
Calculation method	Number of patients screened for tuberculosis prior to starting anti-TNF therapy/number of patients treated with anti-TNF agents * 100
Periodicity (frequency of measurement)	Semiannual
Responsible (for monitoring)	IPSs (Spanish for Institutions responsible for the provision of healthcare services), governmental bodies
Goal	100%

Item	Characteristic
Indicator N° 2	Proportion of patients with TPMT testing prior to starting thiopurine therapy
Type of indicator	Process, international healthcare quality indicator
Calculation method	Number of patients with TPMT testing prior to starting thiopurine therapy/number of patients treated with thiopurines * 100
Periodicity (frequency of measurement)	Semiannual
Responsible (for monitoring)	IPSs (Spanish for Institutions responsible for the provision of healthcare services), governmental bodies
Goal	100%

Item	Characteristic
Indicator N° 3	Proportion of patients with Crohn's disease treated with active azathioprine and who are going to undergo biological therapy with infliximab to induce remission
Type of indicator	Process
Calculation method	Number of patients with active Crohn's disease treated with infliximab to induce remission and who were previously administered azathioprine/number of patients with active Crohn's disease treated with infliximab to induce remission * 100
Periodicity (frequency of measurement)	Semiannual
Responsible (for monitoring)	IPSs (Spanish for Institutions responsible for the provision of healthcare services), governmental bodies
Goal	100%

Item	Characteristic
Indicator N° 4	Proportion of patients in remission without steroid therapy
Type of indicator	Outcome, international healthcare quality indicator
Calculation method	Number of patients in remission without steroid therapy/number of patients in remission * 100
Periodicity (frequency of measurement)	Semiannual
Responsible (for monitoring)	IPSs (Spanish for Institutions responsible for the provision of healthcare services), governmental bodies
Goal	100%

Item	Characteristic
Indicator N° 5	Annual proportion of patients who were hospitalized due to Crohn's disease
Type of indicator	Outcome
Calculation method	Number of patients who were hospitalized due to Crohn's disease per year/number of patients with Crohn's disease per year * 100
Periodicity (frequency of measurement)	Annual
Responsible (for monitoring)	IPSs (Spanish for Institutions responsible for the provision of healthcare services), governmental bodies

ANNEXES

ANNEX N° 1

Conflicts of interest analysis

Member of the GDG	¿Does the member have any personal financial conflict of interest?	¿Does the member have any non-personal financial conflict of interest?	¿Does the member have any personal non-financial conflict of interest?	¿Does the member have any first-degree relative with a financial conflict of interest?	Analysis and Decision
Fabián Juliao	Yes	No	Yes	No	• The member has a conflict of interest since he is a speaker for pharmaceutical companies in topics that involve the use of biological drugs for treating Crohn's disease. • The member was partially excluded from the questions about biological drugs.
William Otero	No	No	No	No	• Full participation
Luis Pineda	No	No	No	No	• The member has worked in the pharmaceutical industry, but he has not been involved in fields related to Crohn's disease. • Full participation
María T. Galeano	Yes	No	Yes	No	• The member has a conflict of interest since he is a speaker for pharmaceutical companies in topics that involve the use of biological drugs for treating Crohn's disease. • The member was partially excluded from the questions about biological drugs.
Carlos Fernando Grillo	None	None	None	None	• Full participation
Ana Marcela Torres	None	None	None	None	• Full participation
María Teresa Vallejo	None	None	None	None	• Full participation

ANNEX N° 2

Questions developed according to the PICO Framework

1. What are the predictors of relapse of Crohn's disease in patients older than 16 years?

Population	Diagnostic test/ comparator	Outcomes
• Patients with Crohn's disease in remission and over 16 years of age	• CRP • Magnetic Resonance Index of Activity (MaRIA) • Calprotectin • Colonoscopy • Lactoferrin • Ultrasound • Capsule endoscopy • anti-*Saccharomyces* cerevisiae antibodies	• Disease activity • Quality of life • Endoscopic relapse • Fistula recurrence • Hospitalization • Surgery

2. What are the safest and most effective non-biological interventions to induce remission of Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• People older than 16 years diagnosed with ileocecal Crohn's disease • People older than 16 years diagnosed with colonic Crohn's disease • People older than 16 years diagnosed with isolated small bowel Crohn's disease • People older than 16 years diagnosed with Crohn's disease affecting the upper GI tract	• Intravenous steroids • Oral steroids (prednisolone, prednisone, ileal release budesonide, budesonide MMX) • 5-aminosalicylates • Azathioprine • 6-mercaptopurine • Methotrexate • Probiotics • Antibiotics (ciprofloxacin, metronidazole, rifaximin)	• Absence of clinical symptoms • Remission rate • Disease activity • Endoscopic improvement (mucosal healing) • Surgery rate • Hospitalization rate • Withdrawal or discontinuation of treatment due to adverse events (adherence to treatment) • Quality of life • Adverse events

3. What are the safest and most effective non-biological interventions to maintain remission of Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• People older than 16 years diagnosed with ileocecal Crohn's disease • People older than 16 years diagnosed with colonic Crohn's disease • People older than 16 years diagnosed with isolated small bowel Crohn's disease • People older than 16 years diagnosed with Crohn's disease affecting the upper GI tract	• Oral steroids (prednisolone, prednisone, ileal release budesonide, budesonide MMX) • 5-aminosalicylates • Azathioprine • 6-mercaptopurine • Methotrexate • Probiotics • Antibiotics (ciprofloxacin, metronidazole, rifaximin)	• Absence of clinical symptoms • Remission rate • Disease activity • Endoscopic improvement (mucosal healing) • Surgery rate • Hospitalization rate • Withdrawal or discontinuation of treatment due to adverse events (adherence to treatment) • Quality of life • Adverse events • Survival

4. What is the safety and efficacy of using biological drugs to treat moderate to severe Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• People older than 16 years diagnosed with ileocecal Crohn's disease • People older than 16 years diagnosed with colonic Crohn's disease • People older than 16 years diagnosed with isolated small bowel Crohn's disease • People older than 16 years diagnosed with Crohn's disease affecting the upper GI tract	• Monotherapy: • Infliximab • Adalimumab • Vedolizumab • Certolizumab pegol • Ustekinumab • Biological therapy alone or combined with methotrexate or azathioprine • Biosimilars (infliximab, adalimumab)	• Absence of clinical symptoms • Remission rate • Disease activity • Endoscopic improvement (mucosal healing) • Surgery rate • Hospitalization rate • Withdrawal or discontinuation of treatment due to adverse events (adherence to treatment) • Quality of life • Adverse events

5. What are the safest and most effective interventions to treat perianal Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• People older than 16 years diagnosed with perianal Crohn's disease	• Surgical treatment • Metronidazole • Ciprofloxacin • Intravenous steroids • Oral steroids (prednisolone, prednisone, budesonide) • 5-aminosalicylates • Azathioprine • 6-mercaptopurine • Methotrexate • Probiotics • Biological therapy alone or in combination	• Disease activity • Quality of life • Endoscopic relapse • Fistula recurrence • Hospitalization • Surgery • Adverse events

6. What are the safest and most effective surgical and endoscopic interventions to treat Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• People older than 16 years diagnosed with ileocecal Crohn's disease • People older than 16 years diagnosed with colonic Crohn's disease • People older than 16 years diagnosed with isolated small bowel Crohn's disease • People older than 16 years diagnosed with Crohn's disease affecting the upper GI tract • People older than 16 years diagnosed with fistulizing Crohn's disease	• Bowel resection • Percutaneous drainage • Strictureplasty • Intestinal anastomosis • Operative laparoscopy • Endoscopic dilation • Fistulotomy	• Disease activity • Quality of life • Endoscopic relapse • Fistula recurrence • Hospitalization • Reoperation • Mortality • Perioperative complications

7. What are the safest and most effective interventions to prevent postoperative recurrence of Crohn's disease in patients older than 16 years?

Population	Intervention / comparator	Outcomes
• Patients older than 16 years diagnosed with Crohn's disease and who required surgical treatment	• Oral steroids (prednisolone, prednisone, ileal release budesonide, budesonide MMX) • 5-aminosalicylates • Azathioprine • 6-mercaptopurine • Methotrexate • Metronidazole • Nutritional management • Probiotics • Antibiotics (ciprofloxacin, metronidazole, rifaximin)	• Absence of clinical symptoms • Remission rate • Disease activity • Endoscopic improvement (mucosal healing) • Surgery rate • Hospitalization rate • Withdrawal or discontinuation of treatment due to adverse events (adherence to treatment) • Quality of life • Adverse events

ANNEX N° 3

Search log

Prognosis

Electronic Search Report #1		
Type of search	New	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	16/08/2017	
Update date (AutoAlert)	Indefinite	
Search date range	2012-2017	
Language restrictions	None	
Other limits	None	
Search strategy (results)	1. exp C-Reactive Protein/ (40622) 2. (c adj5 reacti$ adj5 protein).tw. (57641) 3. (creactive adj5 protein).tw. (68) 4. crp.tw. (39222) 5. exp Magnetic Resonance Imaging/ (388612) 6. (magnetic adj5 resonance adj5 tomography).tw. (28751) 7. (magnetization adj5 transfer adj5 imaging).tw. (853) 8. (imaging adj5 magnetic adj5 resonance).tw. (199952) 9. (imaging$ adj5 chemical adj5 shift).tw. (1176) 10. (tomography adj5 mr$).tw. (8914) 11. (tomography adj5 proton adj5 spin).tw. (42) 12. (spin ajd5 echo adj5 imaging).tw. (0) 13. zeugmatography.tw. (23) 14. nmr.tw. (150492) 15. mri.tw. (197942) 16. (mr adj5 imaging).tw. (43265) 17. (maria adj5 score).tw. (13) 18. exp Leukocyte L1 Antigen Complex/ (1830) 19. calgranulin.tw. (278) 20. calprotectin.tw. (1989) 21. (calcium-binding adj5 protein).tw. (5779) 22. (L1 adj5 antigen).tw. (264) 23. (L1 adj5 protein).tw. (2034) 24. ((migratory adj5 inhibitory) and (factor-related adj5 protein)).tw. (0) 25. exp Lactoferrin/ (5666) 26. lactoferrin$.tw. (7191) 27. lactotransferrin.tw. (252)	28. exp Ultrasonography/ (400680) 29. exp Ultrasonography, Doppler/ (66581) 30. echogra$.tw. (10041) 31. ultraso$.tw. (323134) 32. sonography.tw. (30920) 33. echotomography.tw. (623) 34. doptone.tw. (12) 35. echoscopy.tw. (51) 36. echosound.tw. (1) 37. sonogram.tw. (1492) 38. exp Capsule Endoscopy/ (2452) 39. (capsule adj5 endoscop$).tw. (3577) 40. (capsule adj5 enteroscopy).tw. (405) 41. ASCA$.tw. (11244) 42. or/1-41 (1271843) 43. exp Crohn Disease/ (35815) 44. crohn$.tw. (40956) 45. (regional$ adj5 enter$).tw. (1167) 46. (regional adj5 ileiti$).tw. (295) 47. (regional adj5 colitis).tw. (182) 48. (enteritis adj5 granulomatous).tw. (196) 49. (colitis adj5 granulomatous).tw. (442) 50. ileocolitis.tw. (415) 51. (terminal adj5 ileitis).tw. (416) 52. (cleron adj5 disease).tw. (0) 53. or/43-52 (50141) 54. 42 and 53 (4966) 55. limit 54 to (yr="2012 - 2017" and "reviews (best balance of sensitivity and specificity)") (407)
# of references that were identified	407	
# of references after removing duplicates	352 (see EndNote file)	

Electronic Search Report #2	
Type of search	New
Data bases	• EMBASE
Platform	EMBASE.com
Search date	16/08/2017
Update date (AutoAlert)	Indefinite
Search date range	2012-2017
Language restrictions	None
Other limits	None
Search strategy (results)	1. 'c reactive protein'/exp (130934) 2. (c NEAR/5 reacti* NEAR/5 protein):ab,ti (76716) 3. (creactive NEAR/5 protein):ab,ti (934) 4. crp:ab,ti (70211) 5. 'nuclear magnetic resonance imaging'/exp (743843) 6. magnetic:ab,ti AND ((resonance NEAR/5 tomography):ab,ti) (31138) 7. magnetization:ab,ti AND ((transfer NEAR/5 imaging):ab,ti) (1069) 8. imaging:ab,ti AND ((magnetic NEAR/5 resonance):ab) (232834) 9. imaging:ab,ti AND ((chemical NEAR/5 shift):ab,ti) (2339) 10. (tomography NEAR/5 mr*):ab,ti (366762) 11. tomography:ab,ti AND ((proton NEAR/5 spin):ab,ti) (38) 12. spin:ab,ti AND ((echo NEAR/5 imaging):ab,ti) (3521) 13. zeugmatography:ab,ti (26) 14. nmr:ab,ti (165303) 15. mri:ab,ti (310434) 16. (mr NEAR/5 imaging):ab,ti (53137) 17. (maria NEAR/5 score):ab,ti (38) 18. 'calgranulin'/exp (5216) 19. calgranulin:ab,ti (410) 20. calprotectin:ab,ti (3775) 21. ('calcium binding' NEAR/5 protein):ab,ti (6239) 22. (l1 NEAR/5 antigen):ab,ti (308) 23. (l1 NEAR/5 protein):ab,ti (2467) 24. ((migratory NEAR/5 inhibitory):ab,ti) AND (('factor related' NEAR/5 protein):ab,ti) (1) 25. 'lactoferrin'/exp (9094) 26. lactoferrin*:ab,ti (7938) 27. lactotransferrin:ab,ti (291) 28. 'echography'/exp (673488) 29. 'doppler ultrasonography'/exp (60536) 30. echogra*:ab,ti (15066) 31. ultraso*:ab,ti (434187) 32. sonography:ab,ti (39307) 33. echotomography:ab,ti (774) 34. doptone:ab,ti (13) 35. echoscopy:ab,ti (60) 36. echosound:ab,ti (4) 37. sonogram:ab,ti (2095) 38. 'capsule endoscopy'/exp (7111) 39. (capsule NEAR/5 endoscop*):ab,ti (6170) 40. (capsule NEAR/5 enteroscopy):ab,ti (683) 41. anti–saccharomyces:ab,ti AND ((cerevisiae NEAR/5 antibody):ab,ti) (125) 42. asca*:ab,ti (12964) 43. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 (2155398) 44. 'crohn disease'/exp (75375) 45. 'colon crohn disease'/exp (1841) 46. crohn*:ab,ti (63039) 47. (regional* NEAR/5 enter*):ab,ti (1373) 48. (regional NEAR/5 ileiti*):ab,ti (308) 49. (regional NEAR/5 colitis):ab,ti (214) 50. (enteritis NEAR/5 granulomatous):ab,ti (194) 51. (colitis NEAR/5 granulomatous):ab,ti (570) 52. ileocolitis:ab,ti (563) 53. (terminal NEAR/5 ileitis):ab,ti (543) 54. (cleron NEAR/5 disease):ab,ti (0) 55. #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 (13399) 56. #43 AND #55 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [2012-2017]/py (147)
# of references that were identified	147
# of references after removing duplicates	145 (see EndNote file)

Electronic Search Report #3	
Type of search	New
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick
Platform	Wiley
Search date	07/07/2017
Update date (AutoAlert)	Indefinite
Search date range	No restrictions
Language restrictions	None
Other limits	None
Search strategy (results)	1. MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 7463 2. (magnetic near/5 resonance near/5 tomography):ti,ab 497 3. (magnetization near/5 transfer near/5 imaging):ti,ab 35 4. (imaging near/5 magnetic near/5 resonance):ti,ab 7893 5. (imaging* near/5 chemical near/5 shift):ti,ab 25 6. (tomography near/5 mr*):ti,ab 195 7. (tomography near/5 proton near/5 spin):ti,ab 2 8. (spin ajd5 echo near/5 imaging):ti,ab 0 9. zeugmatography:ti,ab 0 10. nmr:ti,ab 328 11. mri:ti,ab 8890 12. (mr near/5 imaging):ti,ab 1029 13. (maria near/5 score):ti,ab 0 14. MeSH descriptor: [Leukocyte L1 Antigen Complex] explode all trees 107 15. calgranulin:ti,ab 6 16. calprotectin:ti,ab 300 17. (calcium-binding near/5 protein):ti,ab 21 18. (L1 near/5 antigen):ti,ab 5 19. (L1 near/5 protein):ti,ab 23 20. (migratory near/5 inhibitory):ti,ab and (factor-related near/5 protein):ti,ab 0 21. MeSH descriptor: [Lactoferrin] explode all trees 161 22. lactoferrin*:ti,ab 334 23. lactotransferrin:ti,ab 0 24. MeSH descriptor: [Ultrasonography] explode all trees 12570 25. MeSH descriptor: [Ultrasonography, Doppler] explode all trees 2898 26. echogra*:ti,ab 301 27. ultraso*:ti,ab 19896 28. sonography:ti,ab 1277 29. echotomography:ti,ab 6 30. doptone:ti,ab 0 31. echoscopy:ti,ab 2 32. echosound:ti,ab 0 33. sonogram:ti,ab 41 34. MeSH descriptor: [Capsule Endoscopy] explode all trees 154 35. (capsule near/5 endoscop*):ti,ab 312 36. (capsule near/5 enteroscopy):ti,ab 18 37. (Anti–Saccharomyces near/5 cerevisiae near/5 antibody):ti,ab 4 38. ASCA*:ti,ab 284 39. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 of #37 or #38 40376 40. MeSH descriptor: [Crohn Disease] explode all trees 1144 41. crohn*:ab,ti 2368 42. (regional* near/5 enter*):ab,ti 12 43. (regional near/5 ileiti*):ab,ti 2 44. (regional near/5 colitis):ab,ti 2 45. (enteritis near/5 granulomatous):ab,ti 0 46. (colitis near/5 granulomatous):ab,ti 0 47. ileocolitis:ab,ti 24 48. (terminal near/5 ileitis):ab,ti 1 49. (cleron near/5 disease):ab,ti 0 50. #40 or #41 or #42 or #43 or #44 or #45 or #46 of #47 or #48 or #49 2471 51. #39 and #50 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments 11
# of references that were identified	11
# of references after removing duplicates	11 (see EndNote file)

Non-biologic drugs

Electronic Search Report #1		
Type of search	New	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	16/08/2017	
Update date (AutoAlert)	Indefinite	
Search date range	2012-2017	
Language restrictions	None	
Other limits	None	
Search strategy (results)	56. exp Crohn Disease/ (35795) 57. crohn$.tw. (40970) 58. (regional$ adj5 enter$).tw. (1167) 59. (regional adj5 ileiti$).tw. (295) 60. (regional adj5 colitis).tw. (182) 61. (enteritis adj5 granulomatous).tw. (196) 62. (colitis adj5 granulomatous).tw. (442) 63. ileocolitis.tw. (415) 64. (terminal adj5 ileitis).tw. (416) 65. (cleron adj5 disease).tw. (0) 66. or/1-10 (50154) 67. exp Adrenal Cortex Hormones/ (382543) 68. cortic$.tw. (378388) 69. (adren$ adj5 cort$).tw. (30413) 70. (adren$ adj5 steroid$).tw. (8473) 71. adrenocorticosteroid.tw. (142) 72. (adreno$ adj5 hormone$).tw. (12527) 73. exp Glucocorticoids/ (184091) 74. gl?cocort$.tw. (64780) 75. exp Prednisone/ (38793) 76. predniso$.tw. (48789) 77. exp Methylprednisolone/ (18648) 78. methylpredniso$.tw. (14683) 79. exp Betamethasone/ (7082) 80. betamet?a$.tw. (4614) 81. (beta adj5 methason$).tw. (144) 82. betadexamethasone.tw. (0) 83. flubenisolone.tw. (0) 84. exp Budesonide/ (4165)	85. budesonide.tw. (4741) 86. dexbudesonide.tw. (0) 87. exp Mesalamine/ (3214) 88. mesala?ine.tw. (2122) 89. meta-aminosalicylic.tw. (0) 90. 5-aminosalicyli$.tw. (1752) 91. 5-asa.tw. (1422) 92. exp Azathioprine/ (14342) 93. az?thiop$.tw. (14633) 94. exp 6-Mercaptopurine/ (19317) 95. mercaptopurine.tw. (4326) 96. exp Methotrexate/ (36982) 97. meth?otrexat$.tw. (38521) 98. metot?rexate.tw. (65) 99. methohexate.tw. (0) 100. amethopterin.tw. (407) 101. methylaminopterin$.tw. (8) 102. mtx.tw. (11536) 103. exp Probiotics/ (12966) 104. probiotic$.tw. (16678) 105. exp Ciprofloxacin/ (12241) 106. ciprofloxacin.tw. (22416) 107. exp Metronidazole/ (12192) 108. metronidazol$.tw. (14418) 109. rifaximin.tw. (944) 110. or/12-54 (854013) 111. 11 and 55 (7187) 112. limit 56 to (yr="2012 -Current" and "reviews (best balance of sensitivity and specificity)") (507)
# of references that were identified	507	
# of references after removing duplicates	429 (see EndNote file)	

Electronic Search Report #2	
Type of search	New
Data bases	• EMBASE
Platform	EMBASE.com
Search date	16/08/2017
Update date (AutoAlert)	Indefinite
Search date range	2012-2017
Language restrictions	None
Other limits	None
Search strategy (results)	57. 'crohn disease'/exp (75362) 58. 'colon crohn disease'/exp (1841) 59. crohn*:ab,ti (63024) 60. (regional* NEAR/5 enter*):ab,ti (1373) 61. (regional NEAR/5 ileiti*):ab,ti (308) 62. (regional NEAR/5 colitis):ab,ti (214) 63. (enteritis NEAR/5 granulomatous):ab,ti (194) 64. (colitis NEAR/5 granulomatous):ab,ti (570) 65. ileocolitis:ab,ti (563) 66. (terminal NEAR/5 ileitis):ab,ti (543) 67. (cleron NEAR/5 disease):ab,ti (0) 68. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (84850) 69. 'corticosteroid'/exp (864629) 70. cortic*:ab,ti (470550) 71. (adren* NEAR/5 cort*):ab,ti (33200) 72. (adren* NEAR/5 steroid*):ab,ti (9680) 73. adrenocorticosteroid:ab,ti (159) 74. (adreno* NEAR/5 hormone*):ab,ti (13482) 75. 'glucocorticoid'/exp (659233) 76. gl?cocort* (120992) 77. 'prednisone'/exp (155867) 78. predniso*:ab,ti (71867) 79. 'methylprednisolone'/exp (81407) 80. methylpredniso*:ab,ti (21346) 81. 'betamethasone'/exp (15990) 82. betamet?a* (21804) 83. (beta NEAR/5 methason*):ab,ti (82) 84. betadexamethasone:ab,ti (0) 85. flubenisolone:ab,ti (0) 86. 'budesonide'/exp (18062) 87. budesonide:ab,ti (7001) 88. dexbudesonide:ab,ti (0) 89. 'mesalazine'/exp (15217) 90. mesala?ine (15433) 91. 'meta aminosalicylic':ab,ti (0) 92. 5- AND aminosalicyli*:ab,ti (3493) 93. '5 asa':ab,ti (2683) 94. 'azathioprine'/exp (84068) 95. 'azathioprine derivative'/exp (54) 96. az?thiop* (86559) 97. 'mercaptopurine'/exp (25094) 98. mercaptopurine:ab,ti (5839) 99. 'methotrexate'/exp (156067) 100. 'methotrexate derivative'/exp (310) 101. meth?otrexat* (70) 102. metot?rexate (95) 103. methohexate:ab,ti (0) 104. amethopterin:ab,ti (414) 105. methylaminopterin* (16) 106. mtx:ab,ti (18766) 107. 'probiotic agent'/exp (25142) 108. probiotic*:ab,ti (20884) 109. 'ciprofloxacin'/exp (83382) 110. ciprofloxacin:ab,ti (29300) 111. 'metronidazole'/exp (59462) 112. metronidazol*:ab,ti (19135) 113. 'rifaximin'/exp (3589) 114. rifaximin:ab,ti (1628) 115. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 (1493677) 116. #12 AND #359 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [2012-2017]/py (303)
# of references that were identified	303
# of references after removing duplicates	300 (see EndNote file)

