ORIGINAL ARTICLE

AG-2022-122
doi.org/10.1590/S0004-2803.2022005S1-02

Second Brazilian Consensus on the Management of Crohn's disease in adults: a consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

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Received: 17 August 2022
Accepted: 5 September 2022

ABSTRACT – **Background –** Inflammatory bowel disease (IBD) is an immune-mediated disorder that includes Crohn's disease (CD) and ulcerative colitis. CD is characterized by a transmural intestinal involvement from the mouth to the anus with recurrent and remitting symptoms that can lead to progressive bowel damage and disability over time. **Objective –** To guide the safest and effective medical treatments of adults with CD. **Methods –** This consensus was developed by stakeholders representing Brazilian gastroenterologists and colorectal surgeons (Brazilian Organization for Crohn's disease and Colitis (GEDIIB)). A systematic review of the most recent evidence was conducted to support the recommendations/statements. All included recommendations and statements were endorsed in a modified Delphi panel by the stakeholders and experts in IBD with an agreement of at least 80% or greater consensus rate. **Results and conclusion –** The medical recommendations (pharmacological and non-pharmacological interventions) were mapped according to the stage of treatment and severity of the disease in three domains: management and treatment (drug and surgical interventions), criteria for evaluating the effectiveness of medical treatment, and follow-up/patient monitoring after initial treatment. The consensus is targeted towards general practitioners, gastroenterologists, and surgeons interested in treating and managing adults with CD and supports the decision-making of health insurance companies, regulatory agencies, and health institutional leaders or administrators.

Keywords – Crohn's disease; adults; inflammatory bowel diseases; drug therapy; disease management.

INTRODUCTION

In 2010, the Brazilian Organization for Crohn's disease and Colitis (GEDIIB) published the first Brazilian Consensus on inflammatory bowel disease (IBD)[1] aiming to provide a comprehensive, evidence-based medical recommendation on the management of Crohn's disease (CD) in acute and remission phases. The purpose of the consensus was to supplement the 2010 and 2018 guidelines[1,2]. The current update was critical to guide structured discussions that culminated in recommendations to be issued in the new version of the consensus. The recommendations are not meant to substitute clinical judgment. Clinicians should consider the individuality of their patients and the availability of local healthcare resources.

Declared conflict of interest of all authors: The authors receive support for conferences, lectures, or clinical research at the aforementioned laboratories. Abel Botelho Quaresma: AbbVie, Apsen, Janssen; Gilmara Pandolfo Zabot: Abbvie, Takeda, Janssen; Júlio Pinheiro Baima: Janssen, Takeda, Pfizer; Marcello Imbrizi: Abbvie, Takeda, Janssen; Ornella Sari Cassol: Janssen, Abbvie, Takeda, Nestle, Buhlmann; Paulo Gustavo Kotze: Abbvie, Takeda, Pfizer, Janssen; Rogerio Serafim Parra: Takeda, Pfizer, Janssen; Matheus Freitas Cardoso de Azevedo: Janssen, Takeda, Pfizer, Abbvie; Natália Souza Freitas Queiroz: Abbvie, Takeda, Janssen; Júlio Maria Fonseca Chebli: Abbott, Abbivie, Jansen, Takeda; Liliane Andrade Chebli: Jansen, Takeda; Marjorie Costa Argollo: Janssen, Takeda, Pfizer, Abbvie, Sandoz; Ligia Yukie Sassaki: Janssen, Takeda; Adérson Omar Mourão Cintra Damião: Janssen, Takeda, Abbvie, Ferring; Antonio Carlos da Silva Moraes: Abbvie, Takeda, Jansen, FQM, Pfizer; Cristina Flores: Takeda, Janssen, Pfizer, Abbvie; Cyrla Zaltman: Takeda, Abbvie, Janssen, Pfizer, Ferring; Eduardo Garcia Vilela: Ferring; Eloá Marussi Morsoletto: Takeda, Janssen; Francisco de Assis Gonçalves Filho: Takeda, Janssen; Francisco Guilherme Cancela e Penna: Abbvie, Janssen, Novartis, Takeda; Genoile Oliveira Santana: Abbvie, Ferring, Janssen, Pfizer, Takeda; José Miguel Luz Parente: Abbvie, Janssen, Takeda, Pfizer ; Marcia Henriques de Magalhães Costa: Janssen, Abbvie, Takeda, Pfizer ; Marco Antonio Zerônco: Takeda, Janssen, Abbvie; Marta Brenner Machado: Janssen, Abbvie, Takeda, Ferring, Pfizer; Renata de Sá Brito Fróes: Janssen, Takeda, Abbvie, Pfizer; Orlando Ambrogini Junior: Abbvie, Janssen, Pfizer, Takeda; Rogério Saad-Hossne: Abbvie, Takeda, Janssen, Pfizer, Sandoz.
Disclosure of funding: the consensus was funded by Ferring, Janssen, and Takeda for its execution, without any interference in the construction process, the decision of recommendations, validation, or publication.
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Crohn's disease

Crohn's disease is caused by the interaction of genetic factors, abnormal intestinal microbiota, and dysregulated mucosal immunoregulation[3-6]. UC involves the rectum and colon, whereas CD may occur in any part of the digestive tract from the mouth to the anus; most commonly, it affects the terminal ileum and cecum. The hallmark of CD is discontinuous areas of inflammation characterized by ulceration, erythema, mucosal edema, or luminal narrowing. It can involve the entire intestinal wall (transmural inflammation) and cause non-caseating granulomatous reactions.