Electronic Search Report #3		
Type of search	New	
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick	
Platform	Wiley	
Search date	07/07/2017	
Update date (AutoAlert)	Indefinite	
Search date range	No restrictions	
Language restrictions	None	
Other limits	None	
Search strategy (results)	52. MeSH descriptor: [Crohn Disease] explode all trees (1144) 53. crohn*:ab,ti (2368) 54. (regional* near/5 enter*):ab,ti (12) 55. (regional near/5 ileiti*):ab,ti (2) 56. (regional near/5 colitis):ab,ti (2) 57. (enteritis near/5 granulomatous):ab,ti (0) 58. (colitis near/5 granulomatous):ab,ti (0) 59. ileocolitis:ab,ti (24) 60. (terminal near/5 ileitis):ab,ti (1) 61. (cleron near/5 disease):ab,ti (0) 62. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (2471) 63. MeSH descriptor: [Adrenal Cortex Hormones] explode all trees (13079) 64. cortic*:ti,ab (18763) 65. (adren* near/5 cort*):ti,ab (1292) 66. (adren* near/5 steroid*):ti,ab (197) 67. adrenocorticosteroid:ti,ab (11) 68. (adreno* near/5 hormone*):ti,ab (822) 69. MeSH descriptor: [Glucocorticoids] explode all trees (4091) 70. gl?cocort*:ti,ab (3204) 71. MeSH descriptor: [Prednisone] explode all trees (2944) 72. predniso*:ti,ab (8028) 73. MeSH descriptor: [Methylprednisolone] explode all trees (1702) 74. methylpredniso*:ti,ab (2334) 75. MeSH descriptor: [Betamethasone] explode all trees (1096) 76. betamet?a*:ti,ab (398) 77. (beta near/5 methason*):ti,ab (26) 78. betadexamethasone:ti,ab (0) 79. flubenisolone:ti,ab (0) 80. MeSH descriptor: [Budesonide] explode all trees (1320) 81. budesonide:ti,ab (3147) 82. dexbudesonide:ti,ab (0) 83. MeSH descriptor: [Mesalamine] explode all trees (441)	84. mesala?ine:ti,ab (561) 85. meta-aminosalicylic:ti,ab (0) 86. 5-aminosalicyli*:ti,ab (267) 87. 5-asa:ti,ab (270) 88. MeSH descriptor: [Azathioprine] explode all trees (1124) 89. az?thiop*:ti,ab (1703) 90. MeSH descriptor: [6-Mercaptopurine] explode all trees (1268) 91. mercaptopurine:ti,ab (337) 92. MeSH descriptor: [Methotrexate] explode all trees (2981) 93. meth?otrexat*:ti,ab (3) 94. metot?rexate:ti,ab(4) 95. methohexate:ti,ab (0) 96. amethopterin:ti,ab (2) 97. methylaminopterin*:ti,ab (0) 98. mtx:ti,ab (2370) 99. MeSH descriptor: [Probiotics] explode all trees (1643) 100. probiotic*:ti,ab (2741) 101. MeSH descriptor: [Ciprofloxacin] explode all trees (947) 102. ciprofloxacin:ti,ab (1755) 103. MeSH descriptor: [Metronidazole] explode all trees (1862) 104. metronidazol*:ti,ab (2997) 105. rifaximin:ti,ab (297) 106. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 of #37 or #38 or #39 or 40 or #41 or #42 or #43 or #44 or #45 or #46 of #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 (167288) 107. #11 and #55 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments (37)
# of references that were identified	37	
# of references after removing duplicates	37 (see EndNote file)	

Biologic drugs

Electronic Search Report #1		
Type of search	New	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	28/06/2017	
Update date (AutoAlert)	Indefinite	
Search date range	2012-2017	
Language restrictions	None	
Other limits	None	
Search strategy (results)	113. exp Crohn Disease/ (35172) 114. crohn$.tw. (40339) 115. (regional$ adj5 enter$).tw. (1150) 116. (regional adj5 ileiti$).tw. (293) 117. (regional adj5 colitis).tw. (182) 118. (enteritis adj5 granulomatous).tw. (194) 119. (colitis adj5 granulomatous).tw. (432) 120. ileocolitis.tw. (407) 121. (terminal adj5 ileitis).tw. (414) 122. (cleron adj5 disease).tw. (0) 123. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (49372) 124. (TNFadj5 alpha adj5 inhibitor$).tw. (0) 125. (tumor adj5 necrosis adj5 factor adj5 alpha adj5 inhibitor).tw. (772) 126. (anti adj5 TNF adj5 alpha).tw. (5876) 127. exp Immunosuppressive Agents/ (292319) 128. immunosuppress$.tw. (127557) 129. (immun$ adj5 supress$).tw. (40) 130. immunodepressant.tw. (136) 131. exp Biological Therapy/ (407582) 132. (biologic$ adj5 therap$).tw. (14333) 133. biotherap$.tw. (2564) 134. (biologic$ adj5 response adj5 modifier$).tw. (2376) 135. (brm adj5 therap$).tw. (65) 136. immunotherap$.tw. (62645) 137. (immun$ adj5 therap$).tw. (63325) 138. (immun$ adj5 treatment).tw. (47952) 139. exp Antibodies, Monoclonal, Humanized/ (37036) 140. exp Antibodies, Monoclonal/ (210243)	141. antibod$.tw. (788906) 142. vedolizumab.tw. (310) 143. exp Ustekinumab/ (568) 144. ustekinumab.tw. (948) 145. exp Immunoglobulin Fab Fragments/ (25144) 146. immunoglobulin$.tw. (140889) 147. (fab adj5 fragment$).tw. (6473) 148. exp Certolizumab Pegol/ (457) 149. certolizumab.tw. (762) 150. exp Infliximab/ (8873) 151. infliximab.tw. (10182) 152. exp Adalimumab/ (4071) 153. adalimumab.tw. (5024) 154. Crohn Disease/ or Adalimumab/ or Biosimilar Pharmaceuticals/ or Biological Products/ or abp-501.mp. (58223) 155. Biosimilar Pharmaceuticals/ or Antibodies, Monoclonal/ or ct-p13.mp. or Infliximab/ (182962) 156. 40 or 41 or 42 or 43 (236345) 157. exp Biosimilar Pharmaceuticals/ (895) 158. biosimilar$.tw. (1889) 159. 45 or 46 (1976) 160. 44 and 47 (1159) 161. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 48 (1644661) 162. 11 and 49 (11203) 163. limit 50 to (“reviews (best balance of sensitivity and specificity)” and last 5 years) (969)
# of references that were identified	969	
# of references after removing duplicates	913 (see EndNote file)	

Electronic Search Report #2		
Type of search	New	
Data bases	• EMBASE	
Platform	EMBASE.com	
Search date	28/06/2017	
Update date (AutoAlert)	Indefinite	
Search date range	2012-2017	
Language restrictions	None	
Other limits	None	
Search strategy (results)	117. 'crohn disease'/exp (74811) 118. 'colon crohn disease'/exp (1830) 119. crohn*:ab,ti (62562) 120. (regional* NEAR/5 enter*):ab,ti (1371) 121. (regional NEAR/5 ileiti*):ab,ti (308) 122. (regional NEAR/5 colitis):ab,ti (214) 123. (enteritis NEAR/5 granulomatous):ab,ti (191) 124. (colitis NEAR/5 granulomatous):ab,ti (570) 125. ileocolitis:ab,ti (562) 126. (terminal NEAR/5 ileitis):ab,ti (540) 127. (cleron NEAR/5 disease):ab,ti (0) 128. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (84213) 129. 'tumor necrosis factor alpha inhibitor'/exp (67178) 130. (tnf NEAR/5 alpha):ab,ti AND inhibitor*:ab,ti (5067) 131. (tumor NEAR/5 necrosis):ab,ti AND (factor NEAR/5 alpha):ab,ti AND inhibitor:ab,ti (2535) 132. (anti NEAR/5 tnf):ab,ti AND alpha:ab,ti (3165) 133. 'immunosuppressive agent'/exp (830811) 134. immunosuppress*:ab,ti (176239) 135. (immu* NEAR/5 supress*):ab,ti (155) 136. immunodepressant:ab,ti (215) 137. 'biological therapy'/exp (1401311) 138. (biologic* NEAR/5 therap*):ab,ti (22249) 139. biotherap*:ab,ti (3617) 140. (biologic* NEAR/5 response):ab,ti AND modifier*:ab,ti (2772) 141. (brm NEAR/5 therap*):ab,ti (111) 142. 'immunotherapy'/exp (164044) 143. immunotherap*:ab,ti (86340) 144. (immun* NEAR/5 therap*):ab,ti (88930) 145. (immun* NEAR/5 treatment):ab,ti (66616)	146. 'monoclonal antibody'/exp (441198) 147. antibod*:ab,ti (945991) 148. 'vedolizumab'/exp (1247) 149. vedolizumab:ab,ti (666) 150. 'ustekinumab'/exp (3513) 151. ustekinumab:ab,ti (1841) 152. 'immunoglobulin f (ab) fragment'/exp (7979) 153. immunoglobulin*:ab,ti (166007) 154. (fab NEAR/5 fragment*):ab,ti (7069) 155. 'certolizumab pegol'/exp (4353) 156. certolizumab:ab,ti (2059) 157. 'infliximab'/exp (39304) 158. infliximab:ab,ti (18947) 159. 'adalimumab'/exp (23391) 160. adalimumab:ab,ti (11714) 161. 'abp-501' (34) 162. 'ct-p13' (197) 163. #41 OR #42 OR #43 OR #44 OR #45 OR #46 (46994) 164. 'biosimilar agent'/exp (2220) 165. biosimilar*:ab,ti (3444) 166. #48 OR #49 (3928) 167. #47 AND #50 (835) 168. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR)#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #50 OR #51 (3085383) 169. #12 AND #52 (32841) 170. #53 AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [2012-2017]/py AND [embase]/lim (468)
# of references that were identified	468	
# of references after removing duplicates	373 (see EndNote file)	

Electronic Search Report #3	
Type of search	New
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick
Platform	Wiley
Search date	28/06/2017
Update date (AutoAlert)	Indefinite
Search date range	No restrictions
Language restrictions	None
Other limits	None
Search strategy (results)	1. MeSH descriptor: [Crohn Disease] explode all trees (1134) 2. crohn*:ab,ti (2347) 3. (regional* near/5 enter*):ab,ti (12) 4. (regional near/5 ileiti*):ab,ti (2) 5. (regional near/5 colitis):ab,ti (2) 6. (enteritis near/5 granulomatous):ab,ti (0) 7. (colitis near/5 granulomatous):ab,ti (8) 8. ileocolitis:ab,ti (24) 9. (terminal near/5 ileitis):ab,ti (1) 10. (cleron near/5 disease):ab,ti (0) 11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (2450) 12. (TNF near/5 alpha near/5 inhibitor*):ti,ab (102) 13. (tumor near/5 necrosis near/5 factor near/5 alpha near/5 inhibitor):ti,ab (36) 14. (anti near/5 TNF near/5 alpha):ti,ab (205) 15. MeSH descriptor: [Immunosuppressive Agents] explode all trees (4965) 16. Immunosuppressive Agents (6506) 17. (immun* near/5 supress*):ti,ab (3) 18. immunodepressant:ti,ab (5) 19. MeSH descriptor: [Biological Therapy] explode all trees (12375) 20. (biologic* near/5 therap*):ti,ab (859) 21. biotherap*:ti, (89) 22. (biologic* near/5 response near/5 modifier*):ti,ab (160) 23. (brm near/5 therap*):ti,ab (7) 24. immunotherap*:ti,ab (5019) 25. (immun* near/5 therap*):ti,ab (7933) 26. (immun* near/5 treatment):ti,ab (3602) 27. MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees (3389) 28. MeSH descriptor: [Antibodies, Monoclonal] explode all trees (6991) 29. antibod*:ti,ab (18526) 30. vedolizumab:ti,ab (104) 31. MeSH descriptor: [Ustekinumab] explode all trees (56) 32. ustekinumab:ti,ab (247) 33. MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees (669) 34. immunoglobulin*:ti,ab (4113) 35. (fab near/5 fragment*):ti,ab (65) 36. MeSH descriptor: [Certolizumab Pegol] explode all trees (70) 37. certolizumab:ti,ab (282) 38. MeSH descriptor: [Infliximab] explode all trees (465) 39. infliximab:ti,ab (1229) 40. MeSH descriptor: [Adalimumab] explode all trees (285) 41. adalimumab:ti,ab (1189) 42. abp-501:ti,ab (7) 43. ct-p13:ti,ab (31) 44. #38 or #39 or #40 or #41 or #42 or #43 (2205) 45. MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees (33) 46. biosimilar*:ab,ti (273) 47. #45 or #46 (276) 48. #44 and #47 (84) 49. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 of #37 or #38 or #39 or 40 or #41 or #48 (163231) 50. #11 and #49 Publication, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments (105)
# of references that were identified	63
# of references after removing duplicates	52 (see EndNote file)

Perianal Crohn's Disease

Electronic Search Report #1		
Type of search	New	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	15/08/2017	
Update date (AutoAlert)	Indefinite	
Search date range	No limits	
Language restrictions	None	
Other limits	None	
Search strategy (results)	164. exp Crohn Disease/ (35805) 165. crohn$.tw. (40988) 166. (regional$ adj5 enter$).tw. (1167) 167. (regional adj5 ileiti$).tw. (295) 168. (regional adj5 colitis).tw. (182) 169. (enteritis adj5 granulomatous).tw. (196) 170. (colitis adj5 granulomatous).tw. (442) 171. ileocolitis.tw. (416)	172. (terminal adj5 ileitis).tw. (416) 173. (cleron adj5 disease).tw. (0) 174. or/1-10 (50174) 175. perianal.tw. (6225) 176. 11 and 12 (1534) 177. limit 13 to "reviews (best balance of sensitivity and specificity)"
# of references that were identified	320	
# of references after removing duplicates	307 (see EndNote file)	

Electronic Search Report #2		
Type of search	New	
Data bases	• EMBASE	
Platform	EMBASE.com	
Search date	16/08/2017	
Update date (AutoAlert)	Indefinite	
Search date range	No limits	
Language restrictions	None	
Other limits	None	
Search strategy (results)	171. 'crohn disease'/exp (75362) 172. 'colon crohn disease'/exp (1841) 173. crohn*:ab,ti (63024) 174. (regional* NEAR/5 enter*):ab,ti (1373) 175. (regional NEAR/5 ileiti*):ab,ti (308) 176. (regional NEAR/5 colitis):ab,ti (214) 177. (enteritis NEAR/5 granulomatous):ab,ti (194) 178. (colitis NEAR/5 granulomatous):ab,ti (570) 179. ileocolitis:ab,ti (563)	180. (terminal NEAR/5 ileitis):ab,ti (543) 181. (cleron NEAR/5 disease):ab,ti (0) 182. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (84850) 183. perianal:ab,ti (9455) 184. #12 AND #13 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [2012-2017]/py (62)
# of references that were identified	62	
# of references after removing duplicates	37 (see EndNote file)	

Electronic Search Report #3		
Type of search	New	
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick	
Platform	Wiley	
Search date	16/08/2017	
Update date (AutoAlert)	Indefinite	
Search date range	No restrictions	
Language restrictions	None	
Other limits	None	
Search strategy (results)	108. MeSH descriptor: [Crohn Disease] explode all trees 1144 109. crohn*:ab,ti 2368 110. (regional* near/5 enter*):ab,ti 12 111. (regional near/5 ileiti*):ab,ti 2 112. (regional near/5 colitis):ab,ti 2 113. (enteritis near/5 granulomatous):ab,ti 0 114. (colitis near/5 granulomatous):ab,ti 0 115. ileocolitis:ab,ti 24	116. (terminal near/5 ileitis):ab,ti 1 117. (cleron near/5 disease):ab,ti 0 118. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 2471 119. perianal:ti,ab 398 120. #11 and #12 in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments 3
# of references that were identified	3	
# of references after removing duplicates	3 (see EndNote file)	

Surgical and endoscopic treatment

Electronic Search Report #1		
Type of search	New	
Data bases	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update	
Platform	Ovid	
Search date	06/067/2017	
Update date (AutoAlert)	Indefinite	
Search date range	No limits	
Language restrictions	None	
Other limits	None	
Search strategy (results)	178. exp Crohn Disease/ (35172) 179. crohn$.tw. (40339) 180. (regional$ adj5 enter$).tw. (1150) 181. (regional adj5 ileiti$).tw. (293) 182. (regional adj5 colitis).tw. (182) 183. (enteritis adj5 granulomatous).tw. (194) 184. (colitis adj5 granulomatous).tw. (432) 185. ileocolitis.tw. (407) 186. (terminal adj5 ileitis).tw. (414) 187. (cleron adj5 disease).tw. (0) 188. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (49372) 189. exp General Surgery/ (128) 190. surg$.tw. (182708) 191. (operative adj5 intervention).tw. (644) 192. (operative adj5 repair).tw. (273) 193. (operative adj5 treatment).tw. (2017) 194. resection.tw. (28549)	195. exp Drainage/ (23) 196. (drainage adj5 percutaneous).tw. (770) 197. exp Laparoscopy/ (63) 198. (laparoscop$ adj5 surg$).tw. (4544) 199. strictureplasty.tw. (30) 200. bypass.tw. (9612) 201. exp Dilatation/ (1) 202. dilat$.tw. (11489) 203. exp Anastomosis, Surgical/ (41) 204. anastomo$.tw. (6062) 205. exp Endoscopy/ (213) 206. (endoscop$ adj5 surgical).tw. (1072) 207. (endoscop$ adj5 interventional).tw. (143) 208. fistulotomy.tw. (39) 209. or/12-31 (207914) 210. 11 and 32 (965) 211. limit 33 to “reviews (best balance of sensitivity and specificity)” (129)
# of references that were identified	129	
# of references after removing duplicates	123 (see EndNote file)	

Electronic Search Report #2		
Type of search	New	
Data bases	• EMBASE	
Platform	EMBASE.com	
Search date	07/07/2017	
Update date (AutoAlert)	Indefinite	
Search date range	2012-2017	
Language restrictions	None	
Other limits	None	
Search strategy (results)	185. 'crohn disease'/exp (74942) 186. 'colon crohn disease'/exp (1831) 187. crohn*:ab,ti (62691) 188. (regional* NEAR/5 enter*):ab,ti (1372) 189. (regional NEAR/5 ileiti*):ab,ti (308) 190. (regional NEAR/5 colitis):ab,ti (214) 191. (enteritis NEAR/5 granulomatous):ab,ti (192) 192. (colitis NEAR/5 granulomatous):ab,ti (570) 193. ileocolitis:ab,ti (563) 194. (terminal NEAR/5 ileitis):ab,ti (541) 195. (cleron NEAR/5 disease):ab,ti (0) 196. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (4384) 197. 'surgery'/exp (4189568) 198. surg*:ab,ti (2160909) 199. (operative NEAR/5 intervention):ab,ti (7362) 200. (operative NEAR/5 repair):ab,ti (3653) 201. (operative NEAR/5 treatment):ab,ti (23505) 202. resection:ab,ti (330309) 203. 'percutaneous drainage'/exp (6191)	204. (drainage NEAR/5 percutaneous):ab,ti (9303) 205. 'laparoscopy'/exp (130180) 206. (laparoscop* NEAR/5 surg*):ab,ti (49130) 207. strictureplasty:ab,ti (330) 208. bypass:ab,ti (151156) 209. 'dilatation'/exp (14473) 210. dilat*:ab,ti (180987) 211. 'anastomosis'/exp (159915) 212. anastomo*:ab,ti (101621) 213. 'endoscopic therapy'/exp (13188) 214. (endoscop* NEAR/5 surgical):ab,ti (11591) 215. (endoscop* NEAR/5 interventional):ab,ti (1374) 216. fistulotomy:ab,ti (720) 217. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 (4985128) 218. #12 AND #33 (25329) 219. #34 AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [embase]/lim (565)
# of references that were identified	565	
# of references after removing duplicates	550 (see EndNote file)	

Electronic Search Report #3	
Type of search	New
Data bases	Cochrane Library • http://onlinelibrary.wiley.com/cochranelibrary/search/quick
Platform	Wiley
Search date	07/07/2017
Update date (AutoAlert)	Indefinite
Search date range	No restrictions
Language restrictions	None
Other limits	None
Search strategy (results)	121. MeSH descriptor: [Crohn Disease] explode all trees (1134) 122. crohn*:ab,ti (2347) 123. (regional* near/5 enter*):ab,ti (12) 124. (regional near/5 ileiti*):ab,ti (2) 125. (regional near/5 colitis):ab,ti (2) 126. (enteritis near/5 granulomatous):ab,ti (0) 127. (colitis near/5 granulomatous):ab,ti (8) 128. ileocolitis:ab,ti (24) 129. (terminal near/5 ileitis):ab,ti (1) 130. (cleron near/5 disease):ab,ti (0) 131. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (2450) 132. MeSH descriptor: [General Surgery] explode all trees (365) 133. surg*:ti,ab (116447) 134. (operative near/5 intervention):ab,ti (271) 135. (operative near/5 repair):ab,ti (148) 136. (operative near/5 treatment):ab,ti (1317) 137. resection:ti,ab (10916) 138. MeSH descriptor: [Drainage] explode all trees (2735) 139. (drainage near/5 percutaneous):ab,ti (202) 140. MeSH descriptor: [Laparoscopy] explode all trees (6088) 141. (laparoscop* near/5 surg*):ab,ti (5454) 142. strictureplasty:ab,ti (6) 143. bypass:ab,ti (12893) 144. MeSH descriptor: [Dilatation] explode all trees (406) 145. dilat*:ab,ti (7654) 146. MeSH descriptor: [Anastomosis, Surgical] explode all trees (2378) 147. anastomo*:ab,ti (2680) 148. MeSH descriptor: [Endoscopy] explode all trees (17762) 149. (endoscop* near/5 surgical):ab,ti (398) 150. (endoscop* near/5 interventional):ab,ti (40) 151. fistulotomy:ab,ti (49) 152. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 144793 153. #11 and #32 in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments (43)
# of references that were identified	43
# of references after removing duplicates	43 (see EndNote file)

ANNEX N° 4. EVIDENCE PROFILES

1. What are the predictors of relapse of Crohn's disease in patients older than 16 years?

C-Reactive Protein

References: Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut. 2008;57(10):1386-92. Consigny Y, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY, et al. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. Inflamm Bowel Dis. 2006;12(7):551-7. Kallel L, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol. 2010;22(3):340-5.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	C-reactive protein	Absence of use	Relative (95% CI)	Absolute (95% CI)		
Risk of relapse (assessed with: risk of relapse, no further specifications)												
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	-/29	-/50	**HR 1,5** (1.1 to 1.9) [c]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Relapse, cut-off point 20 mg/L (assessed with: risk of relapse, no further specifications)												
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	-/71 [e]		**RR 10,5** (2.3 to 48.1)	**11 fewer per 1000** (from 2 fewer to 48 fewer)	⊕OOO VERY LOW	CRITICAL
Relapse - cut-off point 9 mg/L (assessed with: risk of relapse, no further specifications)												
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [f]	None	-/53		**RR 9,1** (0.5 to 53.3)	**9 fewer per 1000** (from 1 fewer to 53 fewer)	⊕OOO VERY LOW	CRITICAL

HR: Hazard ratio; CI: Confidence interval; RR: Risk ratio.

Explanations

a. High risk of selection bias and confounding.
b. Low sample size; confidence interval crosses 1.25.
c. Multivariate analysis results.
d. Wide confidence interval.
e. Total patients included in the study; the number of patients has not been discriminated in terms of RCP values or relapse.
f. Low sample size. Confidence interval crosses 0.75 and 1.25.

Erythrocyte sedimentation rate

Reference: Consigny Y, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY, et al. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. Inflamm Bowel Dis. 2006;12(7):551-7.

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Erythrocyte sedimentation rate	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow-up: range: 12 to 18 months; assessed with: CDAI score >150)											
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	-/71	**HR 1,3** (1.0 to 1.7) [c]	**1 fewer per 1000** (from 1 fewer to 2 fewer)	⊕OOO VERY LOW	

CI: Confidence interval; HR: Hazard ratio.

Explanations

a. High risk of selection bias and confounding.
b. Low sample size. Confidence interval crosses a null value and 1.25.
c. Bivariate analysis

ASCA (Anti-Saccharomyces cerevisiae antibodies)

Reference: Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut. 2008;57(10):1386-92.

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	ASCA	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow-up: range: 12 to 18 months; assessed with: CDAI score >150)											
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	-/71	**HR 1,20** (0.54 to 2.54) [c]	**1 fewer per 1000** (from 1 fewer to 3 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio.

Explanations

a. High risk of selection bias and confounding.
b. Low sample size. Confidence interval crosses 0.75 and 1.25.

Fecal calprotectin

Reference: Mao R, Xiao YL, Gao X, Chen BL, He Y, Yang L, et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Inflamm Bowel Dis. 2012;18(10):1894-9.

Sensitivity	0.75 (95% CI: 0.64-0.84)	Prevalence rates	30%
Specificity	0.71 (95% CI: 0.64-0.76)		

Outcome	№ de studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested	Test accuracy CoE
			Risk of bias	Indirect evidence	Inconsistency	Imprecision	Publication bias	Pre-test probability 0%	
True positives (patients with)	6 studies 672 patients [c]	Cohort and case-control studies	No serious risk of bias	Serious indirect evidence [a]	Very serious inconsistency [b]	No serious imprecision	None	0 (0 to 0)	⊕OOO VERY LOW
False negatives (patients incorrectly classified as not having)								0 (0 to 0)	
True negatives (patients without)	6 studies 672 patients [c]	Cohort and case-control studies	No serious risk of bias	Serious indirect evidence [a]	Very serious inconsistency [b]	No serious imprecision	None	710 (640 to 760)	⊕OOO VERY LOW
False positives (patients incorrectly classified as having)								290 (240 to 360)	

Explanations

a. Two studies included population under 18 years of age and patients with ulcerative colitis (inflammatory bowel disease).
b. High heterogeneity among studies. I2 = 57.5 for pooled analysis - sensitivity and 70% for pooled analysis - specificity. Wide area of prediction.
c. 672 patients with inflammatory bowel disease, 354 with Crohn's disease.