Disease classification

CD can be classified according to severity, extension and disease behavior[7]. Among several scales, the Harvey Bradshaw Index (HBI) (TABLE 1)[8] and the Crohn's Disease Activity Index (CDAI) (TABLE 2)[9] are most often used in clinical studies. However, in clinical practice, an assessment by the attending physician may be sufficient to evaluate the severity of the disease. Such assessment must include a workup of comprehensive medical history (including signs, symptoms, and extraintestinal manifestations), laboratory and endoscopic evaluations, and histologic and imaging evaluations. These components provide essential information on disease location, extension, and behavior for proper diagnosis and risk assessment[10].

TABLE 1. Harvey Bradshaw Index.

Variable	Options	Points
General well-being*	Very well	0
	Slightly below par	1
	Poor	2
	Very poor	3
	Terrible	4
Abdominal pain*	None	0
	Mild	1
	Moderate	2
	Severe	3
Number of liquid/soft stools*		1 per stool
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite and tender	3
Complications		
Arthralgia		
Uveitis		
Erythema nodosum		
Aphthous ulcers		
Pyoderma gangrenosum		
Anal fissures		
New fistula		
Abscess		

*For the previous day, as reported by the patient.

Calculation formula: sum of the scores of all five parameters. A score below five is generally considered clinical remission. A reduction of 3 points is considered relevant to define a clinical response. A score of 5 to 7 refers to mild activity, 8 to 16 refers to moderate activity, and >16 refers to severe activity.

TABLE 2. Crohn's disease Activity Index.

	Weighing factor
1) Sum of the number of liquid or soft stools for the previous seven days	x2
2) Abdominal pain (none = 0; mild = 1; moderate = 2; severe = 3) Consider the total sum of individual data during the previous week	x5
3) General well-being (excellent = 0; good = 1; average = 2; bad =3; terrible = 4) Consider the total sum of individual data during the previous week	x7
4) Number of associated symptoms (list by category) Arthralgia/arthritis Inflammation of the iris/uveitis erythema nodosum/oral aphthae Anal fissure, fistulae, or abscesses other types of fistulae fever	x20 (Maximum value =120)
Use of antidiarrheic drugs (No = 0; Yes = 1)	x30
Abdominal mass (none = 0; questionable = 2; definite = 5)	x10
Absolute deviation of hematocrit: men 47-Ht; women 42-Ht (subtract instead of adding if patient's Ht is higher than standard)	x6
Weight*: percentage deviation from standard weight (subtract instead of adding if patient's weight is higher than expected) *Expected or ideal weight = height (m)2 x 25.5=_____ kg (men) Height (m)2 x 22.5=_____ kg (women)	x1
Total CDAI score ≤150 = Remission 150–250 = Mild 250–350 = Moderate 350 = Severe	

Calcul ation formula: CDAI = (P1 x 2) + (P2 x 5) + (P3 x 7) + (P4 x 20) + (P5 x 30) + (P6 x 10) + (P7 x 6) + P8. In the formula, the last parameter (P8) is not multiplied by the relevant 'weight factor,' given that in this parameter, the 'weight factor' is equal to 1.

Clinicians may also categorize patients using the Montreal classification (modified from the Vienna classification), described in BOX 1, which was developed to standardize the case description of CD patients in clinical studies[11,12].

BOX 1. The Montreal Classification.

1. Age at onset/diagnosis
(_) A1: <16 years of age
(_) A2: between 17 and 40 years of age
(_) A3: >40 years of age

2. Disease location
(_) L1: ileal
(_) L2: colonic disease
(_) L3: ileocolonic
(_) L4*: isolated upper GI tract disease

3. Behavior
(_) B1 – Non-stenosing, non-penetrating
(_) B2 – Stenosing
(_) B3 – Penetrating
'p': modifier for perianal disease

* a modifier that can be added to L1–3 in case of concomitant disease involving the upper GI tract; 'p' is added to B1–3 when concomitant perianal disease is present.

Clinical response

There is substantial heterogeneity across studies in definitions of clinical response, clinical remission, and endoscopic remission[13,15]. Most pivotal studies evaluating the efficacy of IBD treatments consider clinical response as a decrease of 70–100 points from the baseline of the CDAI score. However, this definition is difficult to apply in clinical practice. To consider symptom improvement only, rather than an improvement in symptoms and laboratory indices, it is possible to use the HBI. This questionnaire refers to disease symptoms in the previous 24 hours and includes 12 items. It is composed of five domains: general well-being; abdominal pain; the number of liquid stools per day; abdominal mass (limited physical examination by the clinician); extraintestinal manifestations of CD (e.g., arthralgia, uveitis, erythema nodosum, aphthous ulcer, pyoderma gangrenosum, anal fissure, new fistula, and abscess). A three-point change in the index is used to define clinical response[16]. However, it should be noted that neither HBI nor patient-reported outcome measures correlate well with objective markers of inflammation in CD[17]. These measures are thus complementary to objective measures of disease activity obtained at endoscopy, imaging, and surrogate markers, including fecal calprotectin[18].