Serum levels of infliximab

Reference: Moore C, Corbett G, Moss AC. Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(5):619-25.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab serum levels <2 micrograms/mL	Infliximab serum levels >2 micrograms/mL	Relative (95% CI)	Absolute (95% CI)		
Infliximab serum levels and remission (follow-up: range: 8 to 54 weeks)												
6	Observational studies [b]	Serious risk of bias [c,d]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	[e]		-	SMD **0.7 Higher SD** (0.3 higher to 1.1 higher)	⊕OOO VERY LOW	CRITICAL
Disease remission (follow-up: range: 8 to 54 weeks; assessed with: clinical remission, no further specifications)[f]												
7	Observational studies	Serious risk of bias [d]	Serious inconsistency [g]	Serious indirect evidence [h]	No serious imprecision	None	[e]	e	**RR 3.04** (1.42 to 6.51)	**3 fewer per 1000** (from 1 fewer to 7 fewer)	⊕OOO VERY LOW	CRITICAL
Endoscopic remission (follow-up: range: 8 to 68 weeks; assessed with: endoscopic remission, no further specifications)												
4	Observational studies	Serious risk of bias [d]	Serious inconsistency [i]	Serious indirect evidence [h]	No serious imprecision	None	[e]	e	**RR 3.0** (1.4 to 6.5)	**3 fewer per 1000** (from 1 fewer to 7 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard ratio; SMD: standardized mean difference.

Explanations

a. Measured by ELISA or immunoassay.
b. It includes the results of 3 clinical trials.
c. Clinical trials were evaluated using a scale for assessing cohort studies.
d. High risk of confounding bias and outcomes measurement bias (items 4 and 5 of the Newcastle-Otawa scale).
e. Not reported.
f. Levels measurement time.
g. High heterogeneity among studies. I2 = 88%.
h. Pooled analysis included patients with inflammatory bowel disease, not further specifications were provided, and patients with ulcerative colitis.
i. Information not provided by the authors who conducted the review.

Using magnetic resonance imaging to predict deep remission

Reference: Thomassin L, Armengol-Debeir L, Charpentier C, Bridoux V, Koning E, Savoye G, et al. Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn's disease. World J Gastroenterol. 2017;23(23):4285-92.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Magnetic resonance imaging		Relative (95% CI)	Absolute (95% CI)		
Clinical remission (assessed with: clinical remission)												
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	11/26 (42.3%) [c]	16/23 (69.6%)	**OR 4.70** (1.21 to 49.00) [d]	**219 more per 1000** (from 39 more to 295 more)	⊕OOO VERY LOW	CRITICAL
Deep remission (assessed with: absence of ulcers in the anal canal and mucosal healing).												
1	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	10/26 (38.5%) [c]	15/23 (65.2%)	**OR 4.60** (1.03 to 20.50)	**244 more per 1000** (from 7 more to 322 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. High risk of confounding bias and suspected selection bias.
b. Low sample size. Confidence interval crosses 1.25.
c. Finding: absence of rectal involvement.
d. Multivariate analysis result.

Mucosal healing

Reference: Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther. 2016;43(3):317-33.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Endoscopic mucosal healing	Absence of mucosal healing	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (follow-up: range: 50 weeks to 4 years; assessed with: clinical remission)												
7	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	No serious imprecision	None	181/260 (69.6%) [c]	123/285 (43.2%)	**OR 2.70** (1.82 to 3.99) [d]	**241 more per 1000** (from 149 more to 320 more)	⊕OOO VERY LOW	CRITICAL
Long-term presence of improvement (follow-up: range: 50 weeks to 4 years; assessed with: duration of improvement)												
6	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirect evidence [b]	Serious imprecision [c]	None	29/37 (78.4%)	23/128 (18.0%)	**OR 14.30** (5.57 to 36.74)	**578 more per 1000** (from 370 more to 710 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. It includes RCTs with high risk of bias.
b. Pediatric population was included in this analysis.
c. Wide confidence interval.

Question N° 2. What are the safest and most effective non-biological interventions to induce remission of Crohn's disease in patients older than 16 years?

Using probiotics to induce remission in patients with active Crohn's disease

Reference: Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. Inflamm Bowel Dis. 2013;20(1):21-35.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Use of probiotics alone or plus standard treatment	Use of placebo plus standard treatment	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (probiotic plus standard treatment) (follow-up: range: 3 months to 24 months; assessed with CDAI score <150 or a 100 points decrease compared to the baseline score)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	29/40 (72.5%)	27/34 (79.4%)	**RR 0,89** (0,70 to 1,13)	**87 fewer per 1000** (from 103 more to 238 fewer)	⊕OOO VERY LOW	CRITICAL
Induction of remission (probiotic versus placebo) (follow-up: range: 3 months to 24 months; assessed with CDAI score <150 or a 100 points decrease compared to the baseline score)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	29/40 (72.5%)	27/34 (79.4%)	**RR 0,89** (0,70 to 1,13)	**87 fewer per 1000** (from 103 more to 238 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 8/11.
b. Studies with a Jadad scale score ≥3.
c. Non-optimal sample size.
d. Confidence interval crosses passes the critical value 1.25 and/or 0.75.
e. I2 >40%.

Use of antibiotics to induce remission in patients with active Crohn's disease

Reference: Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58-66.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement or remission (follow-up: range: 3 months to 6 months; assessed with: CDAI score <150 and/or a ≥70 points decrease or a >50% reduction in the number of fistulas for at least 4 weeks)												
15	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	416/823 (50.5%)	219/584 (37.5%)	**RR 1.33** (1.17 to 1,51) [e]	**124 more per 1000** (from 64 more to 191 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Ciprofloxacin, clarithromycin, metronidazole, rifaximin and ornidazole were the antibiotics included in the systematic review. AMSTAR score 7/11.

b. Patients with fistulizing CD disease, with a CDAI score >200 or a PCDAI ≥5 or with postoperative recurrence of Crohn's disease were included. All studies allowed concomitant use of other interventions (immunomodulators).

c. Assessed using the Jadad scale. Limitations regarding sequence generation and allocation concealment were observed.

d. CI crosses the critical value 1.25 and/or 0.75.

e. In the case of ciprofloxacin: RR: 1.29; 95% CI: 1.02-1.63; in the case of rifaximin: RR: 1.28; 95% CI: 1.02-1.62; in the case nitroimidazole antibiotics: RR: 1.55; 95% CI: 1.12-2.15.

Use of azathioprine or 6-mercaptopurine to induce remission in patients with active Crohn's disease

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(10):CD000545. https://doi.org/10.1002/14651858.CD000545.pub5.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Remission (follow-up: range: 12 weeks to 17 weeks; assessed with: CDAI <150 or HBI <3)												
5	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	95/197 (48.2%)	68/183 (37.2%)	**RR 1.23** (0.97-1.55)	**85 more per 1000** (from 11 fewer to 204 more)	⊕⊕OO LOW	CRITICAL
Remission or improvement (follow-up: range: 6 weeks to 28 weeks; assessed with: CDAI <150 or HBI <3)												
9	Randomized trials	Serious risk of bias [b]	Serious inconsistency [d]	No serious indirect evidence	Serious imprecision [c]	None	133/261 (51.0%)	80/245 (32.7%)	**RR 1.53** (1.05 to 2.22)	**173 more per 1000** (from 16 more to 398 more)	⊕OOO VERY LOW	CRITICAL
Steroid dose tapering (follow-up: range: 6 weeks to 28 weeks; assessed with: prednisone, <10 mg/d dose)												
4	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, e]	None	47/73 (64.4%)	32/70 (45.7%)	**RR 1.34** (1.02 to 1.77)	**155 more per 1000** (from 9 more to 352 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up: range: 6 weeks to 28 weeks; assessed with: Fever, rash, arthritis, or leukopenia or pancreatitis or nausea)												
8	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, e]	None	28/266 (10.5%)	13/244 (5.3%)	**RR 1.70** (0.94 to 3.08)	**37 more per 1000** (from 3 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Clinical improvement or fistula closure (follow-up: range: 6 weeks to 28 weeks; assessed with: lesion complete healing or decreased discharge)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, e]	None	6/11 (54.5%)	2/7 (28.6%)	**RR 2.00** (0.67 to 5.93)	**286 more per 1000** (from 94 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: range: 6 weeks to 28 weeks; assessed with: arthritis, or leukopenia or pancreatitis)												
8	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, e]	None	15/111 (13.5%)	4/105 (3.8%)	**RR 2.57** (0.92 to 7.13)	**60 more per 1000** (from 3 fewer to 234 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Adult population with active Crohn's disease, defined as having a CDAI >150 points or a HBI >7 or moderate or severe symptoms at the time of enrollment in the study. AMSTAR 10/11.
b. Unclear risk of bias for the sequence generation and allocation concealment domains. Some limitations regarding blinding.
c. CI crosses the critical value 0.75 and/or 1.25.
d. I2> 40%.
e. Very wide CI. Non-optimal sample size.

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(10):CD000545. https://doi.org/10.1002/14651858.CD000545.pub5.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	Methotrexate	Relative (95% CI)	Absolute (95% CI)		
Steroid-free remission (follow-up: range: 12 weeks to 17 weeks)												
3	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	41/75 (54.7%)	34/68 (50.0%)	**RR 1.13** (0.85 to 1.49)	**65 more per 1000** (from 75 fewer to 245 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events (follow-up: range: 12 weeks to 17 weeks)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	4/43 (9.3%)	5/42 (11.9%)	**RR 0.78** (0.23 to 2.71)	**26 fewer per 1000** (from 92 fewer to 204 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Unclear risk of bias in the sequence generation and allocation concealment domains. Some limitations regarding blinding.
b. CI crosses the critical value 0.75 and/or 1.25.
c. Non-optimal sample size.

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(10):CD000545. https://doi.org/10.1002/14651858.CD000545.pub5.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	5-aminosalicylates or sulfasalazine	Relative (95% CI)	Absolute (95% CI)		
Induction of steroid-free remission (follow-up: range: 12 weeks to 17 weeks)												
2	Randomized trials	Serious risk of bias [a]	Serious inconsistency [b]	No serious indirect evidence	Very serious imprecision [c]	None	36/75 (48.0%)	29/81 (35.8%)	**RR 1.24** (0.80 to 1.91)	**86 more per 1000** (from 72 fewer to 326 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up: range: 12 weeks to 17 weeks)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	7/75 (9.3%)	8/81 (9.9%)	**RR 0.98** (0.38 to 2.54)	**2 fewer per 1000** (from 61 fewer to 152 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Unclear risk of bias for the sequence generation and allocation concealment domains. Some limitations regarding blinding.
b. I2> 40%.
c. Wide CI and it crosses the critical value 0.75 and/or 1.25. Non-optimal sample size

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(10):CD000545. https://doi.org/10.1002/14651858.CD000545.pub5.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine	Infliximab	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: mean: 26 weeks; assessed with: CDAI <150 or HBI <3)												
1	Randomized trials	No serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	54/170 (31.8%)	81/169 (47.9%)	**RR 0.66** (0.51 to 0.87)	**163 fewer per 1000** (from 62 fewer to 235 fewer)	⊕⊕OO LOW	CRITICAL
Steroid-free remission (follow-up: mean: 6 weeks; assessed with: CDAI <150 or HBI <3 without using steroids)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	51/170 (30.0%)	75/169 (44.4%)	**RR 0.68** (0.51 to 0.90)	**142 fewer per 1000** (from 44 fewer to 217 fewer)	⊕⊕OO LOW	CRITICAL
Healthy mucosa (follow-up: mean: 26 weeks; assessed with: absence of ulcers)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	18/115 (15.7%)	28/99 (28.3%)	**RR 0.55** (0.33 to 0.94)	**127 fewer per 1000** (from 17 fewer to 189 fewer)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events (follow-up: mean: 26 weeks; assessed with: arthritis or leukopenia or pancreatitis)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	42/161 (26.1%)	29/163 (17.8%)	**RR 1.47** (0.96 to 2.23)	**84 more per 1000** (from 7 fewer to 219 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Unclear risk of bias regarding sequence generation and allocation concealment.
b. Wide CI. Non-optimal sample size.
c. Wide CI and it crosses the critical value 0.75 and/or 1.25.

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(10):CD000545. https://doi.org/10.1002/14651858.CD000545.pub5.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine plus infliximab	Infliximab	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: mean: 26 weeks; assessed with: CDAI <150 or HBI <3)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	102/169 (60.4%)	81/169 (47.9%)	**RR 1.26** (1.03 to 1.54)	**125 more per 1000** (from 14 more to 259 more)	⊕⊕OO LOW	CRITICAL
Steroid-free remission (follow-up: mean: 6 weeks; assessed with: CDAI <150 or HBI <3 without using steroids)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	116/194 (59.8%)	91/189 (48.1%)	**RR 1.23** (1.02 to 1.47)	**111 more per 1000** (from 10 more to 226 more)	⊕⊕OO LOW	CRITICAL
Healthy mucosa (follow-up: mean: 26 weeks; assessed with: absence of ulcers)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	47/111 (42.3%)	28/99 (28.3%)	**RR 1.50** (1.02 to 2.19)	**141 more per 1000** (from 6 more to 337 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events (follow-up: mean: 26 weeks; assessed with: arthritis or leukopenia or pancreatitis)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	37/179 (20.7%)	29/163 (17.8%)	**RR 1.16** (0.75 to 1.80)	**28 more per 1000** (from 44 fewer to 142 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Wide CI and it crosses the critical value 0.75 and/or 1.25.

b. Non-optimal sample size.

Using 5-aminosalicylates to induce remission in patients with active Crohn's disease

Question: sulfasalazine versus placebo for induction of remission in Crohn's disease [a]

Reference: Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2016;(7):CD008870. https//:doi.org/10.1002/14651858.CD008870.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sulfasalazine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Induction of remission or clinical improvement (follow-up: range: 17 weeks to 26 weeks; assessed with: CDAI <150 or response to treatment (a ≥25% decrease in the VHI)												
3	Randomized trials	Serious risk of bias [b]	Serious inconsistency [c]	No serious indirect evidence	Serious imprecision [d]	None	63/141 (44.7%)	43/148 (29.1%)	**RR 1.52** (0.95 to 2.43)	**151 more per 1000** (from 15 fewer to 415 more)	⊕OOO VERY LOW	CRITICAL
Induction of remission (follow-up: range: 17 weeks to 26 weeks; assessed with: CDAI <150)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	55/128 (43.0%)	42/135 (31.1%)	**RR 1.38** (1.01 to 1.90)	**118 more per 1000** (from 3 more to 280 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: range: 17 weeks to 26 weeks)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	0/74 (0.0%)	1/77 (1.3%)	**RR 0.35** (0.01 to 8.38)	**8 fewer per 1000** (from 13 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: range: 17 weeks to 26 weeks)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	10/141 (7.1%)	9/148 (6.1%)	**RR 1.00** (0.26 to 8.83)	**0 fewer per 1000** (from 45 fewer to 476 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients with mild to moderate Crohn's disease. AMSTAR score 10/11.
b. Some limitations regarding incomplete data, selective outcome reporting, and blinding.
c. I2 >40%.
d. Wide CI and it crosses the critical value 1.25 and/or 0.75.
e. Non-optimal sample size.

Reference: Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2016;(7):CD008870. https//:doi.org/10.1002/14651858.CD008870.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sulfasalazine	Corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: mean: 18 weeks; assessed with: CDAI <150)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	55/128 (43.0%)	79/132 (59.8%)	**RR 0.68** (0.51 to 0.91)	**192 fewer per 1000** (from 54 fewer to 293 fewer)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: mean: 18 weeks; assessed with: acne, ecchymosis, moon facies, psychiatric disorder, dyspepsia and hypertension)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	10/74 (13.5%)	27/85 (31.8%)	**RR 0.43** (0.22 to 0.82)	**181 fewer per 1000** (from 57 fewer to 248 fewer)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to very serious adverse events (follow-up: mean: 18 weeks; assessed with: acne, ecchymosis, moon facies, psychiatric disorder, dyspepsia and hypertension)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	9/128 (7.0%)	14/132 (10.6%)	**RR 0.72** (0.33 to 1.59)	**30 fewer per 1000** (from 63 more to 71 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Some limitations regarding incomplete data, selective outcome reporting, and blinding.
b. Wide CI and it crosses the critical value 1.25 and/or 0.75.
c. Wide CI, non-optimal sample size.

Question: sulfasalazine therapy versus combination therapy with sulfasalazine plus steroids to induce remission in patients with Crohn's disease
Reference: Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2016;(7):CD008870. https//:doi.org/10.1002/14651858.CD008870.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sulfasalazine	Sulfasalazine plus steroids	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: mean: 18 weeks; assessed with: CDAI <150)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	27/54 (50.0%)	44/56 (78.6%)	**RR 0.64** (0.47 to 0.86)	**283 fewer per 1000** (from 110 fewer to 416 fewer)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: mean: 18 weeks; assessed with: acne, ecchymosis, moon facies, psychiatric disorder, dyspepsia and hypertension)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	1/54 (1.9%)	2/56 (3.6%)	**RR 0.52** (0.05 to 5.55)	**17 fewer per 1000** (from 34 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Some limitations regarding blinding, selective outcome reporting, and incomplete data.
b. Wide CI, non-optimal sample size. CI crosses critical values 1.25 and/or 0.75

Question: Mesalazine therapy versus sulfasalazine therapy, with or without steroids use, to induce remission in patients with Crohn's disease
Reference: Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2016;(7):CD008870. https//:doi.org/10.1002/14651858.CD008870.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Mesalazine	Sulfasalazine, with or without steroids	Relative (95% CI)	Absolute (95% CI)		
Induction of remission or clinical improvement (assessed with: CDAI <150)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	33/39 (84.6%)	34/41 (82.9%)	**RR 1.02** (0.84 to 1.24)	**17 more per 1000** (from 133 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	3/39 (7.7%)	10/41 (24.4%)	**RR 0.35** (0.11 to 1.09)	**159 fewer per 1000** (from 22 more to 217 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Some limitations regarding blinding, incomplete data, and selective outcome reporting were observed.
b. Non-optimal sample size. CI crosses the critical value 0.75 and/or 1.25.

Using methotrexate to induce remission in patients with active Crohn's disease

Question: Methotrexate use versus placebo use to induce remission in patients with refractory Crohn's disease a

Reference: McDonald JWD, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev. 2014;(8):CD003459. https//:doi.org/10.1002/14651858.CD003459.pub4.b

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Methotrexate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve remission (follow-up: mean: 16 weeks)												
3	Randomized trials	Serious risk of bias [c]	Very serious inconsistency [d]	No serious indirect evidence	Very serious imprecision [e]	None	78/135 (57.8%)	54/91 (59.3%)	**RR 1.02** (0.60 to 1.73)	**12 more per 1000** (from 237 fewer to 433 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: mean: 16 weeks)												
3	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [e]	None	20/135 (14.8%)	1/91 (1.1%)	**RR 6.97** (1.61 to 30.10)	**66 more per 1000** (from 7 more to 320 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 8/11.

b. Patients with active disease (CDAI >150) in the presence or absence of steroid therapy.

c. Some limitations regarding sequence generation and allocation concealment. Serious limitations regarding blinding.

d. I2 >40%.

e. Wide CI and it crosses the critical value 0.75 and/or 1.25. Non-optimal sample size.

Using budesonide to induce remission in patients with active Crohn's disease

Question: Budesonide therapy versus placebo to induce remission in patients with Crohn's disease

Reference: Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(6):CD000296. https//:doi.org/10.1002/14651858.CD000296.pub4.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Budesonide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Induction of remission, 9 mg dose (follow-up: median: 8 weeks; assessed with: CDAI <150)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [b]	Serious imprecision [c]	None	115/246 (46.7%)	29/133 (21.8%)	**RR 1.93** (1.37 to 2.73) [d]	**203 more per 1000** (from 81 more to 377 more)	⊕⊕OO LOW	CRITICAL
Clinical improvement, 9 mg dose (follow-up: mean: 8 weeks; assessed with: a >100 points decrease in the CDAI score or a total CDAI<150)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [b]	Serious imprecision [c]	None	108/185 (58.4%)	22/67 (32.8%)	**RR 1.46** (1.03 to 2.07) [e]	**151 more per 1000** (from 10 more to 351 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: mean: 8 weeks)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [b]	Very serious imprecision [c, f]	None	18/246 (7.3%)	7/133 (5.3%)	**RR 1.14** (0.46 to 2.79) [g]	**7 more per 1000** (from 28 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients with active Crohn's disease (CDAI >150). Patients with ileal, colonic, or ileocolonic Crohn's disease. AMSTAR score 10/11.
b. The meta-analysis included pediatric population.
c. Non-optimal sample size.
d. RR of 2.25 (1.35-3.76) in the case of a 15 mg dose.
e. RR of 2.34 (0.83-6.63) in the case of a 15 mg dose.
f. Wide CI, and it crosses critical values 1.25 and/or 0.75.
g. RR of 1.55 (0.45-5.34) in the case of a 15 mg dose.

Question: Budesonide versus mesalamine for induction of remission in Crohn's disease.
Reference: Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(6):CD000296. https//:doi.org/10.1002/14651858.CD000296.pub4.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Budesonide	Mesalamine	Relative (95% CI)	Absolute (95% CI)		
Induction of remission, 9 mg dose (follow-up: mean: 12 weeks; assessed with: CDAI <150)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very Serious imprecision [a]	None	58/93 (62.4%)	35/89 (39.3%)	**RR 1.59** (1.17 to 2.15) [b]	**232 more per 1000** (from 67 more to 452 more)	⊕⊕OO LOW	CRITICAL
Clinical improvement, 9 mg dose (follow-up: range: 6 weeks to 16 weeks; assessed with: a >100 points decrease in the CDAI score or a total CDAI<150)												
2	Randomized trials	No serious risk of bias	Serious inconsistency [b]	No serious indirect evidence	Serious imprecision [a]	None	180/247 (72.9%)	150/242 (62.0%)	**RR 1.18** (0.99 to 1.42)	**112 more per 1000** (from 6 fewer to 260 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to serious adverse events, 9 mg dose (follow-up: range: 6 weeks to 12 weeks)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a]	None	7/247 (2.8%)	16/242 (6.6%)	**RR 0.43** (0.18 to 1.03)	**38 fewer per 1000** (from 2 more to 54 fewer)	⊕⊕OO LOW	CRITICAL
Induction of remission in severe Crohn's disease (follow-up: mean: 8 weeks; assessed with: CDAI >300)												
2	Randomized trials	No serious risk of bias	Serious inconsistency [c]	No serious indirect evidence	Very serious imprecision [a]	None	30/66 (45.5%)	24/60 (40.0%)	**RR 1.55** (0.28 to 8.60)	**220 more per 1000** (from 288 fewer to 1.000 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Non-optimal sample size. Wide CI, and it crosses the critical value 1.25 and/or 0.75.
b. RR of 1.79 (1.28-2.50) for 16 weeks.
c. I2> 40%.

Question: Budesonide versus conventional steroids for induction of remission in Crohn's disease
Reference: Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(6):CD000296. https//:doi.org/10.1002/14651858.CD000296.pub4.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Budesonide	Conventional steroids	Relative (95% CI)	Absolute (95% CI)		
Induction of remission, 9 mg dose (follow-up: mean: 8 weeks; assessed with: CDAI ≤150)												
8	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [a]	None	211/406 (52.0%)	210/344 (61.0%)	**RR 0.85** (0.75 to 0.97) [b]	**92 fewer per 1000** (from 18 fewer to 153 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawal due to adverse events, 9 mg dose (follow-up: range: 6 weeks to 12 weeks)												
5	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, c]	None	6/259 (2.3%)	13/263 (4.9%)	**RR 0.57** (0.18 to 1.84)	**21 fewer per 1000** (from 41 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Adverse events caused by the use of steroids (follow-up: range: 6 weeks to 12 weeks; assessed with: acne, moon facies and hypertension)												
6	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [a]	None	156/383 (40.7%)	203/320 (63.4%)	**RR 0.64** (0.54 to 0.76)	**228 fewer per 1000** (from 152 fewer to 292 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Induction of remission in severe Crohn's disease, 9 mg dose (follow-up: mean: 8 weeks; assessed with: CDAI >300)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, c]	None	11/41 (26.8%)	13/23 (56.5%)	**RR 0.52** (0.28 to 0.95)	**271 fewer per 1000** (from 28 fewer to 407 fewer)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Wide CI and it crosses the critical value 0.75 and/or 1.25.
b. RR of 1.02 (0.81-1.30) for 12 weeks.
c. Non-optimal sample size.

Oral or intravenous corticosteroids for the induction of remission in patients with active Crohn's disease

Question: oral or intravenous corticosteroids therapy versus placebo or 5-ASA or sulfasalazine therapy to induce remission in patients with Crohn's disease [a]

Reference: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008;(2):CD006792. https://doi.org/10.1002/14651858.CD006792.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Oral or intravenous corticosteroids	Placebo or 5-ASA or sulfasalazine	Relative (95% CI)	Absolute (95% CI)		
Remission: corticosteroids versus placebo (follow-up: mean: 15 weeks; assessed with: CDAI <150)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	[c]	[c]	**RR 1.99** (1.51 to 2.64)	**2 fewer per 1000** (from 2 fewer to 3 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Remission: corticosteroids versus 5-ASA (follow-up: mean: 15 weeks; assessed with: CDAI <150)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	[d]	d	**RR 1.65** (1.33 to 2.03)	**2 fewer per 1000** (from 1 fewer to 2 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawal due to adverse events: corticosteroids versus placebo (follow-up: mean: 15 weeks)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [e]	None	[c]	c	**RR 4.57** (0.75 to 27.83)	**5 fewer per 1000** (from 1 fewer to 28 fewer)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events: corticosteroids versus 5-ASA (follow-up: mean: 15 weeks)												
6	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, e]	None	[f]	f	**RR 1.18** (0.61 to 2.29)	**1 fewer per 1000** (from 1 fewer to 2 fewer)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients with active Crohn's disease: CDAI >150 or Harvey-Bradshaw index. AMSTAR score 8/11.
b. Non-optimal sample size.
c. Not informed by the review. N: 267.
d. Not informed by the review. N: 322.
e. Wide CI, it crosses the critical value 1.25 and/or 0.75.
f. Not informed by the review. N: 478.

Question: What is the safety and efficacy of using mesalamine, sulfasalazine, corticosteroids, and budesonide to induce remission in patients with Crohn's disease? [a]

Reference: Coward S, Kuenzig ME, Hazlewood G, Clement F, McBrien K, Holmes R, et al. Comparative Effectiveness of Mesalamine, Sulfasalazine, Corticosteroids, and Budesonide for the Induction of Remission in Crohn's Disease: A Bayesian Network Meta-analysis. Inflamm Bowel Dis. 2017;23(3):461-72.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Network induction	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: range: 8 weeks to 17 weeks; assessed with: CDAI <150)												
19	Randomized trials	Very serious risk of bias [b]	Serious inconsistency [c]	Serious indirect evidence [d]	Serious imprecision [e]	None	[f]	[g]	It was not possible to estimate the relative CI [h]		⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up: range: 8 weeks to 17 weeks)												
19	Randomized trials	Very serious risk of bias [b]	Serious inconsistency [c]	Serious indirect evidence [d]	Serious imprecision [e]	None	[f]	g	It was not possible to estimate the relative CI [h]		⊕OOO VERY LOW	CRITICAL

IC: Confidence interval.

Explanations

a. Population over 18 years of age. Studies that included combination therapy or were conducted in patients with postoperative recurrence of CD were excluded. Crohn's disease affecting the ileum, the colon, the ileum and colon, the cecum or the rectum. Patients with active Crohn's disease (CDAI = 150 to 400). AMSTAR score 8/11.

b. Some limitations regarding sequence generation and allocation concealment.

c. Heterogeneity range for meta-analyses: 10% to 100%.

d. Network meta-analysis with indirect comparisons.

e. Non-optimal sample size, wide CIs.

f. The network meta-analysis showed that corticosteroids (OR: 3.86; 95% CI: 2.51-6.06), high-dose (>6 mg/d) budesonide (OR: 3.18; 95% CI: 2.11-4.30) and high-dose (>2.4 g/d) mesalamine (OR: 2.11; 95% CI: 1.39-3.31) were significantly superior to placebo in inducing remission.

g. Information not reported by the review.

h. When trying to determine which intervention was the best therapeutic option, corticosteroids ranked first, followed by high-dose bunesonide, high-dose mesalazine, and, finally, with a similar probability, low-dose budesonide, and sulfasalazine. Sulfasalazine therapy was not superior to placebo (OR: 1.56; 95% CI: 0.83-2.88). High-dose budesonide and high-dose corticosteroids were significantly superior to low-dose mesalamine, sulfasalazine, and low-dose budesonide. Corticosteroids were superior to high-dose mesalamine (OR: 1.83; 95% CI: 1.16-2.88). Traditional corticosteroids efficacy was similar to that of high-dose budesonide (OR: 1.21; 95% CI: 0.84-1.76).

i. All pharmacological interventions showed adverse events rates and withdrawal rates similar to placebo: low-dose mesalamine: OR: 1.74 (0.33-8.99); high-dose mesalamine: OR: 1.07 (0.36-3.43); sulfasalazine: OR: 0.79 (0.01-14.36); low-dose budesonide: OR: 0.35 (0.03-2.45); high-dose budesonide: OR: 0.94 (0.36-2.81); and finally, corticosteroids: OR: 2.19 (0.59-8.70). However, withdrawal due to adverse events was 93% and 90% more likely in corticosteroids therapy when compared with budesonide or high-dose mesalamine therapy.

Question N° 3. What are the safest and most effective non-biological interventions to maintain remission of Crohn's disease in patients older than 16 years?

Using 5-aminosalicylates for maintenance of remission in Crohn's disease

Question: 5-aminosalicylates therapy versus placebo for maintenance of remission in Crohn's disease [a]

Reference: Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically- induced remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(9):CD003715. https://doi.org/10.1002/14651858.CD003715.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	5-aminosalicylates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical or endoscopic recurrence (follow-up: mean: 12 months; assessed with: CDAI >150 or a >60 points increase or a Harvey-Bradshaw Index >4)												
11	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	No serious imprecision	Publication bias was highly suspected [b]	526/998 (52.7%)	544/1016 (53.5%)	**RR 0.98** (0.91 to 1.07)	**11 fewer per 1000** (from 37 more to 48 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (follow-up: range: 12 months to 24 months)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	3/293 (1.0%)	2/283 (0.7%)	**RR 1.43** (0.24 to 8.44)	**3 more per 1000** (from 5 fewer to 53 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events (follow-up: range: 12 months to 24 months)												
10	Randomized trials	No serious risk of bias	Serious inconsistency [e]	No serious indirect evidence	Serious imprecision [d]	None	127/917 (13.8%)	119/916 (13.0%)	**RR 1.11** (0.88 to 1.38)	**14 more per 1000** (from 16 fewer to 49 more)	⊕⊕OO LOW	CRITICAL
Clinical or endoscopic recurrence (follow-up: mean: 24 months; assessed with: CDAI >150 or a >60 points increase or a Harvey-Bradshaw Index >4)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	54/80 (67.5%)	55/81 (67.9%)	**RR 0.99** (0.80 to 1.23)	**7 fewer per 1000** (from 136 fewer to 156 more)	⊕⊕⊕O MODERATE	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Minimum duration of treatment: 6 months. Patients with controlled Crohn's disease during 1 to 28 months prior to being included in the study. AMSTAR score 9/11.
b. Evident asymmetric funnel plot.
c. Non-optimal sample size.
d. Wide CI, and it crosses the critical value 1.25 y/0 0.75.
e. I2>40%.

Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease

Question: azathioprine or 6-mercaptopurine versus placebo to maintain remission in patients with Crohn's disease [a]

Reference: Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(10):CD000067. https://doi.org/10.1002/14651858.CD000067.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission (follow-up: range: 6 months to 18 months; assessed with: CDAI <150)												
8	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	175/244 (71.7%)	168/288 (58.3%)	**RR 1.25** (1.11 to 1.42)	**146 more per 1000** (from 64 more to 245 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse events (follow-up: range: 6 months to 18 months)												
4	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	22/245 (9.0%)	9/311 (2.9%)	**RR 2.45** (1.22 to 4.90)	**42 more per 1000** (from 6 more to 113 more)	⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: range: 6 months to 18 months)												
6	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	28/299 (9.4%)	9/362 (2.5%)	**RR 3.12** (1.59 to 6.09)	**53 more per 1000** (from 15 more to 127 more)	⊕⊕◯◯ LOW	CRITICAL
Steroid dose tapering (follow-up: range: 6 months to 18 months)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	13/15 (86.7%)	8/15 (53.3%)	**RR 1.59** (0.97 to 2.61)	**315 more per 1000** (FROM 16 fewer to 859 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients in remission for 3 to 6 months prior to their inclusion in the study and without steroid use or with minimal steroid dose use. AMSTAR score 9/11.

b. Some limitations in the participants or staff blinding domain.

c. Wide CI, and it crosses the critical value 1.25 and/or 0.75.

d. Wide confidence interval, non-optimal sample size.

Question: azathioprine or 6-mercaptopurine therapy versus mesalazine or sulfasalazine therapy for maintenance of remission in Crohn's disease
Reference: Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(10):CD000067. https://doi.org/10.1002/14651858.CD000067.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	Mesalazine or sulfasalazine	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission (follow-up: mean: 12 months; assessed with: CDAI <150)												
3	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	61/88 (69.3%)	52/78 (66.7%)	**RR 1.09** (0.88 to 1.34)	**60 more per 1000** (from 80 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: mean: 12 months)												
3	Randomized trials	Serious risk of bias [a]	Serious inconsistency [c]	No serious indirect evidence	Very serious imprecision [b]	None	18/143 (12.6%)	10/147 (6.8%)	**RR 1.86** (0.87 to 3.97)	**59 more per 1000** (from 9 fewer to 202 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: mean: 12 months)												
3	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	16/125 (12.8%)	0/110 (0.0%)	**RR 9.37** (1.84 to 47.72)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Some limitations in the participants or staff blinding domain.
b. Wide CI, and it crosses the critical value 1.25 and/or 0.75. Non-optimal sample size.
c. I2 >40%.

Question: azathioprine plus infliximab combination therapy versus infliximab therapy for maintenance of remission in Crohn's disease
Reference: Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(10):CD000067. https://doi.org/10.1002/14651858.CD000067.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine plus infliximab	Infliximab	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission (follow-up: mean: 12 months; assessed with: CDAI <150)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	13/16 (81.3%)	16/20 (80.0%)	**RR 1.02** (0.74 to 1.40)	**16 more per 1000** (from 208 fewer to 320 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up: mean: 12 months)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	1/25 (4.0%)	0/20 (0.0%)	**RR 2.42** (0.10 to 56.46)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: mean: 12 months)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	1/25 (4.0%)	0/20 (0.0%)	**RR 2.42** (0.10 to 56.46)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Participants and staff blinding errors.
b. Non-optimal sample size. Wide CI, and it crosses the critical value 1.25 and/or 0.75.

Using budesonide for maintenance of remission in Crohn's disease

Question: budesonide vs placebo for maintenance of remission in Crohn's disease [a]

Reference: Kuenzig ME, Rezaie A, Seow CH, Otley AR, Steinhart AH, Griffiths AM, et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;(8):CD002913. https://doi.org/10.1002/14651858.CD002913.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Budesonide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission, 6 mg dose (follow-up: median: 12 months; assessed with: CDAI ≤150)												
5	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	114/208 (54.8%)	101/212 (47.6%)	**RR 1.13** (0.94 to 1.35) [d]	**62 more por 1000** (from 29 fewer to 167 more)	⊕⊕OO LOW	CRITICAL
Changes in the CDAI score compared to the baseline score, 6 mg dose (follow-up: mean: 12 months; assessed with: CDAI; scale: from 0 to 600)												
5	Randomized trials	Serious risk of bias [b]	Serious inconsistency [e]	No serious indirect evidence	Serious imprecision [f]	None	208	212	-	MD **23.49 CDAI fewer** (46.65 fewer to 0.32 fewer) [g]	⊕OOO VERY LOW	CRITICAL
Time to relapse, 6 mg dose (follow-up: mean: 12 months; assessed with: days without active disease; scale: from 0 to 1000)												
5	Randomized trials	Serious risk of bias [b]	Serious inconsistency [e]	No serious indirect evidence	Serious imprecision [f]	None	83	88	-	MD **59.93 days more** (19.02 more to 100.84 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events, 6 mg dose (follow-up: mean: 12 months)												
5	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	20/231 (8.7%)	19/235 (8.1%)	**RR 1.08** (0.60 to 1.95)	**6 more per 1000** (from 32 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Maintenance of clinical remission, 9 mg dose versus 6 mg dose (follow-up: mean: 12 months; assessed with: CDAI ≤150)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, f]	None	66/81 (81.5%)	58/76 (76.3%)	**RR 1.07** (0.91 to 1.26)	**53 more per 1000** (from 69 fewer to 198 more)	⊕OOO VERY LOW	CRITICAL
Changes in CDAI score, 9 mg dose versus 6 mg dose (follow-up: mean: 12 months; assessed with: CDAI; scale: from 0 to 600)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, f]	None	81	76	-	MD **18 CDAI fewer** (41.06 fewer to 5.06 higher)	⊕OOO VERY LOW	CRITICAL

Withdrawal due to adverse events, 9 mg versus 6 mg dose (follow-up: mean: 12 months)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, f]	None	1/81 (1.2%)	3/76 (3.9%)	**RR 0.31** (0.03 to 2.94)	**27 fewer per 1000** (from 38 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Maintenance of clinical remission, 9 mg budesonide versus prednisolone 40mg/d (follow-up: mean: 12 months; assessed with: CDAI <150)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, f]	None	23/46 (50.0%)	28/44 (63.6%)	**RR 0.79** (0.55 to 1.13) [h]	**134 fewer per 1000** (from 83 more to 286 fewer)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events, 9 mg budesonide versus prednisolone 40mg/d (follow-up: mean: 12 months)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, f]	None	4/46 (8.7%)	0/44 (0.0%)	**RR 8.62** (0.48 to 155.52)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; MD; Mean difference; RR: Risk ratio.

Explanations

a. Patients with proximal colon, ileocecal or ileal Crohn's disease. AMSTAR score 10/11.
b. Some limitations in participants and staff blinding.
c. Wide CI, and it crosses the critical value 1.25 and/or 0.75.
d. RR for 6 months: 1.15 (0.95-1.39).
e. I2 >40%.
f. Non-optimal sample size.
g. Change in CDAI score at 6 months: -24.30 (-46.31, -2.29).
h. RR for 6 months: 0.79 (0.56-1.12).

Using methotrexate to maintain remission in patients with Crohn's disease

Question: Methotrexate versus any other intervention for maintenance of remission in Crohn's disease [a]

Reference: Patel V, Wang Y, MacDonald JK, McDonald JWD, Chande N. Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;(8):CD006884. https://doi.org/10.1002/14651858.CD006884.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Methotrexate	Any other intervention	Relative (95% CI)	Absolute (95% CI)		
Efficacy for maintenance of remission compared to placebo (follow-up: range: 36 weeks to 40 weeks; assessed with: CDAI <150)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	35/50 (70.0%)	22/48 (45.8%)	**RR 1.57** (1.10 to 2.23)	**261 more per 1000** (from 46 more to 564 more)	⊕OOO VERY LOW	CRITICAL
Efficacy for maintenance of remission compared to 6-MP (follow-up: range: 36 weeks to 76 weeks; assessed with: CDAI <150)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	17/22 (77.3%)	16/28 (57.1%)	**RR 1.36** (0.92 to 2.00)	**206 more per 1000** (from 46 fewer to 571 more)	⊕OOO VERY LOW	CRITICAL
Efficacy for maintenance of remission compared to 5-ASA (follow-up: mean: 30 weeks; assessed with: CDAI <150)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	8/12 (66.7%)	0/1 (0.0%)	**RR 2.62** (0.23 to 29.79)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL
Efficacy of methotrexate plus infliximab for maintenance of remission compared to infliximab monotherapy (follow-up: range: 36 weeks to 48 weeks; assessed with: CDAI <150)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	40/74 (54.1%)	38/71 (53.5%)	**RR 1.02** (0.76 to 1.38)	**11 more per 1000** (from 128 fewer to 203 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 8/11.

b. Some limitations regarding blinding of participants and staff.

c. Non-optimal sample size. Wide CI, and it crosses the critical value 1.25 and/or 0.75.

Using elemental nutrition (also elemental diet, a type o enteral nutrition) to maintain remission in patients with Crohn's disease

Question: Using elemental nutrition for maintenance of remission in Crohn's disease versus any other intervention [a, b]

Reference: Tsertsvadze A, Gurung T, Court R, Clarke A, Sutcliffe P. Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis. Health Technol Assess. 2015;19(26)1-38.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Elemental nutrition	Other intervention	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission (elemental nutrition vs. no intervention) (follow-up: range: 6 months to 24 months; assessed with: CDAI score ≤150 alone or with additional criteria [e.g., absence of diarrhea or abdominal pain or ESR <20 mm/h] or Rutgeerts score <2)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	27/32 (84.4%)	23/33 (69.7%)	**RR 1.21** (0.92 to 1.58) [f]	**146 more per 1000** (from 56 fewer to 404 more)	⊕OOO VERY LOW	CRITICAL
Relapse (elemental nutrition vs. no intervention) (follow-up: range: 12 months to 24 months; assessed with: CDAI score ≥200 points alone or with additional criteria [need to start the administration of another drug, a 100 points increase in CDAI score compared to the baseline score] or a IOIBD score ≥2 or a CDAI score >150 points at endpoint or need for surgery or increased steroid dose)												
2	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d]	None	21/58 (36.2%)	37/58 (63.8%)	**RR 0.57** (0.38 a 0.84)	**274 fewer per 1000** (from 102 fewer to 396 fewer)	⊕⊕OO LOW	CRITICAL
Maintenance of remission (elemental nutrition vs. 6-MP) (follow-up: range: 6 months to 24 months; assessed with: CDAI score ≤150 alone or with additional criteria [e.g., absence of diarrhea or abdominal pain or ESR <20 mm/h] or Rutgeerts score <2)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	27/32 (84.4%)	24/30 (80.0%)	**RR 1,05** (0.83 a 1.33) [g]	**40 more per 1000** (from 136 fewer to 264 more)	⊕OOO VERY LOW	CRITICAL
Relapse (elemental nutrition vs. 6-MP) (follow-up: mean: 24 months; assessed with: CDAI score ≥200 points alone or with additional criteria [need to start the administration of another drug, a 100 points increase in CDAI score compared to the baseline score] or a IOIBD score ≥2 or a CDAI score >150 points at endpoint or need for surgery or increased steroid dose)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	12/32 (37.5%)	7/30 (23.3%)	**RR 1.61** (0.73 to 3.53)	**142 more per 1000** (from 63 fewer to 590 more)	⊕OOO VERY LOW	CRITICAL
Need for surgery (elemental nutrition vs. no intervention) (follow-up: mean: 24 months)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	1/32 (3.1%)	1/33 (3.0%)	**RR 1,03** (0.06 a 15.79)	**1 more per 1000** (from 28 fewer to 448 more)	⊕OOO VERY LOW	CRITICAL

Need for surgery (elemental nutrition vs. 6-MP) (follow-up: mean: 24 months)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	1/32 (3.1%)	1/30 (3.3%)	**RR 0.93** (0.06 to 14.32)	**2 fewer per 1000** (from 31 fewer to 444 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal from steroids (elemental nutrition vs. polymeric enteral nutrition formula) (follow-up: mean: 12 months)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	8/19 (42.1%)	6/14 (42.9%)	**RR 0.98** (0.44 a 2.19)	**9 fewer per 1000** (from 240 fewer to 510 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up: mean: 12 months; assessed with: Inflammatory Bowel Disease Questionnaire (IBDQ); scale: from 32 to 224)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [e]	None	26	25	-	MD **4.9 IBDQ higher** (6.3 higher to 16,1 higher)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio.

Explanations:

a. Three of the studies were RCTs. In these trials, the intervention consisted of administering elemental diet with usual diet. Controls received usual diet, 6-MP or polymeric enteral nutrition formula. AMSTAR score 7/11.

b. Patients aged 29 to 44 years were included; 23% to 68% were women with Crohn's disease in the large and small intestine.

c. Some limitations regarding blinding of participants and staff in the RCTs. Limitations in the selective outcome reporting domain.

d. CI crosses the critical value 1.25 and/or 0.75.

e. Non-optimal sample size.

f. For 6 months. RR for 12 months: 1.37 (95% CI: 0.86-2.17); RR for 24 months: 2.06 (95% CI: 1.00-4.43).

g. For 6 months. RR for 12 months: 0.93 (95% CI: 0.64-1.35); RR for 24 months: 0.77 (95% CI: 0.46-1.27).

Using probiotics for maintenance of remission in Crohn's disease

Question: Probiotics versus placebo to treat patients with Crohn's disease [a]

Reference: Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(4):389-400.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Probiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Prevention of relapse (follow-up: mean: 12 months; assessed with: CDAI >220 or a CDAI 150-220 with an ≥70 points increase compared to the baseline score)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c, d]	None	52/100 (52.0%)	50/95 (52.6%)	**RR 1.03** (0.70 to 1.51)	**16 more per 1000** (from 158 fewer to 268 more)	⊕⊕OO LOW	CRITICAL
Adverse events (follow-up: mean: 12 months; assessed with: gastrointestinal symptoms)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	49/84 (58.3%)	45/81 (55.6%)	**RR 1.05** (0.80 to 1.37)	**28 more per 1000** (from 111 fewer to 206 more)	⊕OOO VERY LOW	CRITICAL
Prevention of clinical relapse after surgery (follow-up: range: 3 months to 12 months; assessed with: need for additional therapy or CDAI >15 or a >70 points increase compared to the baseline score)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	28/105 (26.7%)	28/108 (25.9%)	**RR 1.06** (0.59 to 1.92)	**16 more per 1000** (from 106 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Prevention of endoscopic relapse after surgery (follow-up: range: 3 months to 12 months; assessed with: Rutgeerts score >2)												
4	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	94/163 (57.7%)	96/170 (56.5%)	**RR 1.04** (0.82 to 1.31)	**23 more per 1000** (from 102 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 9/11.

b. Some limitations in the sequence generation and allocation concealment domains.

c. CI crosses the critical value 1.25 and/or 0.75.

d. Non-optimal sample size.

Use of corticosteroids for maintenance of remission in Crohn's disease

Question: oral corticosteroids versus placebo for maintenance of remission in Crohn's disease [a]

Reference: Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2003;(4):CD000301. https://doi.org/10.1002/14651858.CD000301.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Corticosteroids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical relapse (follow-up: range: 6 months; assessed with: CDAI >150 or a >100 points increase compared to the baseline score)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c]	None	23/142 (16.2%)	33/161 (20.5%)	**RR 0.71** (0.38 to 1,31) [d]	**59 fewer per 1000** (from 64 more to 127 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients with a CDAI <150 and without symptoms. AMSTAR score 8/11.

b. One of the three studies included in the review was classified as having a very high risk of bias.

c. Wide CI, and it crosses the critical value 1.25 and/or 0.75. Non-optimal sample size.

d. RR for 12 months: 0.82 (0.47-1.44); RR for 24 months: 0.72 (0.39-1.35).

Safety and efficacy of different strategies to induce and maintain remission in patients with Crohn's disease.

Question: What is the most effective strategy to induce and maintain remission in patients with Crohn's disease? [a, b]

Reference: Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015;148(2):344-54.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Strategy to induce and maintain remission	Placebo	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: range: 4 weeks to 17 weeks; assessed with: CDAI score less than or equal to 150 points or as defined by the authors of each study)												
24	Randomized trials	Serious risk of bias [c]	Serious inconsistency [d]	Serious indirect evidence [e]	Serious imprecision [f]	None	1002/2888 (34.7%)	611/1806 (33.8%)	It was not possible to estimate the relative CI [g]		⊕OOO VERY LOW	CRITICAL
Maintenance of remission (follow-up: mean: 24 weeks; assessed with: keeping a CDAI score less than or equal to 150 points or as defined by the authors of each study)												
24	Randomized trials	Serious risk of bias [c]	Serious inconsistency [d]	Serious indirect evidence [e]	Serious imprecision [f]	None	1105/2548 (43.4%)	605/2139 (28.3%)	It was not possible to estimate the relative CI [h]		⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events associated with the therapy (assessed with: based on clinical judgement)												
24	Randomized trials	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [e]	Serious imprecision [i]	None	[j]	[j]	It was not possible to estimate the relative CI [h]		⊕OOO VERY LOW	CRITICAL

CI: Confidence interval.

Explanations

a. The use of azathioprine/6-mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab and vedolizumab as monotherapy or as part of combination therapy were evaluated. Natalizumab was not included because the available studies recruited patients who failed to respond to anti-TNF therapy. At the time of inclusion, patients showed disease activity, defined as having a CDAI score between 150 and 450 points or a HBI >7 or patients with CD disease refractory to steroid or azathioprine therapy or who were steroid-dependent. AMSTAR score 7/11.

b. 15 studies evaluated anti-TNF therapy; 4, vedolizumab; 15 immunosuppressants, and 5, combination therapy.

c. Some limitations in the sequence generation, allocation concealment, and blinding of participants and personnel domains.

d. The SD for the log (OR) reflecting between-study variance was 0.25 (95% CI 0.03-0.56), indicating significant heterogeneity.

e. This was a network meta-analysis.

f. Wide confidence interval, and it crosses the critical value 0.75 or 1.25.

g. Azathioprine/6-mercaptopurine and methotrexate efficacy to induce remission was similar to that of placebo (OR: 1.2, 95% CI: 0.76-2.1; and OR: 1.5, 95% CI: 0.72-3.2, respectively). The likelihood of infliximab (OR: 2.8; 95% CI: 1.4-7.2), infliximab plus azathioprine (OR: 4.3; 95% CI: 2.0-9.8), adalimumab (OR: 2.9; 95% CI: 1.6-5.5) and vedolizumab (OR: 2.0; 95% CI: 1.2-3.3) interventions being superior to placebo was >99%.

h. The likelihood of azathioprine/6-mercaptopurine (OR: 1.7; 95% CI: 1.3-2.6), methotrexate (OR: 2.4; 95% CI: 1.1-4.8), infliximab (OR: 2.8; 95% CI: 1.8-4.5), certolizumab (OR: 2.0; 95% CI: 1.4-3.0), infliximab plus azathioprine (OR: 5.2; 95% CI: 2.8-11.0), adalimumab (OR: 5.1; 95% CI: 3.3-8.1) and vedolizumab (OR: 2.2; 95% CI: 1.3-3.7) bing superior to placebo in maintaining remission was >99%.

i. Non-optimal sample size.

j. Data not provided by the authors.

k. The frequency of withdrawal due to adverse events was higher in the case of azathioprine/6-mercaptopurine (OR: 3.9; 95% CI: 2.4-6.4), methotrexate (OR: 13; 95% CI: 3.2-109), infliximab (OR: 2.7; 95% CI: 1.6-4.7) and infliximab plus azathioprine (OR: 3.2; 95% CI: 1.6-6.1) when compared with placebo.

Question N° 4. What is the safety and efficacy of using biological drugs to treat moderate to severe Crohn's disease in patients older than 16 years?

anti-TNF agents (infliximab, adalimumab or certolizumab pegol) or anti-integrins (natalizumab or vedolizumab) or IL-12/23 antagonists (ustekinumab) versus placebo for induction or maintenance of remission in moderate or severe luminal Crohn's disease

Question: anti-TNF agents (infliximab, adalimumab or certolizumab pegol) or anti-integrins (natalizumab or vedolizumab) or IL-12/23 antagonists (ustekinumab) versus placebo for induction or maintenance of remission in moderate or severe luminal Crohn's disease [a]

Reference: Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014;89(12):1621-35.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	anti-TNF agents (IFX, ADA or CZ) or anti-integrins (NAT or VEDO) or IL-12/23 antagonists (UST)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Induction of remission (follow-up: mean: 4 weeks to 17 weeks; assessed with: CDAI <150 or a decrease by more than 100 or 70 points)[b]												
11	Randomized trials	No serious risk of bias	Serious inconsistency [c]	No serious indirect evidence	Serious imprecision [d]	None	571/1579 (36.2%)	245/951 (25.8%)	**RR 1.44** (1.19 to 1.75) [e, f]	**113 more per 1000** (from 49 more to 193 more)	⊕⊕OO LOW	CRITICAL
Maintenance of remission (follow-up: mean: 60 weeks; assessed with: keeping a CDAI <150 points or a decrease by more than 100 or 70 points compared to the baseline score)[g]												
9	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, h]	None	620/1402 (44.2%)	212/963 (22.0%)	**RR 2,06** (1.73 a 2.45) [i, j]	**233 more per 1000** (from 161 more to 319 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Biologic-naïve patients; they had not been exposed to anti-TNF agents (IFX, ADA or CZP), anti-integrins (NAT or VEDO) or anti-IL-12/23 (UST). Patients had colonic, ileal or ileocolonic Crohn's disease. All studies included in the review allowed concomitant use of immunomodulators, corticosteroids and/or 5-aminosalicylates. AMSTAR score 9/11.

b. IFX (2 studies), ADA (2 studies), CZP (2 studies), UST (1 study), NAT (2 studies) and VEDO (2 studies).

c. I2 >40%.

d. CI crosses 1.25 and/or 0.75.

e. When the analysis was performed according to drug class, anti-TNF: OR: 1.63; 95% CI: 1.24-2.14; anti-integrins: OR: 1.20; 95% CI: 0.97-1.49, and IL-12/23 antagonist ustekinumab: OR: 0.79; 95% CI: 0.44-1.39. When the analysis was performed considering each biologic drug independently, IFX: RR: 3.11; 95% CI: 0.72-13.45; ADA: RR: 2.30; 95% CI: 1.27-4.16; CZP: RR: 1.31; 95% CI: 1.06-1.65; UST: RR: 0.79; 95% CI: 0.44-1.39; NAT: RR: 1.19; 95% CI: 0.94-1.52, and VEDO: RR: 1.76; 95% CI: 1.11-2.78.

f. When the network analysis was performed it was found that IFX (RR: 6.11; 95% CI: 2.49-18.29) and ADA (RR: 2.98; 95% CI: 1.12-8.18) were superior to placebo in terms of inducing remission, while CZP (RR: 1.48; 95% CI: 0.76-2.93), NAT (RR: 1.36; 95% CI: 0.69-2.86), VEDO (RR: 1.40; 95% CI: 0.63-3.28) or ustekinumab (RR: 0.61; 95% CI: 0.15-2.49) were not superior to placebo. IFX had an 86% probability of being the best therapeutic alternative, followed by ADA, with a 16% probability.

g. IFX (2 studies), ADA (3 studies), CZP (1 study), UST (1 study), NAT (1 study) and VEDO (1 study).

h. Non-optimal sample size.
i. When the analysis was conducted according to drug class, anti-TNF (OR: 2.18; 95% CI: 1.65-2.88) and anti-IL-12/23 ustekinumab (OR: 2.09; 95% CI: 1.49-2.92), but anti-integrins (OR: 1.52; 95% CI: 0.96-2.42) were not. When the analysis was performed considering each biologic drug independently, IFX (RR: 2.15 95% CI: 1.52-3.05), ADA (RR: 2.65; 95% CI: 1.63-4.32), CZP (RR: 1.73; 95% CI: 1.35-2.22), UST (RR: 1.52; 95% CI: 0.96-2.42), NAT (RR: 2.46; 95% CI: 1.80-3.37) and VEDO (RR: 1.75; 95% CI: 1.25-2.44).
j. In the network analysis ADA (RR: 5.16; 95% CI: 1.78-18.00) was superior to placebo, while IFX (RR: 3.31; 95% CI: 0.98-14.01), CZP (RR: 2.26; 95% CI: 0.38-13.57), NAT (RR: 4.26; 95% CI: 0.71-25.49), VEDO (RR: 2.20; 95% CI: 0.37-13.54) and UST (RR: 0.91; 95% CI: 0.31-12.31) were not. ADA had a 48% probability of being the best therapeutic alternative, followed by NAT and IFX, with a 29 and a 11% probability, respectively.

TNF inhibitors (infliximab or adalimumab) versus placebo to treat fistulizing Crohn's disease

Question: anti-TNF agents (infliximab or adalimumab) versus placebo to treat fistulizing Crohn's disease [a]

Reference: de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis. 2016;18(7):667-75.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Anti-TNF agents (infliximab or adalimumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete fistula closure (follow-up: range: 4 weeks to 26 weeks; assessed with: proportion of patients with complete closure of the fistula)												
4	Randomized trials	Serious risk of bias [b]	No serious inconsistency [c]	No serious indirect evidence	Serious imprecision [d]	None	54/179 (30.2%)	13/109 (11.9%)	**RR 2.40** (1.36 to 4.22)	**167 more per 1000** (from 43 more to 384 more)	⊕⊕OO LOW	CRITICAL
Partial fistula closure (follow-up: range: 4 weeks to 18 weeks; assessed with: improvement of 50% or more)												
3	Randomized trials	Serious risk of bias [e]	Serious inconsistency [f]	No serious indirect evidence	Very serious imprecision [d]	None	48/109 (44.0%)	15/62 (24.2%)	**RR 1.27** (0.51 to 3.14)	**65 more per 1000** (from 119 fewer to 518 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Patients were administered either infliximab 5 mg/kg or adalimumab 40 mg to 80 mg. AMSTAR score 8/11.
b. 3 of 4 studies were sponsored by the pharmaceutical industry.
c. I2=10% and p-value= 0.34. CIs overlap.
d. CI crosses the critical value 1.25 and/or 0.75.
e. 2 of 3 studies were sponsored by the pharmaceutical industry.
f. I2 >50%.

anti-IL-12/23p40 antibodies versus placebo for induction of remission in moderate to severe Crohn's disease

Question: anti-IL-12/23p40 antibodies versus placebo to induce remission in patients with moderate to severe Crohn's disease [a]

Reference: MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016;(11):CD007572. https://doi.org/10.1002/14651858.CD007572.pub3.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	anti-IL-12/23p40 antibodies	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to induce clinical remission using briakinumab (follow-up: mean: 6 weeks; assessed with: CDAI score <150)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	154/184 (83.7%)	42/46 (91.3%)	**RR 0.92** (0.83 to 1.03)	**73 fewer per 1000** (from 27 more to 155 fewer)	⊕⊕OO LOW	CRITICAL
Failure to induce clinical response using briakinumab (follow-up: mean: 6 weeks; assessed with: a ≥100 points decrease in CDAI score)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	117/184 (63.6%)	36/46 (78.3%)	**RR 0.82** (0.67 to 0.99)	**141 fewer per 1000** (from 8 fewer to 258 fewer)	⊕⊕OO LOW	CRITICAL
Occurrence of serious adverse events associated with briakinumab use (follow-up: mean: 6 weeks; assessed with: this information is not reported by the authors of the review)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	16/263 (6.1%)	6/62 (9.7%)	**RR 0.64** (0.26 to 1.56)	**35 fewer per 1000** (from 54 more to 72 fewer)	⊕⊕OO LOW	CRITICAL
Withdrawal due to serious adverse events when using briakinumab (follow-up: mean: 6 weeks; assessed with: this information is not reported by the authors of the review)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	8/263 (3.0%)	4/62 (6.5%)	**RR 0.47** (0.15 to 1.53)	**34 fewer per 1000** (from 34 more to 55 fewer)	⊕⊕OO LOW	CRITICAL
Failure to induce clinical remission using ustekinumab (follow-up: mean: 6 weeks; assessed with: CDAI score <150)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	1049/1332 (78.8%)	539/615 (87.6%)	**RR 0.91** (0.86 to 0.95)	**79 fewer per 1000** (from 44 fewer to 123 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Failure to induce clinical response using ustekinumab (follow-up: mean: 6 weeks; assessed with: a ≥70 points decrease in CDAI score)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	662/1332 (49.7%)	415/615 (67.5%)	**RR 0.73** (0.66 to 0.81)	**182 fewer per 1000** (from 128 fewer to 229 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow-up: mean: 6 weeks; assessed with: this information is not reported by the authors of the review)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	75/1386 (5.4%)	41/637 (6.4%)	**RR 0.83** (0.58 to 1.20)	**11 fewer per 1000** (from 13 more to 27 fewer)	⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to serious adverse events (follow-up: mean: 6 weeks; assessed with: this information is not reported by the authors of the review)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	10/473 (2.1%)	10/184 (5.4%)	**RR 0.44** (0.18 to 1.05)	**30 fewer per 1000** (from 3 more to 45 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 9/11. Ustekinumab was used in patients with moderate to severe Crohn's disease and who had failed to respond to therapy with anti-TNF agents or corticosteroids or immunosuppressants, and briakinumab in patients with moderate to severe Crohn's disease and prior exposure to anti-TNF rugs or corticosteroids or immunosuppressants.

b. Non-optimal sample size.

c. CI crosses the critical value 0.75 and/or 1.25.

Safety of biological therapy in patients with moderate to severe inflammatory bowel disease

Question: Does the use of biological therapy increase the risk of developing infections or malignancies in patients with inflammatory bowel disease? [a, b]

Reference: Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, et al. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol. 2016;14(10):1385-97.e10.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Safety of biologic drugs	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Serious infections (follow-up: range: 1 month to 24 months; assessed with: infection requiring hospitalization, use of intravenous antibiotics or resulting in death)[c]												
44	Randomized trials	Serious risk of bias [d]	No serious inconsistency	No serious indirect evidence	Serious imprecision [e]	None	180/8627 (2.1%)	130/5405 (2.4%)	**OR 0,89** (0.71 to 1.12) [f]	**3 fewer per 1000** (from 3 more to 7 fewer)	⊕⊕OO LOW	CRITICAL
Opportunistic infections (follow-up: range: 1 month to 24 months; assessed with: defined as the presence of *Mycobacterium tuberculosis*; infection by John Cunningham virus, infection by *Nocardia*, cytomegalovirus or Epstein-Barr infection; oral or esophageal candida infection; varicella-zoster or herpes zoster infection; *Pneumocystis jirovecii* or *Histoplasma capsulatum* infection or pneumonia caused by any species of *Legionella* bacteria, or herpes simplex infection, or any other infection considered an opportunistic infection)												
24	Randomized trials	Serious risk of bias [d]	No serious inconsistency	No serious indirect evidence	Serious imprecision [e]	None	60/5378 (1.1%)	21/3454 (0.6%)	**OR 1.90** (1.21 to 3.01) [g]	**5 more per 1000** (from 1 more to 12 more)	⊕⊕OO LOW	CRITICAL
Tuberculosis (follow-up: range: 1 month to 24 months; assessed with: confirmed diagnosis of TB, TB reactivation, miliary or cavitary pulmonary TB or TB affecting any other organ)												
9	Randomized trials	Serious risk of bias [d]	No serious inconsistency	Serious indirect evidence [h]	Very serious imprecision [e]	None	9/2500 (0.4%)	1/14285 (0.0%)	**OR 2.04** (0.71 to 5.89)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Any infection (follow-up: range: 1 month to 24 months; assessed with: composite outcome defined as the presences of any of the infection previously described)												
47	Randomized trials	Serious risk of bias [d]	No serious inconsistency	No serious indirect evidence	Serious imprecision [e]	None	2990/8897 (33.6%)	1708/5543 (30.8%)	**OR 1.19** (1.10 to 1.29) [i]	**38 more per 1000** (from 21 more to 57 more)	⊕⊕OO LOW	CRITICAL
Malignancy (follow-up: range: 1 month to 24 months; assessed with: proportion of patients with a confirmed diagnosis of any type of cancer)												
23	Randomized trials	Serious risk of bias [d]	No serious inconsistency	Serious indirect evidence [h]	Serious imprecision [e]	None	26/5718 (0.5%)	21/3737 (0.6%)	**OR 0.90** (0.54 to 1.50)	**1 fewer per 1000** (from 3 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. Adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, and vedolizumab. AMSTAR score 10/11.
b. Patients' age ranged from 27 to 43 years, disease duration ranged from 4.7 to 12.4 years and follow-up period ranged from 1 to 24 months.
c. Total observation period of 8000 people/ years (6.5 months per patient on average).
d. 45% and 39% of the studies included in the review were classified as having a high risk of bias in the incomplete data domain and in the "other threats to validity" domain, respectively. Overall, the authors of the review consider that 65% of the studies have some type of limitation in their design or execution.
e. CI crosses the critical value 0.75 and/or 1.25.
f. When subgroup analysis was performed: limited to Crohn's disease OR: 0.87; 95% CI: 0.65-1.14; by type of anti-TNF drug: OR: 0.90; 95% CI: 0.69-1.17; versus anti-integrin: OR: 0.87; 95% CI: 0.54-1.39; p-value for subgroup difference = 0.89 and p-value by type of biologic drug = 0.76.
g. When subgroup analysis was performed: limited to Crohn's disease: OR: 2.39; 95% CI: 1.32-4.34; by type of anti-TNF drug: OR: 1.89; 95% CI: 1.15-3.12; versus anti-integrin: OR: 1.99; 95% CI: 0.64-6.18; p-value for subgroup difference = 0.94 and p-value by type of biologic drug = 0.35.
h. The authors of the systematic review do not report specific outcomes for patients with Crohn's disease.
i. When subgroup analysis was performed: limited to Crohn's disease: OR: 1.19, 95% CI: 1.09-1.31; by type of anti-TNF drug: OR: 1.21, 95% CI: 1.10-1.33; versus anti-integrin: OR: 1.14, 95% CI: 0.99-1.32; p-value for subgroup difference = 0.49 and p-value by type of biologic drug = 0.63.

Efficacy of using a second anti-TNF agent in patients with inflammatory bowel disease and treatment failure or intolerance to a first biologic drug

Question: what is the safety and efficacy of using a second anti-TNF agent in patients with inflammatory bowel disease and treatment failure or intolerance to a first biologic drug? [a]

Reference: Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015;41(7):613-23.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Second biologic drug or failure to first biologic drug	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Overall remission rate after primary failure to IFX and switching to ADA (follow-up: range: 4 weeks to 208 weeks; assessed with: remission was defined as a HBI <4 points, a CDAI score <150 o a wPCDAI score <12.5 o a PGA=0)												
9	Observational studies [b]	Very serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	[e]	[e]	**Percentage of remission 30** (22 to 37) [f]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Overall response rate after primary failure to IFX and switching to ADA (follow-up: range: 4 weeks to 208 weeks; assessed with: response was defined as a >3 points decrease in the HBI or a ≥70 points decrease in the CDAI score or a ≥17.5 points decrease in the wPCDAI score or reduction in the PGA)												
7	Observational studies [b]	Very serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	[e]	e	**Percentage of response 53** (40 to 65) [g]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Overall remission rate after secondary failure to IFX and switching to ADA or CZP (follow-up: range: 4 weeks to 208 weeks; assessed with: remission was defined as a HBI <4 points, a CDAI score <150 o a wPCDAI score <12.5 o a PGA=0)												
11	Observational studies [b]	Very serious risk of bias [c]	Serious inconsistency [h]	No serious indirect evidence	Serious imprecision [d]	None	[e]	e	**Percentage of remission 45** (34 to 37) [i]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Overall response rate after secondary failure to IFX and switching to ADA or CZP (follow-up: range: 4 weeks to 208 weeks; assessed with: response was defined as a >3 points decrease in the HBI or a ≥70 points decrease in the CDAI score or a ≥17.5 points decrease in the wPCDAI score or reduction in the PGA)												
11	Observational studies [b]	Very serious risk of bias [c]	Serious inconsistency [h]	No serious indirect evidence	Serious imprecision [d]	None	[e]	e	**Percentage of response 66** (44 to 80) [j]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL

Overall remission rate after intolerance to IFX and switching to ADA (follow-up: range: 4 weeks to 208 weeks; assessed with: remission was defined as a HBI <4 points, a CDAI score <150 o a wPCDAI score <12.5 o a PGA=0)											
10	Observational studies [b]	Very serious risk of bias [c]	Serious inconsistency [h]	No serious indirect evidence	Serious imprecision [d]	None	[e]	[e]	**Percentage of remission 61** (40 to 82) [k]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Overall response rate after intolerance to IFX and switching to ADA (follow-up: range: 4 weeks to 208 weeks; assessed with: response was defined as a >3 points decrease in the HBI or a ≥70 points decrease in the CDAI score or a ≥17.5 points decrease in the wPCDAI score or reduction in the PGA)											
9	Observational studies [b]	Very serious risk of bias [c]	Serious inconsistency [h]	No serious indirect evidence	Serious imprecision [d]	None	[e]	e	**Percentage of response 78** (62 to 94) [l]	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval.

Explanations

a. Patients with inflammatory bowel disease and primary or secondary failure to an anti-TNF drug or intolerance to a first TNF inhibitor. Of the studies included in the review, 32 evaluated switching from IFX to ADA, 4, from IFX to CZP, and 1, from ADA to IFX. These were patients with luminal or fistulizing Crohn's disease with a 220-450 points CDAI score or a HBI ≥7 points or patients with "moderate to severe Crohn's disease" or "steroid-dependent" Crohn's disease or who had experienced "failure to treatment with immunomodulators". AMSTAR score 8/11.

b. Only 4 of the studies included in the review were RCTs. The others were cohort studies, case reports, case series, and non-randomized clinical trials.

c. Observational studies were included. High risk of selection bias, measurement bias and presence of confounding factors.

d. Non-optimal sample size.

e. Information not provided in the review.

f. Remission rates in the short, medium and long term were 18%, 30% and 28%, respectively.

g. Response rates in the short, medium and long term were 35%, 67%, and 42%, respectively.

h. I2 >40%.

i. Remission rates in the short, medium and long term were 41%, 38% and 60%, respectively.

j. Response rates in the medium and the long term were 66% and 42%, respectively.

k. Remission rates in the short, medium and long term were 50%, 60% and 83%, respectively.

l. Response rates in the medium and the long term were 70% and 77%, respectively.

Safety and efficacy of using CT-P13 (a biosimilar of infliximab) in patients with moderate to severe Crohn's disease

Question: What is the safety and efficacy of using CT-P13 (a biosimilar of infliximab) in patients with ulcerative colitis? [a, b]

Reference: Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakuraba A. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45(8):1043-57.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Biosimilars	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Clinical response rate (follow-up: range: 8 weeks to 14 weeks; assessed with: a ≥25% decrease in the CDAI score or a ≥70 points decrease [in case of fistulizing CD, a ≥50% decrease in the number or size of fistulas])												
7	Observational studies [c]	Serious risk of bias [d]	Serious inconsistency [e]	Serious indirect evidence [f]	No serious imprecision	None	178/225 (79.1%)		It was not possible to estimate the relative CI [g]		⊕OOO VERY LOW	CRITICAL
Clinical response rate (follow-up: range: 24 weeks to 30 weeks; assessed with: a ≥25% decrease in the CDAI score or a ≥70 points decrease [in case of fistulizing CD, a ≥50% decrease in the number or size of fistulas])												
5	Observational studies	Serious risk of bias [d]	No serious inconsistency [h]	Serious indirect evidence [f]	Serious imprecision [i]	None	98/128 (76.6%)		It was not possible to estimate the relative CI [j]		⊕OOO VERY LOW	CRITICAL
Remission rate (follow-up: range: 8 weeks to 14 weeks; assessed with: CDAI <150 [in case of fistulizing CD, complete fistula closure or a HBI <5 and absence of active fistulas])												
7	Observational studies	Serious risk of bias [d]	Serious inconsistency [k]	Serious indirect evidence [f]	Serious imprecision [i]	None	164/256 (64.1%)		It was not possible to estimate the relative CI [l]		⊕OOO VERY LOW	CRITICAL
Remission rate (follow-up: range: 24 weeks to 30 weeks; assessed with: CDAI <150 [in case of fistulizing CD, complete fistula closure or a HBI <5 and absence of active fistulas])												
5	Observational studies	Serious risk of bias [d]	No serious inconsistency [m]	Serious indirect evidence [f]	Serious imprecision [i]	None	77/128 (60.2%)		It was not possible to estimate the relative CI [n]		⊕OOO VERY LOW	CRITICAL
Clinical response rate (follow-up: range: 48 weeks to 63 weeks; assessed with: a ≥25% decrease in the CDAI score or a ≥70 points decrease [in case of fistulizing CD, a ≥50% decrease in the number or size of fistulas])												
2	Observational studies	Serious risk of bias [d]	No serious inconsistency [o]	Serious indirect evidence [f]	Serious imprecision [i]	None	9/12 (75.0%)		It was not possible to estimate the relative CI [p]		⊕OOO VERY LOW	CRITICAL
Adverse events rate (follow-up: range: 8 weeks to 63 weeks; assessed with: reactions to the infusion, latent tuberculosis or development of infections)												
3	Observational studies [b]	Serious risk of bias [d]	No serious inconsistency	Serious indirect evidence [f]	Serious imprecision [i]	None	1/19 (5.3%)		It was not possible to estimate the relative CI [q]		⊕OOO VERY LOW	CRITICAL

CI: Confidence interval.

Explanations

a. Patients in which infliximab therapy was switched to CT-P13 therapy. AMSTAR score 9/11.
b. Five of the studies retrieved in the review reported that Crohn's disease was located in the terminal ileum, the colon, the ileum and colon, or the upper GI tract. Two studies did not report any information about CD location. Disease activity was defined as having a HBI>3.0 or a PCDAI=53 or a CDAI >266.
c. There were 4 retrospective and 3 prospective cohort studies.
d. All studies were given a 2 to 5 stars score according to the Newcastle-Ottawa scale.
e. I2 = 66.4%; Q = 17.87; p = 0.0066.
f. Head-to-head studies between the biosimilar and the anti-TNF drug are not available.
g. Overall clinical response rate of 79% with 95% CI of 65% to 88%. In patients with fistulizing Crohn's disease, the overall clinical response rate was 67% with a 95% CI of 27% to 92%.
h. I2 = 36.5%, Q = 6.30, p = 0.18.
i. Non-optimal sample size.
j. Overall clinical response rate of 77% with a 95% CI of 63% to 86%. In patients with fistulizing Crohn's disease, the overall clinical response rate was 67% with a 95% CI 27% to 92%.
k. I2 = 69.0%, Q = 19.33, p = 0.0036.
l. Overall clinical response rate of 66% with a 95% CI of 53% to 77%. In patients with fistulizing Crohn's disease, the overall clinical response rate was 33% with a 95% CI of 8% to 73%.
m. I2 = 18.1%, Q = 4.88, p = 0.30.
n. Overall clinical response rate of 60% with a 95% CI of 49% to 70%. In patients with fistulizing Crohn's disease, the overall clinical response rate was 50% with a 95% CI of 17% to 83%.
o. I2 <0.0001%, Q = 0.11, p = 0.74.
p. Overall clinical response rate of 75% with a 95% CI of 44% to 92%.
q. Overall adverse events rate of 10% with a 95% CI of 2% to 31%.

Question N° 5. What are the safest and most effective interventions to treat perianal Crohn's disease in patients older than 16 years?

Use of antibiotics

Question: ciprofloxacin compared to no antibiotic administration in patients with perianal fistulizing Crohn's disease [a]
Reference: Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58-66.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Ciprofloxacin	No antibiotic	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (follow-up: 12 weeks; assessed with: a > 50% reduction in the number of fistulas) [b]												
3	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	39/55 (70.9%)	24/57 (42.1%)	**RR 1.64** (1.16 to 2.32)	**269 more per 1000** (from 67 more to 556 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. One study compared ciprofloxacin with placebo and two studies, ciprofloxacin +anti-TNF with placebo + anti-TNF.
b. Treatment time. Information regarding follow-up was not reported.
c. 1/3 studies with high risk of bias (Jadad scale).
d. The confidence interval of the summary estimator crosses 1.25. Low sample sizes.

Monotherapy with biologics

Question: infliximab versus placebo in perianal Crohn's disease

Reference: Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004;350(9):876-85.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Maintenance of remission (follow-up: 54 weeks; assessed with: time with complete absence of draining fistulas)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [b]	No serious imprecision	None	Time without draining fistulas: infliximab: 40 weeks; placebo; 14 weeks. *p*=<0.001				⊕⊕OO LOW	CRITICAL
Loss of response (follow-up: 54 weeks; assessed with: CDAI)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [b]	Serious imprecision [c]	None	40/96 (41.7%)	61/99 (61.6%)	**RR 0.66** (0.50 to 0.88) [d]	**209 fewer per 1000** (from 74 fewer to 308 fewer)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up: 54 weeks; assessed with: Inflammatory Bowel Disease Questionnaire)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [b]	No serious imprecision	None	Median increase with infliximab therapy: 14; median increase with placebo; 4; *p*=0.002				⊕⊕OO LOW	CRITICAL
Clinical remission - patients who failed to respond (follow-up: 54 weeks; assessed with: CDAI)												
1	Randomized trials	Serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [b]	Very serious imprecision [e]	None	9/43 (20.9%)	7/44 (15.9%)	**RR 1.31** (0.53 to 3.31)	**49 more per 1000** (from 75 fewer to 368 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up: 54 weeks; assessed with: serious adverse events)												
1	Randomized trials	Very serious risk of bias [a, f]	No serious inconsistency	Serious indirect evidence [b]	Very serious imprecision [g]	None	19/138 (13.8%)	33/144 (22.9%)	**RR 0.60** (0.35 to 1.00)	**92 fewer per 1000** (from 0 fewer to 149 fewer)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up: 54 weeks; assessed with: withdrawal/discontinuation of therapy due to adverse events)												
1	Randomized trials	Very serious risk of bias [a, f]	No serious inconsistency	Serious indirect evidence [b]	Very serious imprecision [e]	None	5/138 (3.6%)	12/144 (8.3%)	**RR 0.43** (0.15 to 1.20)	**48 fewer per 1000** (from 17 more to 71 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. High risk of bias of incomplete outcome data for all subgroups and high risk of selective outcome reporting.
b. Not all patients had perianal fistulas (82% to 87%).
c. Confidence interval crosses 0.75. Low sample size of the subgroup that was assessed.
d. It was estimated based on the data that were reported.
e. Low sample size. Confidence interval crosses 0.75 and 1.25.
f. This outcome is not reported individually. Outcomes were not reported according to the type of initial response.
g. Confidence interval crosses 0.75 and the null value.

Combination therapy with an anti-TNF agent plus seton drainage versus monotherapy in patients with perianal fistulas and Crohn's disease

Question: anti-TNF agents plus seton drainage combination therapy compared to monotherapy in patients with perianal fistulas and Crohn's disease [a]

Reference: de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis. 2016;18(7):667-75.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Combination therapy with an anti-TNF agent plus seton drainage	Mono-therapy	Relative (95% CI)	Absolute (95% CI)		
Complete fistula closure (follow-up: range: 4 months to 30 months; assessed with: proportion of patients in which complete fistula closure was reported)												
3	Observational studies [b]	Serious risk of bias [c]	Serious inconsistency [d]	No serious indirect evidence	Serious imprecision [e]	None	[f]	[g]	It was not possible to estimate the relative CI	It was not possible to estimate the absolute CI	⊕OOO VERY LOW	CRITICAL
Partial fistula closure (follow-up: range: 4 months to 30 months; assessed with: proportion of patients in which response to therapy was observed, but complete fistula closure was no achieved)												
2	Observational studies	Serious risk of bias [c]	Serious inconsistency [d]	No serious indirect evidence	Serious imprecision [h]	None	[i]	[j]	It was not possible to estimate the relative CI		⊕OOO VERY LOW	CRITICAL
Fistula recurrence (follow-up: range: 4 months to 30 months; assessed with: proportion of patients who experienced fistula recurrence)												
2	Observational studies	Serious risk of bias [c]	Serious inconsistency [d]	No serious indirect evidence	Serious imprecision [k]	None	[l]	[m]	It was not possible to estimate the relative CI		⊕OOO VERY LOW	CRITICAL

CI: Confidence interval.

Explanations

a. Infliximab; ADA use was not included in any of the studies. Concomitant medical treatment was allowed in three of the four studies included in the review. AMSTAR score 8/11.
b. Three retrospective cohort studies and one prospective cohort study.
c. Risk of detection bias and performance bias. Possible effect of confounding variables.
d. Considerable variations in effect estimates are evident.
e. Three studies with a total sample size of 293 participants.
f. Range of effect: 45% to 100%.
g. Range of effect of seton drainage monotherapy: 17% to 70%; range of effect of anti-TNF monotherapy: 63% to 82%.
h. Two studies with a total sample size of 97 participants.
i. Range of effect: 14% to 88%.
j. Response frequency range in patients who underwent seton drainage: 20% to 72%; response frequency in patients in the anti-TNF therapy group: 27%.
k. Two studies with a total sample size of 67 participants.
l. Range of effect: 18% to 44%.
m. Range of effect of anti-TNF monotherapy: 42% to 78%; effect of seton drainage monotherapy: 42%.

Tacrolimus

Question: oral or intravenous administration of tacrolimus versus placebo in patients with perianal Crohn's disease.

References: McSharry K, Dalzell AM, Leiper K, El-Matary W. Systematic review: the role of tacrolimus in the management of Crohn's disease. Aliment Pharmacol Ther. 2011;34(11-12):1282-94. 2. Sandborn WJ, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. Gastroenterology. 2003;125(2):380-8.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Intravenous or oral tracolimus	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical response (follow-up: 10 weeks; assessed with: fistula clinical improvement)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [a]	Serious imprecision [b]	None	9/21 (42.9%)	2/25 (8.0%)	**OR 7.74** (1.28 to 46.80) [c]	**322 more per 1000** (from 20 more to 723 more)	⊕⊕OO LOW	CRITICAL
Fistula remission (follow-up: 10 weeks; assessed with: fistula remission)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [a]	Very serious imprecision [b, d]	None	2/21 (9.5%)	2/25 (8.0%)	**RR 1.19** (0.18 to 7.74) [d]	**15 more per 1000** (from 66 fewer to 539 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up: 10 weeks; assessed with: patients with serious adverse events)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious indirect evidence [a]	Very serious imprecision [b, d]	None	6/21 (28.6%)	2/25 (8.0%)	**RR 3.57** (0.80 to 15.87)	**206 more per 1000** (from 16 fewer to 1.000 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio.

Explanations

a. Pediatric population was included.
b. Low sample size. Wide confidence interval.
c. OR adjusted for concomitant treatment (azathioprine, antibiotics or infliximab).
d. RR was calculated using the data reported in the review.

Fibrin glue versus surgical treatment

Question: fibrin glue versus surgery in patients with perianal Crohn's disease.

Reference: Cirocchi R, Santoro A, Trastulli S, Farinella E, Di Rocco G, Vendettuali D, et al. Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano. Ann Ital Chir. 2010;81(5):349-56.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Fibrin glue	Surgery	Relative (95% CI)	Absolute (95% CI)		
New outcome (assessed with: risk of anal fistula recurrence)[a]												
3	Randomized trials [b]	Serious risk of bias [c]	Serious inconsistency [d]	No serious indirect evidence	Serious imprecision [e]	Publication bias is highly suspected [f]	44/81 (54.3%)	108/230 (47.0%)	**OR 0.44** (0.12 to 1.68)	**189 fewer per 1000** (de 128 más to 374 fewer)	⊕OOO VERY LOW	CRITICAL
Anal incontinence [a]												
3	Randomized trials [b]	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [e]	Publication bias is highly suspected [f]	10/81 (12.3%)	9/230 (3.9%)	**OR 1.00** (0.43 to 2.34)	**0 fewer per 1000** (from 22 fewer to 48 more)	⊕OOO VERY LOW	IMPORTANT

CI: Confidence interval; OR: Odds ratio.

Explanations

a. This information is not specified.

b. 2 RCTs, 1 CCT.

c. Studies rating was performed. High risk of bias is found in:

d. The forest plot shows different confidence intervals in 1/3 of the studies included in the review. I2=75%.

e. Clinical trials have a low sample size. Confidence interval crosses the null vale (0), 0.75 and 1.25.

f. Studies describe very similar study population exclusion criteria. The funnel plot for this outcome is asymmetric.

Rectovaginal advancement flaps in patients with perianal fistulas

Question: transrectal advancement flap versus transvaginal advancement flap in patients with perianal Crohn's disease.

Reference: Ruffolo C, Scarpa M, Bassi N, Angriman I. A systematic review on advancement flaps for rectovaginal fistula in Crohn's disease: transrectal vs transvaginal approach. Colorectal Dis. 2010;12(12):1183-91.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Transrectal advancement	Transvaginal advancement	Relative (95% CI)	Absolute (95% CI)		
Primary fistula closure (follow-up: range: 8 months to 87 months; assessed with: primary closure)												
4	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	18/34 (52.9%)	12/22 (54.5%)	**OR 1.02** (0.33 to 3.21) [c]	**5 more per 1000** (from 248 more to 262 fewer)	⊕OOO VERY LOW	CRITICAL
Closure (overall) (follow-up: range: 8 months to 87 months; assessed with: primary or secondary closure)												
4	Observational studies	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	23/45 (51.1%)	17/35 (48.6%)	**OR 1.14** (0.45 to 2.91) [c]	**33 more per 1000** (from 187 fewer to 248 more)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up: range: 8 months to 87 months; assessed with: fistula recurrence)[d]												
2	Observational studies	Serious risk of bias [e]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	4/19 (21.1%)	6/17 (35.3%)	It was not possible to estimate the relative and absolute CI		⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. 3/4 studies had negative ratings on clearly defined outcomes.

b. Low sample size. The summary estimator crosses 0.75 and 1.25.

c. The OR is calculated based on the reported information (Mantel-Haenszel method, random effects model).

d. This outcome was reported by 1 study.

Fecal diversion in patients with refractory perianal Crohn's disease

Question: Fecal diversion in patients with refractory perianal Crohn's disease

Reference: Singh S, Ding NS, Mathis KL, Dulai PS, Farrell AM, Pemberton JH, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. Aliment Pharmacol Ther. 2015;42(7):783-92.

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Fecal diversion	Relative (95% CI)	Absolute (95% CI)		
Early clinical improvement (follow-up: range: 9 months to 135 months; assessed with: perception of early improvement)[a]											
14	Observational studies [b]	No serious risk of bias [c]	Serious inconsistency [d]	Serious indirect evidence [e]	No serious imprecision	None	234/373 (62.7%)	-	-	⊕OOO VERY LOW	CRITICAL
Restoration of bowel continuity after fecal diversion (follow-up: range: 9 months to 135 months; assessed with: successful bowel continuity after fecal diversion)[a]											
15	Observational studies	No serious risk of bias	Serious inconsistency [f]	Serious indirect evidence [e]	No serious imprecision	None	92/545 (16.9%)	-	-	⊕OOO VERY LOW	
Proctectomy after fecal diversion (follow-up: range: 9 months to 135 months; assessed with: frequency of proctectomy after undergoing temporary fecal diversion)[a]											
12	Observational studies	No serious risk of bias	Serious inconsistency [g]	Serious indirect evidence [e]	No serious imprecision	None	92/545 (16.9%)	-	-	⊕OOO VERY LOW	

CI: Confidence interval.

Explanations

a. Range of follow-up medians. This information was not specified for each outcome.
b. Case series were included.
c. Grading with the NICE tool does not evidence serious risks of bias associated with this type of study.
d. High heterogeneity among studies. I2=64%.
e. Pediatric population was included in the studies.
f. High heterogeneity among studies. I2=54%.
g. High heterogeneity among studies. I2=63%.

Stem cell therapy

Question: stem cell therapy versus placebo use in patients with perianal Crohn's disease

Reference: Cao Y, Ding Z, Han C, Shi H, Cui L, Lin R. Efficacy of Mesenchymal Stromal Cells for Fistula Treatment of Crohn's Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2017;62(4):851-60.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Stem cell therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Fistula healing (assessed with: fistula healing)[a]												
14	Observational studies [b]	Very serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	72/136 (52.9%)	40/125 (32.0%)	**RR 1.66** (1.22 to 2.25) [e]	**211 more per 1000** (from 70 more to 400 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. This information is not reported. Regarding quality assessment, 9/14 studies were rated as having insufficient follow-up time.
b. Clinical trials and observational studies with a control group.
c. High risk of selection bias, confounding bias, performance bias (measurement). In addition, follow-up time was considered insufficient for outcome measurement.
d. Confidence interval crosses 1.25. Low sample sizes.
e. RR is calculated based on the data reported in the review. The systematic review reports a risk difference of 0.21, 95% CI: 0.09-0.32.

Question N° 6. What are the safest and most effective surgical and endoscopic interventions to treat Crohn's disease in patients older than 16 years?

Biologic drugs and frequency of postoperative complications in patients with inflammatory bowel disease

Question: Does the use of biologic drugs increase the frequency of postoperative complications in patients with inflammatory bowel disease? [a]

Reference: El-Hussuna A, Krag A, Olaison G, Bendtsen F, Gluud LL. The effect of anti-tumor necrosis factor alpha agents on postoperative anastomotic complications in Crohn's disease: a systematic review. Dis Colon Rectum. 2013;56(12):1423-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Biologics and postoperative complications	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Anastomosis-related complications (follow-up: mean: 30 days; assessed with: defined as the presence of dehiscence, fistula, intra-abdominal abscess or the presence of enteric fistula, all confirmed through a diagnostic imaging study, laparotomy or laparoscopy)												
11	Observational studies [b]	Serious risk of bias [c]	Serious inconsistency [c]	No serious indirect evidence	Serious imprecision [e]	None	45/593 (7.6%) [f]	143/1747 (8.2%)	**OR 0.91** (0.56 to 1.47) [g]	**7 fewer per 1000** (from 34 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Major medical complication (follow-up: mean: 30 days; assessed with: defined as a life-threatening complication or a complication requiring hospitalization, including thrombotic, renal or cardiovascular diseases)												
7	Observational studies	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [h]	Serious imprecision [e]	None	24/458 (5.2%)	51/1594 (3.2%)	**OR 1.97** (1.23 to 3.14)	**31 more per 1000** (from 7 more to 68 more)	⊕OOO VERY LOW	CRITICAL
Reoperation (follow-up: mean: 30 days; assessed with: proportion of patients requiring a new surgery)												
5	Observational studies	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [h]	Very serious imprecision [e]	None	21/212 (9.9%)	89/1106 (8.0%)	**OR 1.09** (0.61 to 1.95)	**7 more per 1000** (from 31 fewer to 76 more)	⊕OOO VERY LOW	CRITICAL
Any postoperative complication (follow-up: mean: 30 days; assessed with: proportion of patients experiencing a postoperative complication)												
13	Observational studies	Serious risk of bias [c]	Serious inconsistency [d]	Serious indirect evidence [h]	Serious imprecision [e]	None	238/419 (56.8%)	589/1627 (36.2%)	**OR 1.18** (0.86 to 1.62) [i]	**39 more per 1000** (from 34 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL

Mortality (follow-up: mean: 30 days; assessed with: death after the intervention)											
5	Observational studies	No serious risk of bias	Serious inconsistency [d]	Serious indirect evidence [h]	Very serious imprecision [e]	None	10/231 (4.3%)	10/792 (1.3%)	**OR 4.80** (0.66 to 34.82)	**45 more per 1000** (from 4 fewer to 295 more)	⊕OOO VERY LOW	CRITICAL
Other minor complications (follow-up: mean: 30 days; assessed with: surgical site infection, prolonged ileus, adhesions, gastric bleeding or wound dehiscence)											
9	Observational studies	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [h]	Serious imprecision [e]	None	74/473 (15.6%)	180/1625 (11.1%)	**OR 1.40** (1.05 to 1.85)	**44 more per 1000** (from 6 more to 94 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio.

Explanations

a. Patients with Crohn's disease who underwent open or laparoscopic surgery and who received anti-TNF therapy within the three months prior to the procedure. AMSTAR score 9/11

b. Of the studies included in the review, 11 recruited only patients with Crohn's disease, and 3, patients with Crohn's disease, ulcerative colitis, or indeterminate colitis.

c. According to the Newcastle-Ottawa Scale, 3 studies were classified as having high risk of bias (≤6 stars), 7 as having intermediate risk (7 stars), and 4 as having low risk of bias (8 stars).

d. I2 >40%.

e. CI crosses the critical value 0.75 and/or 1.25.

f. Patients were administered infliximab in 9 studies, while in 4 they were administered adalimumab or certolizumab. All studies included in the review recruited participants concomitantly receiving steroids and immunomodulators.

g. When sensitivity analysis was performed limiting the population to studies conducted only in patients with Crohn's disease: RR: 1.06; IC 95%: 0.41-2.74. When the analysis was limited to studies with low risk of bias: RR: 1.63; 95% CI: 1.03-2.60; NNH: 37 patients.

h. No subgroup analysis for only patients with Crohn's disease was performed.

i. When a subgroup analysis for studies with low risk of bias was conducted, the risk of complications increased: RR: 1.77; IC 95%: 1.46-2.15.

Use of Immunomodulators prior to bowel resection in patients with Crohn's disease and risk of complications

Question: Does the use of immunomodulators prior to bowel resection increase the risk of complications in patients with Crohn's disease? [a]

Reference: Ahmed Ali U, Martin ST, Rao AD, Kiran RP. Impact of preoperative immunosuppressive agents on postoperative outcomes in Crohn's disease. Dis Colon Rectum. 2014;57(5):663-74.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Immunomodulators an postoperative complication	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Postoperative infection in patients who received anti-TNF therapy within three months prior to undergoing the surgical procedure (follow-up: mean: 30 days; assessed with: soft tissues infection, wound dehiscence, intra-abdominal abscess, sepsis, pneumonia, peritonitis or bacteremia).												
14	Observational studies [b]	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [d]	Serious imprecision [e]	None	70/283 (24.7%)	60/365 (16.4%)	**RR 1.42** (1.05 to 1.92) [f]	**69 more per 1000** (from 8 more to 151 more)	⊕OOO VERY LOW	CRITICAL
Postoperative infection in patients who were administered corticosteroids from 1 week to 1 month prior to undergoing the surgical procedure (follow-up: mean: 30 days; assessed with: soft tissues infection, wound dehiscence, intra-abdominal abscess, sepsis, pneumonia, peritonitis or bacteremia)												
4	Observational studies [b]	Serious risk of bias [c]	No serious inconsistency	Serious indirect evidence [d]	Serious imprecision [e]	None	51/382 (13.4%)	67/644 (10.4%)	**RR 1.45** (1.01 to 2.08) [g]	**47 more per 1000** (from 1 more to 112 more)	⊕OOO VERY LOW	CRITICAL
Postoperative infection in patients who were administered thiopurine drugs from 2 weeks to 3 months prior to undergoing the surgical procedure (follow-up: mean: 30 days; assessed with: soft tissues infection, wound dehiscence, intra-abdominal abscess, sepsis, pneumonia, peritonitis or bacteremia)												
8	Observational studies [b]	Serious risk of bias [c]	Serious inconsistency [h]	Serious indirect evidence [d]	Serious imprecision [e]	None	[i]	[i]	**RR 1.23** (0.66 to 2.29)	**1 fewer per 1000** (from 1 fewer to 2 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Out of the 21 studies included in the systematic review, 5 recruited participants with other types of inflammatory bowel disease; 14 studies reported information on the use of anti-TNF agents; 13, on the use of corticosteroids; 8, on the use of thiopurines; and 6, on the combined use of immunosuppressants. AMSTAR score 7/11.

b. 3 studies were case-control studies and the remaining 18, cohort studies (prospective or retrospective).

c. Observational studies. Limitations in adjustment of confounding factors, risk of selection bias and measurement bias.

d. The effect estimator includes studies conducted in patients with other types of inflammatory bowel disease.

e. CI crosses the critical value 0.75 and/or 1.25.

f. In the subgroup analysis limited to only patients with Crohn's disease: RR: 1.31; 95% CI: 1.06-1.64.

g. When subgroup analysis limited to low risk of bias studies was performed: RR: 1.45; 95% CI: 1.01-2.08; when it was limited to only patients with Crohn's disease: RR: 1.45; 95% CI: 1.13-1.87; when it was conducted according to steroid dose, high dose: RR: 1.67; 95% CI: 1.31-2.13.

h. I2> 40%.

i. Data not provided by the authors of the systematic review.

Surgical management versus medical management in intra-abdominal abscesses

Question: Surgery versus medical management to treat intra-abdominal abscesses in patients with Crohn's disease

Reference: Nguyen DL, Nguyen ET, Bechtold ML. Outcomes of initial medical compared with surgical strategies in the management of intra-abdominal abscesses in patients with Crohn's disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2015;27(3):235-41.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Surgery	Medical management	Relative (95% CI)	Absolute (95% CI)		
Abscess resolution (assessed with: abscess resolution)[a]												
9	Observational studies [b]	No serious risk of bias [c]	Serious inconsistency [d]	No serious indirect evidence	No serious imprecision	None [e]	229/284 (80.6%)	-	-	-	⊕OOO VERY LOW	CRITICAL
Abscess resolution - 1 year (assessed with: abscess resolution)												
7	Observational studies [b]	No serious risk of bias [c]	Serious inconsistency [f]	No serious indirect evidence	No serious imprecision	None [e]	179/207 (86.5%)	-	-	-	⊕OOO VERY LOW	CRITICAL
Need for stoma creation (assessed with: stoma creation frequency)[a]												
6	Observational studies [b]	No serious risk of bias [c]	Serious inconsistency [g]	No serious indirect evidence	No serious imprecision	None [e]	67/196 (34.2%)	-	-	-	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. This information is not specified.
b. The review specified these were retrospective case series.
c. Authors of the review classify all studies as having an overall moderate rating.
d. Intermediate heterogeneity. I2 = 56%, random-effects model.
e. Patients' characteristics presented in Table 1 suggest a possible confounding bias.
f. Intermediate heterogeneity. I2 = 58%, random-effects model.
g. Intermediate heterogeneity. I2 = 54% random effects model.

Endoscopic pneumatic dilation in Crohn's disease

Question: endoscopic pneumatic dilation in patients with Crohn's disease

Reference: Morar PS, Faiz O, Warusavitarne J, Brown S, Cohen R, Hind D, et al. Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures. Aliment Pharmacol Ther. 2015;42(10):1137-48.

Quality assessment							№ of patients	Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Endoscopic pneumatic dilation	Relative (95% CI)	Absolute (95% CI)		
Symptomatic response (follow-up: range: 12 months to 172 months; assessed with: symptomatic response)											
16	Observational studies [a]	Serious risk of bias [b]	Serious inconsistency [c]	No serious indirect evidence	No serious imprecision	Publication bias was strongly suspected [d]	393/615 (63.9%)	**Frequency in percentage (%) 70.2** (60.0 to 78.8)	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Technical response (follow-up: range: 12 months to 172 months; assessed with: endoscopic response)											
19	Observational studies [a]	Serious risk of bias [b]	No serious inconsistency [c]	No serious indirect evidence	No serious imprecision	Publication bias was strongly suspected [d]	403/435 (92.6%)	**Frequency in percentage (%) 90.6** (87.8 to 92.8)	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL
Perforation (follow-up: range: 12 months to 172 months; assessed with: perforation frequency)											
22	Observational studies [a]	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	No serious imprecision	Publication bias was strongly suspected [d]	16/654 (2.4%)	**Frequency in percentage (%) 3.0** (2.2 to 4.0)	**-- per 1000** (from -- to --)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval.

Explanations

a. RCTs and non-randomized clinical trials are included.

b. The outcomes report shows that most studies had high risk of selection bias. No comparisons are included.

c. High heterogeneity (I2 = 63.8%).

d. The funnel plot shows significant asymmetry regarding the distribution of the studies.

Strictureplasty versus bowel resection in patients with small bowel Crohn's disease

Question: strictureplasty versus bowel resection in patients with small bowel Crohn's disease

Reference: Reese GE, Purkayastha S, Tilney HS, von Roon A, Yamamoto T, Tekkis PP. Strictureplasty vs resection in small bowel Crohn's disease: an evaluation of short-term outcomes and recurrence. Colorectal Dis. 2007;9(8):686-94.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Strictureplasty	Bowel resection	Relative (95% CI)	Absolute (95% CI)		
Recurrence-free survival time (assessed with: time to recurrence)												
5	Observational studies [a]	No serious risk of bias [b]	No serious inconsistency	Serious indirect evidence [c]	No serious imprecision	None	[d]	[d]	**HR 1.08** (1.02 to 1.15)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Complications (overall) (follow-up: range: 1 month to 240 months; assessed with: any complication)												
2	Observational studies [a]	No serious risk of bias [b]	No serious inconsistency	Serious indirect evidence [c]	Very serious imprecision [e]	None	[d]	[d]	**OR 0.60** (0.31 to 1.16)	**1 fewer per 1000** (from 0 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Surgical recurrence (follow-up: range: 1 month to 240 months; assessed with: recurrence that required surgical treatment)												
6	Observational studies [a]	No serious risk of bias [b]	No serious inconsistency	Serious indirect evidence [c]	Serious imprecision [f]	None	108/286 (37.8%)	111/358 (31.0%)	**OR 1.36** (0.96 to 1.93)	**69 more per 1000** (from 9 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Medical recurrence (follow-up: range: 1 month to 240 months; assessed with: recurrence that required medical treatment)												
2	Observational studies [a]	No serious risk of bias [b]	Serious inconsistency [g]	Serious indirect evidence [c]	Very serious imprecision [e]	None	[d]	[d]	**OR 0.80** (0.09 to 6.85)	**1 fewer per 1000** (from 0 fewer to 7 fewer)	⊕OOO VERY LOW	CRITICAL
Sepsis (follow-up: range: 1 month to 240 months; assessed with: sepsis)												
2	Observational studies [a]	No serious risk of bias [b]	No serious inconsistency	Serious indirect evidence [c]	Very serious imprecision [e]	None	[d]	[d]	**OR 0.67** (0.27 to 1.67)	**1 fewer per 1000** (from 0 fewer to 2 fewer)	⊕OOO VERY LOW	CRITICAL

HR: Hazard ratio; CI: Confidence interval; OR: Odds ratio.

Explanations

a. Prospective and retrospective studies are included.
b. Most studies were rated as having intermediate quality according to the Newcastle Ottawa scale.
c. Pediatric population was included in the studies.
d. This information is not specified, neither the systematic review provides information to make estimates.
e. Low sample size. Confidence interval of the summary estimator crosses 0.75 and 1.25.
f. Confidence interval of the summary estimator crosses the null value and 1.25.
g. High heterogeneity: X2 = 3.65; p = 0.06.

Laparoscopy versus open surgery

Question: Laparoscopy versus open surgery in patients with small bowel Crohn's disease

Reference: Dasari BV, McKay D, Gardiner K. Laparoscopic versus Open surgery for small bowel Crohn's disease. Cochrane Database Syst Rev. 2011;(1):CD006956.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Laparoscopy	Open surgery	Relative (95% CI)	Absolute (95% CI)		
Surgical wound infection (follow-up: range: 3 months to 21 months; assessed with: surgical wound infection)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	2/61 (3.3%)	9/69 (13.0%)	**OR 0.25** (0.03 to 2.39)	**94 fewer per 1000** (from 126 fewer to 133 more)	⊕OOO VERY LOW	CRITICAL
Anastomotic dehiscence (follow-up: range: 3 months to 21 months; assessed with: anastomotic dehiscence)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	1/61 (1.6%)	0/59 (0.0%)	**OR 2.90** (0.11 to 74.12)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
Intra-abdominal abscesses (follow-up: range: 3 months to 21 month; assessed with: intra-abdominal abscesses)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	0/61 (0.0%)	2/59 (3.4%)	**OR 0.19** (0.01 to 4.06)	**27 fewer per 1000** (from 34 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Hospital stay (follow-up: range: 3 months to 21 months; assessed with: postoperative hospital stay, no further specifications)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	10/61 (16.4%)	13/59 (22.0%)	**OR 0.70** (0.28 to 1.73)	**55 fewer per 1000** (from 108 more to 147 fewer)	⊕OOO VERY LOW	CRITICAL
Postoperative ileus (follow-up: range: 3 months to 21 months; assessed with: postoperative ileus)												
2	Randomized trials	Serious risk of bias [a]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	3/61 (4.9%)	5/59 (8.5%)	**OR 0.55** (0.13 to 2.43)	**36 fewer per 1000** (from 73 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Recurrence that required surgical management (follow-up: range: 6.7 y months to 21 months; assessed with: recurrence that required surgical management)												
2	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	10/57 (17.5%)	11/54 (20.4%)	**OR 0.85** (0.32 to 2.27)	**25 fewer per 1000** (from 128 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. Maartense, 2006: high risk of blinding bias. In addition, possible selection and performance biases associated with the laparoscopy arm (due to learning curve in the technique) are reported // Milsom, 2001: high risk of blinding bias. Intention-to-treat analysis is not reported. In addition, possible selection and performance biases associated with the laparoscopy arm (due to learning curve in the technique) are reported.

b. Low sample size. Confidence interval crosses 0.75 and 1.25.

c. Eshusis, 2010: high risk of performance (blinding). In addition, possible selection and performance biases in the laparoscopy arm (due to learning curve in the technique) are reported. Uncertain risk of selection (randomization)//Stocchi, 2008: high risk of performance (blinding). Intention-to-treat analysis is not reported. Possible selection and performance biases in the laparoscopic arm (due to learning curve in the technique). Uncertain selection risk (randomization and concealment).

Types of anastomosis in ileocolic resection

Question: side-to-side anastomosis versus end-to-end anastomosis in patients with Crohn's disease who underwent ileocolic resection

Reference: He X, Chen Z, Huang J, Lian L, Rouniyar S, Wu X, et al. Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease: a meta-analysis. Dig Dis Sci. 2014;59(7):1544-51.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Side-to-side anastomosis	End-to-end anastomosis	Relative (95% CI)	Absolute (95% CI)		
Overall complications (follow-up: range: 34 months to 92 months; assessed with: any complication)												
7	Observational studies [a]	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	48/366 (13.1%)	87/392 (22.2%)	**OR 0.54** (0.32 to 0.93)	**88 fewer per 1000** (from 12 fewer to 138 fewer)	⊕OOO VERY LOW	CRITICAL
Anastomotic leak (follow-up: range: 34 months to 92 months; assessed with: anastomotic leak or dehiscence)												
7	Observational studies [a]	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	10/366 (2.7%)	29/392 (7.4%)	**OR 0.45** (0.20 to 1.00)	**39 fewer per 1000** (from 0 fewer to 58 fewer)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up: range: 34 months to 92 months; assessed with: recurrence)												
5	Observational studies [a]	Serious risk of bias [b]	Very serious inconsistency [d]	No serious indirect evidence	No serious imprecision	None	52/271 (19.2%)	139/288 (48.3%)	**OR 0.20** (0.07 to 0.55)	**325 fewer per 1000** (from 144 fewer to 421 fewer)	⊕OOO VERY LOW	CRITICAL
Reoperation (follow-up: range: 34 months to 92 months; assessed with: reoperation)												
8	Observational studies [a]	Serious risk of bias [b]	Serious inconsistency [e]	No serious indirect evidence	No serious imprecision	None	21/396 (5.3%)	95/425 (22.4%)	**OR 0.18** (0.07 to 0.45)	**174 fewer per 1000** (from 109 fewer to 204 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. In total, 3 RCTs and 5 non-randomized clinical trials were included.
b. Limitations in the comparability of studies, which was measured using the Newcastle Ottawa scale.
c. Confidence interval of the summary estimator crosses 0.75.
d. High heterogeneity among studies. I2 = 80%.
e. High heterogeneity among studies. I2 = 58%.

Surgical resection in patients with colonic Crohn's disease

Question: total or subtotal colectomy versus segmental colectomy in patients with colonic Crohn's disease.

Reference: Tekkis PP, Purkayastha S, Lanitis S, Athanasiou T, Heriot AG, Orchard TR, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. Colorectal Dis. 2006;8(2):82-90.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Total or subtotal colectomy	Segmental colectomy	Relative (95% CI)	Absolute (95% CI)		
Overall recurrence (assessed with: need for reoperation or medical treatment for managing the relapse)												
4	Observational studies	No serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [b]	Very serious imprecision [c]	None [d]	116/213 (54.5%)	109/201 (54.2%)	**OR 1.01** (0.49 to 2.06)	**2 more per 1000** (from 167 more to 175 fewer)	⊕OOO VERY LOW	CRITICAL
Surgical recurrence (assessed with: need for reoperation due to a Crohn's disease complication or medical treatment failure)												
5	Observational studies	No serious risk of bias [a]	Serious inconsistency [e]	Serious indirect evidence [f]	Very serious imprecision [c]	None [d]	55/111 (49.5%)	63/137 (46.0%)	**OR 1.08** (0.39 to 2.95)	**19 more per 1000** (from 211 fewer to 255 more)	⊕OOO VERY LOW	CRITICAL
Postoperative complications (assessed with: postoperative complications)												
3	Observational studies	No serious risk of bias [a]	Very serious inconsistency [g]	Serious indirect evidence [h]	Very serious imprecision [c]	None	12/96 (12.5%)	12/80 (15.0%)	**OR 1.43** (0.16 to 12.74)	**52 more per 1000** (from 123 fewer to 542 more)	⊕OOO VERY LOW	CRITICAL
Need for a permanent stoma (assessed with: need for a permanent stoma after undergoing the surgical procedure)												
4	Observational studies	No serious risk of bias [a]	No serious inconsistency	Serious indirect evidence [i]	Very serious imprecision [j]	None	13/48 (27.1%)	15/104 (14.4%)	**OR 2.75** (0.78 to 9.71)	**172 more per 1000** (from 28 fewer to 476 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio.

Explanations

a. Score of the studies according to the modified Newcastle-Ottawa Scale (/10): 6 to 7.
b. Pediatric population was included in 2/4 studies.
c. Low sample size. Confidence interval of the summary estimator crosses 0.75 and 1.25.
d. Authors of the systematic review report that graphical exploration of the results with funnel plots of the relevant outcomes did not show any evidence of publication bias; however, the graph is not available.
e. High heterogeneity among studies. I2 = 57.9%.
f. Pediatric population was included in 3/5 studies.
g. High heterogeneity among studies. I2 = 79.4%.
h. Pediatric population was included in 1/3 studies.
i. Pediatric population was included in 1/4 studies.
j. Low sample size. Confidence interval crosses the null value and 1.25.

Question N° 7. What are the safest and most effective interventions to prevent postoperative recurrence of Crohn's disease in patients older than 16 years?

Using probiotics to prevent postoperative recurrence of Crohn's disease

Reference: Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(4):389-400.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Probiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Preventing postoperative clinical relapse (follow-up: range: 3 months to 12 months; assessed with: need for additional therapy or CDAI >150 or a >70 points compared to baseline CDAI score)												
3	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c,d]	None	28/105 (26.7%)	28/108 (25.9%)	**RR 1.06** (0.59 to 1.92)	**16 more per 1000** (from 106 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Preventing postoperative endoscopic relapse (follow-up: range: 3 months to 12 months; assessed with: Rutgeerts score >2)												
4	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c,d]	None	94/163 (57.7%)	96/170 (56.5%)	**RR 1.04** (0.82 to 1.31)	**23 more per 1000** (from 102 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 9/11.
b. Some limitations regarding sequence generation and allocation concealment were observed.
c. CI crosses the critical value 1.25 and/or 0.75.
d. Non-optimal sample size.

Reference: Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. Inflamm Bowel Dis. 2013;20(1): 21-35.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Probiotics alone or plus standard treatment	Placebo plus standard treatment	Relative (95% CI)	Absolute (95% CI)		
Endoscopic relapse (follow-up: range: 3 months to 24 months; assessed with: Rugeerts score)												
3	Randomized trials	Serious risk of bias [b]	Serious inconsistency [e]	No serious indirect evidence	Very serious imprecision [c,d]	None	50/97 (51.5%)	53/103 (51.5%)	**RR 1.08** (0.67 a 1.74)	**41 more per 1000** (from 170 fewer to 381 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. AMSTAR score 8/11.
b. Studies with a Jadad score ≥3.
c. Confidence interval crosses the critical value 1.25 and/or 0.75.
e. I2 >40%.

Using antibiotics to prevent postoperative recurrence of Crohn's disease

Reference: Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58-66.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement or remission (follow-up: range: 3 months to 6 months; assessed with: CDAI score <150 and/or a ≥70 points decrease in the CDAI score or a >50% reduction in the number of fistulas for at least 4 weeks)												
1	Randomized trials	Serious risk of bias [c]	No serious inconsistency	No serious indirect evidence	Serious imprecision [d]	None	6/17 (35.2%)	5/16 (31,2%)	**RR 1.13** (0.43 to 2.98)	**124 more per 1000** (from 64 more to 191 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. Ciprofloxacin was the antibiotic used. AMSTAR score 7/11.
b. Postoperative Crohn's disease. All studies allowed concomitant use of other interventions (immunomodulators).
c. Assessed with the Jadad scale. Limitations regarding sequence generation and allocation concealment.
d. CI crosses the critical value 1.25 and/or 0.75.

Reference: Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009;(4):CD006873. https://doi.org/10.1002/14651858.CD006873.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Interventions	Placebo	Relative (95% CI)	Absolute (95% CI)		
Severe endoscopic recurrence: 5-nitroimidazole vs. placebo (Follow-up: mean: 3 months; assessed with: Rutgeerts score ≥I2)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [a, b]	None	14/70 (20.0%)	32/70 (45.7%)	**RR 0.44** (0.26 to 0.74)	**256 fewer per 1.000** (from 119 fewer to 338 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawal due to adverse events: 5-nitroimidazole vs. placebo (Follow-up: mean: 3 months; assessed with: Rutgeerts score ≥I2)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	21/70 (30.0%)	7/70 (10.0%)	**RR 3.00** (1.37 to 6.58)	**200 more per 1.000** (from 37 more to 558 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Wide CI and it crosses 1.25 and/or 0.75.
b. Non-optimal size sample.
c. AMSTAR score 9/11.

Use of azathioprine or 6-mercaptopurine to prevent postoperative recurrence of Crohn's disease

Question: azathioprine or 6-mercaptopurine versus placebo or any other intervention for maintenance of surgically-induced remission in Crohn's disease [a]

Reference: Gordon M, Taylor K, Akobeng AK, Thomas AG. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2014;(8):CD010233. https//doi.org/10.1002/14651858.CD010233.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Azathioprine or 6-mercaptopurine	Placebo or any other intervention	Relative (95% CI)	Absolute (95% CI)		
Clinical relapse versus placebo (follow-up: range: 3 months to 24 months; assessed with: CDAI score >200 or requiring steroids or a 60-point increase in the CDAI score compared to the baseline score)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	42/87 (48.3%)	51/81 (63.0%)	**RR 0.74** (0.58 to 0.94)	**164 fewer per 1.000** (from 38 fewer to 264 fewer)	⊕⊕OO LOW	CRITICAL
Endoscopic relapse versus placebo (follow-up: range: 3 months to 12 months; assessed with: Rutgeerts score >2)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	8/47 (17.0%)	17/40 (42.5%)	**RR 0.40** (0.19 to 0.83)	**255 fewer per 1.000** (from 72 fewer to 344 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events requiring withdrawal versus placebo (follow-up: range: 3 months to 12 months)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	13/87 (14.9%)	9/81 (11.1%)	**RR 1.33** (0.59 to 2.98)	**37 more per 1.000** (from 46 fewer to 220 more)	⊕OOO VERY LOW	CRITICAL
Clinical relapse versus 5-ASA (follow-up: range: 3 months to 12 months; assessed with: CDAI score >200 or requiring steroids or a 60-point increase in the CDAI score compared to the baseline score)												
5	Randomized trials	Serious risk of bias [b]	Serious inconsistency [e]	No serious indirect evidence	Serious imprecision [c]	None	137/218 (62.8%)	112/207 (54.1%)	**RR 1.14** (0.93 to 1.41)	**76 more per 1.000** (from 38 fewer to 222 more)	⊕OOO VERY LOW	CRITICAL
Endoscopic relapse versus 5-ASA (follow-up: range: 3 months to 12 months; assessed with: Rutgeerts score >2)												
2	Randomized trials	Serious risk of bias [b]	Very serious inconsistency [e]	No serious indirect evidence	Very serious imprecision [c, d]	None	19/64 (29.7%)	36/62 (58.1%)	**RR 0.55** (0.23 to 1.32)	**261 fewer per 1.000** (from 186 more to 447 fewer)	⊕OOO VERY LOW	CRITICAL

Withdrawal due to adverse events versus 5-ASA (follow-up: range: 3 months to 12 months)												
5	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	No serious imprecision	None	44/218 (20.2%)	20/205 (9.8%)	**RR 2.07** (1.26 to 33.90)	**104 more per 1.000** (from 25 more to 1.000 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical relapse versus infliximab or adalimumab (follow-up: range: 3 months to 24 months; assessed with: CDAI score >200 or requiring steroids or a 60-point increase in the CDAI score compared to the baseline score)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	2/11 (18.2%)	1/11 (9.1%)	**RR 2.00** (0.21 to 18.98) [f]	**91 more per 1.000** (from 72 fewer to 1.000 more)	⊕OOO VERY LOW	CRITICAL
Endoscopic relapse, infliximab or adalimumab (follow-up: range: 3 months to 12 months; assessed with: Rutgeerts score >2)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	4/10 (40.0%)	1/11 (9.1%)	**RR 4.40** (0.59 to 33.07) [g]	**309 more per 1.000** (from 37 fewer to 1.000 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events infliximab or adalimumab (follow-up: range: 3 months to 12 months)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	1/11 (9.1%)	0/11 (0.0%)	**RR 3.00** (0.14 to 66.53) [h]	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 9/11.
b. Serious limitations in the participants blinding and the staff blinding domain.
c. Wide CI, and it crosses the critical value 1.25 and/or 0.75.
d. Non-optimal sample size.
e. I2 >40%.
f. Clinical relapse versus ADA: RR: 5.18 (1.35-19.83).
g. Endoscopic relapse versus ADA: RR: 10.35 (1.50-71.32).
h. Withdrawal due to adverse events versus ADA: RR: 1.88 (0.19-18.80).

Using 5-aminosalicylates to prevent postoperative recurrence of Crohn's disease

Question: 5-aminosalicylates versus placebo for maintenance of surgically-induced remission in Crohn's disease

Reference: Gordon M, Naidoo K, Thomas AG, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2011;(1):CD008414. https//doi.org/10.1002/14651858.CD008414.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	5-aminosalicylates	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical relapse versus placebo (follow-up: range: 12 months to 24 months; assessed with: symptoms plus CDAI >150 or >200 or a >60 points increase)												
8 [a]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Serious imprecision [b]	None	225/520 (43.3%)	267/541 (49.4%)	**RR 0.71** (0.54 to 0.94)	**143 fewer per 1.000** (from 30 fewer to 227 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (follow-up: range: 12 months to 24 months)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b, c]	None	29/330 (8.8%)	27/334 (8.1%)	**RR 1.06** (0.61 to 1.85)	**5 more per 1.000** (from 32 fewer to 69 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. AMSTAR score 8/11.

b. Wide CI, and it crosses the critical value 0.75 and/or 1.25

c. Non-optimal sample size.

Using budesonide for the prevention of postoperative recurrence of Crohn's disease

Reference: Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009;(4):CD006873. htpps://doi.org/10.1002/14651858.CD006873.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Interventions	Placebo	Relative (95% CI)	Absolute (95% CI)		
Severe endoscopic relapse: budesonide versus placebo (follow-up: mean: 12 months; assessed with: Rutgeerts score I2 or higher)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	53/106 (50.0%)	57/106 (53.8%)	**RR 0.87** (0.50 to 1.49)	**70 fewer per 1.000** (from 263 more to 269 fewer)	⊕⊕OO LOW	CRITICAL
Serious adverse events: budesonide versus placebo (follow-up: mean: 12 months)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [a, b]	None	7/106 (6.6%)	7/106 (6.6%)	**RR 1.01** (0.37 to 2.78)	**1 more per 1.000** (from 42 fewer to 118 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Wide CI, and it crosses 1.25 and/or 0.75.
b. Non-optimal sample size.
c. AMSTAR score 9/11.

Anti-TNF therapy versus conventional therapy to prevent postoperative recurrence of Crohn's disease

Question: anti-TNF therapy versus conventional therapy for the prevention of postoperative recurrence of Crohn's disease [a]

Reference: Nguyen DL, Solaimani P, Nguyen ET, Jamal MM, Bechtold ML. Antitumor necrosis factor α is more effective than conventional medical therapy for the prevention of postoperative recurrence of Crohn>s disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2014;26(10):1152-9.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Anti-TNF therapy	Conventional therapy	Relative (95% CI)	Absolute (95% CI)		
Prevention of histologic recurrence (follow-up: mean: 54 weeks; assessed with: modified D'Haens histologic scoring system)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirect evidence	Very serious imprecision [b]	None	8/11 (72.7%)	4/13 (30.8%)	**RR 6.00** (1.02 to 35.37)	**1.000 more per 1000** (from 6 more to 1000 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Infliximab versus mesalamine or 6-mercaptopurine. Therapy was started within the first 2 to 4 weeks after performing the surgical procedure. AMSTAR score 7/11.
b. Non-optimal sample size and the CI crosses the critical value 1.25.

Question: anti-TNF therapy versus immunomodulators for the treatment of postoperative relapse of Crohn's disease [a]
Reference: Carla-Moreau A, Paul S, Roblin X, Genin C, Peyrin-Biroulet L. Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: a meta-analysis of controlled trials. Dig Liver Dis. 2015;47(3):191-6.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Anti-TNF therapy	Immunomodulators	Relative (95% CI)	Absolute (95% CI)		
Endoscopic remission (follow-up: range: 6 months to 12 months; assessed with: Rutgeerts score <2)												
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	10/21 (47.6%)	1/29 (3.4%)	**OR 16.64** (2.51 to 110.27)	**338 more per 1000** (from 48 more to 763 more)	⊕⊕OO LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations
a. AMSTAR score 8/11.
b. Serious limitations regarding sequence generation and allocation concealment.
c. Non-optimal sample size.

Safety and efficacy of different pharmacological strategies to prevent postoperative recurrence of Crohn's disease

Question: What is the safety and efficacy of pharmacological interventions for the prevention of postoperative relapse of Crohn's disease? [a]
Reference: Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015;41(7):613-23.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Intervention	Other intervention	Relative (95% CI)	Absolute (95% CI)		
Clinical relapse with immunomodulators versus 5-ASA (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)												
5	Randomized trials	Serious risk of bias [b]	Serious inconsistency [c]	No serious indirect evidence	Serious imprecision [d]	None	50/162 (30.9%)	60/158 (38.0%)	**RR 0.83** (0.54 to 1.30)	**65 fewer per 1000** (from 114 more to 175 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical relapse with immunomodulators plus antibiotics versus antibiotics alone (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	3/32 (9.4%)	7/29 (24.1%)	**RR 0.39** (0.11 to 1.36)	**147 fewer per 1000** (from 87 more to 215 fewer)	⊕OOO VERY LOW	CRITICAL

Clinical relapse with immunomodulators plus antibiotics versus immunomodulators alone (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	1/25 (4.0%)	2/25 (8.0%)	**RR 0.50** (0.05 to 5.17)	**40 fewer per 1000** (from 76 fewer to 334 more)	⊕OOO VERY LOW	CRITICAL
Clinical relapse with anti-TNF therapy versus 5-ASA therapy (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	1/16 (6.3%)	9/18 (50.0%)	**RR 0.13** (0.02 to 0.88)	**435 fewer per 1000** (from 60 fewer to 490 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical relapse with anti-TNF therapy versus immunomodulators (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)											
2	Randomized trials	Serious risk of bias [b]	Serious inconsistency [c]	No serious indirect evidence	Very serious imprecision [d, e]	None	2/27 (7.4%)	13/27 (48.1%)	**RR 0.24** (0.02 to 2.40)	**366 fewer per 1000** (from 472 fewer to 674 more)	⊕OOO VERY LOW	CRITICAL
Clinical relapse with an anti-TNF agent plus 5-ASA versus 5-ASA monotherapy (follow-up: range: 6 months to 24 months; assessed with: CDAI ≥ 150 or according to the criteria established by the researcher)											
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [d, e]	None	2/15 (13.3%)	4/16 (25.0%)	**RR 0.53** (0.11 to 2.50)	**118 fewer per 1000** (from 223 fewer to 375 more)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. The network meta-analysis showed that anti-TNF monotherapy was superior to immunomodulator monotherapy (RR: 0.11; 95% CI: 0.01-0.40); however, it should be noted that the estimate was not statistically significant in the head-to-head comparison. Anti-TNF monotherapy was also superior to antibiotics administration, but this estimator is mainly based on indirect evidence (RR: 0.20; 95% CI: 0.01-0.84). Also, there were no significant differences between combination therapy with immunomodulators plus antibiotics and immunomodulator monotherapy (RR: 0.34; 95% CI: 0.05-1.20) or antibiotic monotherapy (RR: 0.48; 95% CI: 0.08-1.46), even though, based on indirect evidence in the absence of head-to-head comparisons, immunomodulator monotherapy was not superior to antibiotic therapy (RR: 1.92; 95% CI: 0.93-4.00).

b. Some limitations in the participants, staff and reviewers blinding, incomplete data, and sequence generation domains.

c. I2 >40%.

d. Wide CI, and it crosses the critical value 0.75 and/or 1.25.

e. Non-optimal sample size.

Question: What is the safety and efficacy of pharmacological interventions for the prevention of postoperative relapse of Crohn's disease? [a]
Reference: Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 2015;148(1):64-76.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Intervention	Other intervention	Relative (95% CI)	Absolute (95% CI)		
Endoscopic relapse: immunomodulators versus 5-ASA (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)												
5	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	41/96 (42.7%)	54/90 (60.0%)	**RR 0.77** (0.55 to 1.08)	**138 fewer per 1000** (from 48 more to 270 fewer)	⊕OOO VERY LOW	CRITICAL
Endoscopic relapse: immunomodulators plus antibiotics versus antibiotics (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	14/32 (43.8%)	20/29 (69.0%)	**RR 0.63** (0.40 to 1.01)	**255 fewer per 1000** (from 7 more to 414 fewer)	⊕OOO VERY LOW	CRITICAL
Endoscopic relapse: immunomodulators plus antibiotics versus immunomodulators (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	5/23 (21.7%)	8/22 (36.4%)	**RR 0.60** (0.23 to 1.55)	**145 fewer per 1000** (from 200 more to 280 fewer)	⊕OOO VERY LOW	CRITICAL
Endoscopic relapse: anti-TNF therapy versus 5-ASA (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)												
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	0/16 (0.0%)	14/18 (77.8%)	**RR 0.04** (0.00 to 0.60)	**747 fewer per 1000** (from -- to 311 fewer)	⊕OOO VERY LOW	CRITICAL

Endoscopic relapse: anti-TNF therapy versus immunomodulators (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)											
2	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Serious imprecision [c]	None	1/27 (3.7%)	15/27 (55.6%)	**RR 0.13** (0.03 to 0.66)	**483 fewer per 1000** (from 189 fewer to 539 fewer)	⊕⊕OO LOW	CRITICAL
Endoscopic relapse: combination therapy with an anti-TNF agent plus 5-ASA versus 5-ASA (follow-up: range: 6 months to 24 months; assessed with: Rutgeerts score I2-4 or the combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies or as defined by the author)											
1	Randomized trials	Serious risk of bias [b]	No serious inconsistency	No serious indirect evidence	Very serious imprecision [c, d]	None	4/15 (26.7%)	13/16 (81.3%)	**RR 0.33** (0.14 to 0.78)	**544 fewer per 1000** (from 179 fewer to 699 fewer)	⊕OOO VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Based on the results of the network meta-analysis, anti-TNF monotherapy was superior to all other interventions: versus mesalamine (RR: 0.02; 95% CI: 0.00-0.07), antibiotics (RR: 0.03; 95% CI: 0.00-0.15), immunomodulator monotherapy (RR: 0.04; 95% CI: 0.00-0.14), combination therapy with immunomodulators plus antibiotics (RR: 0.03; 95% CI: 0.00-0.49) and budesonide (RR: 0.005; 95% CI: 0.00-0.08). Also, there were no significant differences between combination therapy with immunomodulators plus antibiotics and immunomodulator monotherapy (RR: 0.54; 95% CI: 0.12-1.59) or antibiotic monotherapy (RR: 0.43; 95% CI: 0.10-1.19). Additionally, there were no significant differences between immunomodulator monotherapy and antibiotic monotherapy in terms of reducing the risk of endoscopic relapse (RR: 0.97; 95% CI: 0.26-2.53).

b. Some limitations in the participants, staff and reviewers blinding, incomplete data and sequence generation domains.

c. Non-optimal sample size.

d. CI crosses the critical value 0.75 and/or 1.25.

REFERENCES

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017;389(10080):1741-55. https://doi.org/10.1016/S0140-6736(16)31711-1
2. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-70. https://doi.org/10.1016/S0140-6736(16)32126-2
3. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016;13(1):13-27. https://doi.org/10.1038/nrgastro.2015.186
4. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today. 1993;14(9):426-30. https://doi.org/10.1016/0167-5699(93)90244-F
5. Behr MA, Divangahi M, Lalande JD. What's in a name? The (mis)labelling of Crohn's as an autoimmune disease. Lancet. 2010;376(9736):202-3. https://doi.org/10.1016/S0140-6736(10)60282-6
6. Park H, Bourla AB, Kastner DL, Colbert RA, Siegel RM. Lighting the fires within: the cell biology of autoinflammatory diseases. Nat Rev Immunol. 2012;12(8):570-80. https://doi.org/10.1038/nri3261
7. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol 2015;50(8):942-51. https://doi.org/10.3109/00365521.2015.1014407
8. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54. https://doi.org/10.1053/j.gastro.2011.10.001
9. Ng SC, Shi HY, Hamidi N, Underwood F, Tang W, Benchimol E, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769-78. https://doi.org/10.1016/S0140-6736(17)32448-0
10. Kotze PG, Underwood F, Damiao AOMC, Panaccione R, Ng S, Kaplan G. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: a Systematic Review. Clin Gastroenterol Hepatol. 2020;18(2):304-12. https://doi.org/10.1016/j.cgh.2019.06.030
11. Quaresma AB, Kaplan GG, Kotze PG. The globalization of inflammatory bowel disease: the incidence and prevalence of inflammatory bowel disease in Brazil. Curr Opin Gastroenterol. 2019;35(4):259-64. https://doi.org/10.1097/MOG.0000000000000534
12. Yamamoto-Furusho JK, Sarmiento-Aguilar A, Toledo-Mauriño JJ, Bozada-Gutiérrez K, Bosques-Padilla F, Martínez-Vázquez M, et al. Incidence and prevalence of inflammatory bowel disease in Mexico from a nationwide cohort study in a period of 15 years (2000-2017). Medicine (Baltimore). 2019;98(27):e16291. https://doi.org/10.1097/MD.0000000000016291
13. Juliao F, Damas OM, Arrubla M, Calixto O, Camargo J, Cruz L, et al. The prevalence of inflammatory bowel disease in Colombia is increasing: report on the national prevalente of IBD and description of IBD phenotype. Gastroenterology 2019;156(6):S-405. https://doi.org/10.1016/S0016-5085(19)37865-5
14. Arguello M, Archila P, Sierra F, Otero W. Enfermedad inflamatoria intestinal. Rev Col Gastroenterol. 1991;6(4):237-72.
15. Juliao Baños F, Ruiz Vélez MH, Flórez Arango JF, Donado Gómez JH, Marín Zuluaga JI, Monsalve Arango C, et al. Fenotipo e historia natural de la enfermedad inflamatoria intestinal en un centro de referencia en Medellín-Colombia. Rev Col Gastroenterol. 2010;25(3):240-51.
16. Reyes GA, Gil FL, Carvajal GD, Sánchez C, Aponte D, González C, et al. Enfermedad inflamatoria intestinal: características de fenotipo y tratamiento en un hospital universitario de Bogotá, Colombia. Rev Col Gastroenterol 2018;29 (1):11-8. https://doi.org/10.22516/25007440.196
17. Rojas CA, Sánchez-Londoño S, Rojas NE, Sepúlveda S, García J, Jiménez D, et al. Descripción clínico-epidemiológica de pacientes con enfermedad inflamatoria intestinal en una clínica de cuarto nivel en Cali. Rev Colomb Gastroenterol. 2020;35(2):166-73. https://doi.org/10.22516/25007440.409
18. Shivashankar R, Tremaine WJ, Harmsen WS, Loftus EV. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota from 1970 Through 2010. Clin Gastroenterol Hepatol. 2017;15(6):857-63. https://doi.org/10.1016/j.cgh.2016.10.039
19. Enfermedades huérfanas [Internet]. Ministerio de Salud y Protección Social de Colombia; 2020. Disponible en: https://bit.ly/364B42h
20. Johnston RD, Logan RF. What is the peak age for onset of IBD? Inflamm Bowel Dis. 2008;14(Suppl 2):S4-5. https://doi.org/10.1002/ibd.20545
21. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13(2):144-64. https://doi.org/10.1093/ecco-jcc/jjy113
22. Gomollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017;11(1):3-25. https://doi.org/10.1093/ecco-jcc/jjw168
23. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of

Meta-analyses. Gastroenterology. 2019;157(3):647-59. https://doi.org/10.1053/j.gastro.2019.04.016
24. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2015;110(6):802-19. https://doi.org/10.1038/ajg.2015.120
25. Van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010;341:c3369. https://doi.org/10.1136/bmj.c3369
26. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015;110(3):444-54. https://doi.org/10.1038/ajg.2015.6
27. Vermeire S, Peeters M, Vlietinck R, Joossens S, Den Hond E, Bulteel V, et al. Anti-Saccharomyces cerevisiae antibodies (ASCA), phenotypes of IBD, and intestinal permeability: a study in IBD families. Inflamm Bowel Dis. 2001;7(1):8-15. https://doi.org/10.1097/00054725-200102000-00002
28. Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, et al. European evidence-based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982-1018. https://doi.org/10.1016/j.crohns.2013.09.016
29. Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7(10):827-51. https://doi.org/10.1016/j.crohns.2013.06.001
30. Panes J, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. J Crohns Colitis. 2013;7(7):556-85. https://doi.org/10.1016/j.crohns.2013.02.020
31. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19(Suppl A):5a-36a. https://doi.org/10.1155/2005/269076
32. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut. 2001;49(6):777-82. https://doi.org/10.1136/gut.49.6.777
33. Frolkis AD, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology. 2013;145(5):996-1006. https://doi.org/10.1053/j.gastro.2013.07.041
34. Buisson A, Chevaux JB, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther. 2012;35(6):625-33. https://doi.org/10.1111/j.1365-2036.2012.05002.x
35. Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology. 2014;147(3):702-5. https://doi.org/10.1053/j.gastro.2014.07.022
36. Torres J, Caprioli F, Katsanos KH, Lobatón T, Micic D, Zeronico M, et al. Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases. J Crohns Colitis. 2016;10(12):1385-94. https://doi.org/10.1093/ecco-jcc/jjw116
37. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert J, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020;14(1):4-22. https://doi.org/10.1093/ecco-jcc/jjz180
38. Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther. 2016;43(3):317-33. https://doi.org/10.1111/apt.13475
39. Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(6):1042-50. https://doi.org/10.1016/j.cgh.2013.09.006
40. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelan W, Bryant R, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015;110(9):1324-38. https://doi.org/10.1038/ajg.2015.233
41. Colombel JF, D'haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2020;14(2):254-66. https://doi.org/10.1093/ecco-jcc/jjz131
42. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol. 2015;12(9):537-45. https://doi.org/10.1038/nrgastro.2015.135
43. Côté-Daigneault J, Bouin M, Lahaie R, Colombel JF, Poitras P. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterol J. 2015;3(5):419-28. https://doi.org/10.1177/2050640615590302
44. Khanna R, Jairath V, Feagan BG. The Evolution of Treatment Paradigms in Crohn's Disease: Beyond Better Drugs. Gastroenterol Clin North Am. 2017;46(3):661-77. https://doi.org/10.1016/j.gtc.2017.05.010

45. Fiorino G, Allocca M, Chaparro M, Coenen S, Fidalgo C, Younge L, et al. 'Quality of Care' Standards in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2019;13(1):127-37. https://doi.org/10.1093/ecco-jcc/jjy140
46. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol. 2017;112(2):241-58. https://doi.org/10.1038/ajg.2016.537
47. Juliao-Baños F. Calidad en el manejo de enfermedad inflamatoria intestinal. Rev Col Gastroenterol. 2011; 26(3):211-20.
48. Bitton A, Vutcovici M, Lytvyak E, Kachan N, Bressler B, Jones J, et al. Selection of Quality Indicators in IBD: Integrating Physician and Patient Perspectives. Inflamm Bowel Dis. 2019;25(2):403-9. https://doi.org/10.1093/ibd/izy259
49. Jackson BD, De Cruz P. Quality of Care in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019;25(3):479-89. https://doi.org/10.1093/ibd/izy276
50. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014;8(6):443-68. https://doi.org/10.1016/j.crohns.2013.12.013
51. Hindryckx P, Novak G, Bonovas S, Peyrin-Biroulet L, Danese S. Infection Risk with Biologic Therapy in Patients with Inflammatory Bowel Disease. Clin Pharmacol Ther. 2017;102(4):633-41. https://doi.org/10.1002/cpt.791
52. Nguyen NH, Singh S, Sandborn WJ. Positioning Therapies in the Management of Crohn's Disease. Clin Gastroenterol Hepatol. 2020;18(6):1268-79. https://doi.org/10.1016/j.cgh.2019.10.035
53. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L, Seibold F; on behalf of the Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. Treatment Algorithms for Crohn's Disease. Digestion. 2020;101(Suppl 1):43-57. doi: 10.1159/000506364. Epub 2020 Mar 13. PMID: 32172251.
54. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42. https://doi.org/10.1503/cmaj.090449
55. Grupo de actualización de la Guía Metodológica para el desarrollo de Guías de Práctica Clínica con Evaluación Económica en el SGSSS Colombiano. Guía Metodológica para la elaboración de Guías de Práctica Clínica con Evaluación Económica en el Sistema General de Seguridad Social en Salud Colombiano: Ministerio de Salud y Protección Social; 2014. Disponible en: https://bit.ly/2I8nAdu
56. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20. https://doi.org/10.1016/j.jclinepi.2008.10.009
57. Higgins J, Altman D. Assessing risk of bias in included studies. En: Higgins J, Green S (editores). Cochrane Handbook for Systematic Reviews of Interventions. Londres: The Cochrane Collaboration; 2011.
58. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94. https://doi.org/10.1016/j.jclinepi.2010.04.026
59. National Institute for Health and Clinical Excellence. Crohn's disease: management in adults, children and young people. Disponible en: https://bit.ly/2I6zYe1
60. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut. 2008;57(10):1386-92. https://doi.org/10.1136/gut.2007.134817
61. Consigny Y, Modigliani R, Colombel JF, Dupas JL, Lemann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. Inflamm Bowel Dis. 2006;12(7):551-7. https://doi.org/10.1097/01.ibd.0000225334.60990.5b
62. Kallel L, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol. 2010;22(3):340-5. https://doi.org/10.1097/MEG.0b013e32832bab49
63. Mao R, Xiao YL, Gao X, Chen BL, He Y, Yang L, et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Inflamm Bowel Dis. 2012;18(10):1894-9. https://doi.org/10.1002/ibd.22861
64. Dulai PS, Peyrin-Biroulet L, Danese S, Sands B, Dignass A, Turner D, et al. Approaches to Integrating Biomarkers into Clinical Trials and Care Pathways as Targets for the Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2019;157(4):1032-43. https://doi.org/10.1053/j.gastro.2019.06.018
65. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn>s disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2018;390(10114):2779-89. https://doi.org/10.1016/S0140-6736(17)32641-7
66. Moore C, Corbett G, Moss AC. Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(5):619-25. https://doi.org/10.1093/ecco-jcc/jjw007
67. Thomassin L, Armengol-Debeir L, Charpentier C, Bridoux V, Koning E, Savoye G, et al. Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn>s disease. World J Gastroenterol. 2017;23(23):4285-92. https://doi.org/10.3748/wjg.v23.i23.4285

68. Choi SH, Kim KW, Lee JY, Kim K, Park S. Diffusion-weighted magnetic resonance enterography for evaluating bowel inflammation in Crohn›s disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2016;22(3):669-79. https://doi.org/10.1097/MIB.0000000000000607
69. Allocca M, Danese S, Laurent V, Peyrin-Biroulet L. Use of Cross-Sectional Imaging for Tight Monitoring of Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2020;18(6):1309-23. https://doi.org/10.1016/j.cgh.2019.11.052
70. Niv Y. Small-bowel mucosal healing assessment by capsule endoscopy as a predictor of long-term clinical remission in patients with Crohn›s disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2017;29(7):844-8. https://doi.org/10.1097/MEG.0000000000000881
71. Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn›s disease, and pouchitis: meta-analysis of randomized controlled trials. Inflamm Bowel Dis. 2014;20(1):21-35. https://doi.org/10.1097/01.MIB.0000437495.30052.be
72. Limketkai BN, Akobeng AK, Gordon M, Adepoju AA. Probiotics for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2020;7(7):CD006634. https://doi.org/10.1002/14651858.CD006634.pub3
73. Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn›s disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58-66. https://doi.org/10.1111/1751-2980.12216
74. Townsend CM, Parker CE, MacDonald JK, Nguyen T, Jairath V, Feagan B, et al. Antibiotics for induction and maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2019;2(2):CD012730. https://doi.org/10.1002/14651858.CD012730.pub2
75. Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2016;10:Cd000545. https://doi.org/10.1002/14651858.CD000545.pub5
76. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn›s disease. Cochrane Database Syst Rev. 2016;7:CD008870. https://doi.org/10.1002/14651858.CD008870.pub2
77. McDonald JW, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn›s disease. Cochrane Database Syst Rev. 2014(8): CD003459. https://doi.org/10.1002/14651858.CD003459.pub4
78. Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2015(6): CD000296. https://doi.org/10.1002/14651858.CD000296.pub4
79. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2008(2):CD006792. https://doi.org/10.1002/14651858.CD006792.pub2
80. Coward S, Kuenzig ME, Hazlewood G, Clement F, McBrien K, Holmes R, et al. Comparative Effectiveness of Mesalamine, Sulfasalazine, Corticosteroids, and Budesonide for the Induction of Remission in Crohn›s Disease: A Bayesian Network Meta-analysis. Inflamm Bowel Dis. 2017;23(3):461-72. https://doi.org/10.1097/MIB.0000000000001023
81. Qiu Y, Li MY, Feng T, Feng R, Mao R, Chen BL, et al. Systematic review with meta-analysis: the efficacy and safety of stem cell therapy for Crohn›s disease. Stem Cell Res Ther. 2017;8(1):136. https://doi.org/10.1186/s13287-017-0570-x
82. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn›s disease. Cochrane Database Syst Rev. 2016;9:CD003715. https://doi.org/10.1002/14651858.CD003715.pub3
83. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2015(10):CD000067. https://doi.org/10.1002/14651858.CD000067.pub3
84. Kuenzig ME, Rezaie A, Seow CH, Otley AR, Steinhart AH, Griffiths AM, et al. Budesonide for maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2014(8):CD002913. https://doi.org/10.1002/14651858.CD002913.pub3
85. Patel V, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2014(8):CD006884. https://doi.org/10.1002/14651858.CD006884.pub3
86. Tsertsvadze A, Gurung T, Court R, Clarke A, Sutcliffe P. Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn›s disease: a systematic review and meta-analysis. Health Technol Assess. 2015;19(26):1-138. https://doi.org/10.3310/hta19260
87. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2018;4(4):CD000542. https://doi.org/10.1002/14651858.CD000542.pub3
88. Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(4):389-400. https://doi.org/10.1111/apt.14203
89. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2003(4):CD000301. https://doi.org/10.1002/14651858.CD000301

90. Cottone M, Kohn A, Daperno M, Castiglione F, Annese V, Orlando A. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30-5. https://doi.org/10.1016/j.cgh.2010.09.026
91. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014;89(12):1621-35. https://doi.org/10.1016/j.mayocp.2014.08.019
92. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn›s disease. Aliment Pharmacol Ther. 2018;48(4):394-409. https://doi.org/10.1111/apt.14852
93. Gisbert JP, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015;41(7):613-23. https://doi.org/10.1111/apt.13083
94. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn›s disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis. 2016;18(7):667-75. https://doi.org/10.1111/codi.13311
95. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn›s disease. Cochrane Database Syst Rev. 2016;11:CD007572. https://doi.org/10.1002/14651858.CD007572.pub3
96. Davies SC, Nguyen TM, Parker CE, MacDonald JK, Jairath V, Khanna R. Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn›s disease. Cochrane Database Syst Rev. 2019;12(12):CD012804. https://doi.org/10.1002/14651858.CD012804.pub2
97. Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, et al. Biologic Therapies and Risk of Infection and Malignancy in Patients with Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol. 2016;14(10):1385-97. https://doi.org/10.1016/j.cgh.2016.04.039
98. Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative Risk of Serious Infections with Biologic and/or Immunosuppressive Therapy in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(1):69-81. https://doi.org/10.1016/j.cgh.2019.02.044
99. Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakuraba A. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-alpha agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45(8):1043-57. https://doi.org/10.1111/apt.13990
100. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn›s disease: a network meta-analysis. Gastroenterology. 2015;148(2):344-54. https://doi.org/10.1053/j.gastro.2014.10.011
101. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn›s disease. N Engl J Med. 2004;350(9):876-85. https://doi.org/10.1056/NEJMoa030815
102. McSharry K, Dalzell AM, Leiper K, El-Matary W. Systematic review: the role of tacrolimus in the management of Crohn›s disease. Aliment Pharmacol Ther. 2011;34(11-12):1282-94. https://doi.org/10.1111/j.1365-2036.2011.04873.x
103. Sandborn WJ, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, et al. Tacrolimus for the treatment of fistulas in patients with Crohn›s disease: a randomized, placebo-controlled trial. Gastroenterology. 2003;125(2):380-8. https://doi.org/10.1016/S0016-5085(03)00877-1
104. Cirocchi R, Santoro A, Trastulli S, Farinella E, Di Rocco G, Vendettuali D, et al. Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano. Ann Ital Chir. 2010;81(5):349-56.
105. Ruffolo C, Scarpa M, Bassi N, Angriman I. A systematic review on advancement flaps for rectovaginal fistula in Crohn's disease: transrectal vs transvaginal approach. Colorectal Dis. 2010;12(12):1183-91. https://doi.org/10.1111/j.1463-1318.2009.02029.x
106. Singh S, Ding NS, Mathis KL, Dulai PS, Farrell AM, Pemberton JH, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. Aliment Pharmacol Ther. 2015;42(7):783-92. https://doi.org/10.1111/apt.13356
107. Cao Y, Ding Z, Han C, Shi H, Cui L, Lin R. Efficacy of Mesenchymal Stromal Cells for Fistula Treatment of Crohn's Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2017;62(4):851-60. https://doi.org/10.1007/s10620-017-4453-x
108. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A Systematic Review and Meta-analysis of Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn's Disease: Progress Made and Future Directions. Dis Colon Rectum. 2018;61(5):629-40. https://doi.org/10.1097/DCR.0000000000001093
109. Lee MJ, Parker CE, Taylor SR, Guizzetti L, Feagan B, Lobo A, et al. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(12):1879-92. https://doi.org/10.1016/j.cgh.2018.01.030
110. El-Hussuna A, Krag A, Olaison G, Bendtsen F, Gluud LL. The effect of anti-tumor necrosis factor alpha

agents on postoperative anastomotic complications in Crohn's disease: a systematic review. Dis Colon Rectum. 2013;56(12):1423-33. https://doi.org/10.1097/DCR.0b013e3182a48505
111. Qiu Y, Zheng Z, Liu G, Zhao X, He A. Effects of preoperative anti-tumour necrosis factor alpha infusion timing on postoperative surgical site infection in inflammatory bowel disease: A systematic review and meta-analysis. United Eur Gastroenterol J. 2019;7(9):1198-214. https://doi.org/10.1177/2050640619878998
112. Ahmed Ali U, Martin ST, Rao AD, Kiran RP. Impact of preoperative immunosuppressive agents on postoperative outcomes in Crohn's disease. Dis Colon Rectum. 2014;57(5):663-74. https://doi.org/10.1097/DCR.0000000000000099
113. Nguyen DL, Nguyen ET, Bechtold ML. Outcomes of initial medical compared with surgical strategies in the management of intra-abdominal abscesses in patients with Crohn's disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2015;27(3):235-41. https://doi.org/10.1097/MEG.0000000000000273
114. Morar PS, Faiz O, Warusavitarne J, Brown S, Cohen R, Hind D, et al. Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures. Aliment Pharmacol Ther. 2015;42(10):1137-48. https://doi.org/10.1111/apt.13388
115. Reese GE, Purkayastha S, Tilney HS, von Roon A, Yamamoto T, Tekkis PP. Strictureplasty vs resection in small bowel Crohn's disease: an evaluation of short-term outcomes and recurrence. Colorectal Dis. 2007;9(8):686-94. https://doi.org/10.1111/j.1463-1318.2006.01114.x
116. Dasari BV, McKay D, Gardiner K. Laparoscopic versus open surgery for small bowel Crohn's disease. Cochrane Database Syst Rev. 2011(1):CD006956. https://doi.org/10.1002/14651858.CD006956.pub2
117. He X, Chen Z, Huang J, Lian L, Rouniyar S, Wu X, et al. Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease: a meta-analysis. Dig Dis Sci. 2014;59(7):1544-51. https://doi.org/10.1007/s10620-014-3039-0
118. Tekkis PP, Purkayastha S, Lanitis S, Athanasiou T, Heriot AG, Orchard TR, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. Colorectal Dis. 2006;8(2):82-90. https://doi.org/10.1111/j.1463-1318.2005.00903.x
119. Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009(4):CD006873. https://doi.org/10.1002/14651858.CD006873.pub2
120. Gordon M, Taylor K, Akobeng AK, Thomas AG. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2014(8):CD010233. https://doi.org/10.1002/14651858.CD010233.pub2
121. Gordon M, Naidoo K, Thomas AG, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2011(1):CD008414. https://doi.org/10.1002/14651858.CD008414.pub2
122. Nguyen DL, Solaimani P, Nguyen ET, Jamal MM, Bechtold ML. Anti-tumor necrosis factor alpha is more effective than conventional medical therapy for the prevention of postoperative recurrence of Crohn's disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2014;26(10):1152-9. https://doi.org/10.1097/MEG.0000000000000178
123. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV, Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 2015;148(1):64-76. https://doi.org/10.1053/j.gastro.2014.09.031
124. Burr NE, Hall B, Hamlin PJ, Selinger CP, Ford AC, O'Connor A. Systematic Review and Network Meta-Analysis of Medical Therapies to Prevent Recurrence of Post-Operative Crohn's Disease. J Crohns Colitis. 2019;13(6):693-701. https://doi.org/10.1093/ecco-jcc/jjy216
125. Carla-Moreau A, Paul S, Roblin X, Genin C, Peyrin-Biroulet L. Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: a meta-analysis of controlled trials. Dig Liver Dis. 2015;47(3):191-6. https://doi.org/10.1016/j.dld.2014.11.005
126. McCombie AM, Mulder RT, Gearry RB. How IBD patients cope with IBD: a systematic review. J Crohns Colitis. 2013;7(2):89-106. https://doi.org/10.1016/j.crohns.2012.05.021
127. Ha FJ, Thong L, Khalil H. Quality of Life after Intestinal Resection in Patients with Crohn Disease: A Systematic Review. Dig Surg. 2017;34(5):355-63. https://doi.org/10.1159/000453590
128. Mahadev S, Young JM, Selby W, Solomon MJ. Quality of life in perianal Crohn's disease: what do patients consider important? Dis Colon Rectum. 2011;54(5):579-85. https://doi.org/10.1007/DCR.0b013e3182099d9e
129. Byrne CM, Solomon MJ, Young JM, Selby W, Harrison JD. Patient preferences between surgical and medical treatment in Crohn's disease. Dis Colon Rectum. 2007;50(5):586-97. https://doi.org/10.1007/s10350-006-0847-0