Endoscopic response

Several endoscopic scoring systems define endoscopic activity and therapy response in CD. The two most common tools to assess complete mucosal healing as an endpoint in clinical trials are the Crohn's Disease Endoscopic Index of Severity (CDEIS)[19] and the Simplified Endoscopic activity Score for Crohn's disease (SES-CD)[20] (TABLE 2). Although less frequently used in routine clinical practice, the SES-CD is a simple and reliable endoscopic score based on features in each segment of the colon and the terminal ileum. There is no widely accepted definition of endoscopic response. Endoscopic remission is usually defined as the absence of ulcerations or an SES-CD or CDEIS score <3[21]. (TABLE 3).

Clinical remission

Remission refers to the absence of symptoms or inflammatory sequelae. Patients responding to medical or surgical intervention without evidence of residual disease are said to be in remission; steroid-dependent patients are not in remission[18,22]. The SES-CD (score of ≤4) and CDAI (score of <150) are often used as a definition of clinical remission[23,24].

Steroid-free clinical remission

Corticosteroid-free clinical remission has been used as a primary or secondary endpoint in clinical trials. Corticosteroids are effective at improving symptoms and providing a global sense of well-being; however, they are ineffective as maintenance therapy, and toxicity can be significant[25]. For this reason, steroid-free remission is considered a critical endpoint for evaluating new therapies[26].

Sustained clinical remission

There is also significant variation among studies concerning the definition of sustained remission. Examples include broad definitions such as stable, steroid-free clinical remission during the 1-year follow-up period[27].

Improvement in QoL

With advances in clinical trial designs and the influence of regulatory agencies seeking patient-reported outcomes as primary endpoints, QoL and related psychosocial measures are of growing significance in IBD research[28]. The Inflammatory Bowel Disease Questionnaire is the most widely used QoL instrument for patients with IBD[29]. The scale has 32 items scored on a seven-point Likert scale, ranging from one (worst health) to seven (best health).

Drug classes (TABLE 4)

Salicylic acid derivatives

In this group of drugs, we included sulfasalazine (SSZ) and salicylic acid derivatives (5-ASA), which act through the modulation of proinflammatory cytokine secretion, inhibition of leukotriene and prostaglandin production, and many other purported mechanisms[30-32]. These drugs are available in the controlled-release form, allowing release at specific sites of the gastrointestinal tract and for topical use as suppositories and enema[33,34]; thus, there is a wide range of pharmacologic formulations to tailor individualized treatment depending on tolerance, efficacy, acceptability, and patient preference.

Side effects of SSZ are commonly dose-dependent and related to serum levels of sulfapyridine. Such effects occur mainly in individuals with the low genetic ability of hepatic acetylation of the drug in up to 45% of patients[35,36]. These side effects include abdominal pain, nausea, vomiting, anorexia, headache, hemolysis, and male infertility. SSZ side effects may occur less frequently due to hypersensitivity (allergy or idiosyncratic reactions): fever, rash, lymphadenopathy, Stevens-Johnson syndrome, agranulocytosis, hepatitis, pancreatitis, and diarrhea. Sulfasalazine therapy is accompanied by a relatively high incidence of intolerance-related side effects and includes headache, nausea, dyspepsia, myalgias, and arthralgias[37,38], which are typically not severe but can lead to drug interruption.

Corticosteroids

Corticosteroids (e.g., hydrocortisone, prednisone, and prednisolone) are currently the drugs of choice for moderate and severe cases of IBD, particularly to achieve symptom control; they help to induce clinical remission in 70% to 90% of cases after 4 to 6 weeks of treatment. The corticosteroid course should be as short as possible, and prolonged treatment (i.e., for maintenance of remission) is not recommended[10,25]. In active IBD, oral prednisone is typically indicated; however, it must be avoided for extended periods (>2–3 months), even at low doses. Corticosteroid weaning must be gradual until total withdrawal is achieved. If a relapse oc-

TABLE 3. Simple endoscopic score for Crohn's disease (derived from Lamb et al.[18]).

			Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Size of ulcers (diameter)	Absent	0						
	Aphthous ulcers, 0.1–0.5 cm	1						
	Large ulcers, 0.5–2 cm	2						
	Very large ulcers, > 2 cm	3						
Ulcerated surface	None	0						
	<10% of the segment	1						
	10–30% of the segment	2						
	>30% of the segment	3						
Affected surface	None	0						
	< 50% of the segment	1						
	50–75% of the segment	2						
	75% of the segment	3						
Presence of narrowing	None	0						
	Single, passable by the scope	1						
	Multiple, passable by the scope	2						
	Not passable, frank stenosis	3						
	Total SES-CD =							

A score of 0 to 2 refers to disease remission; 3 to 6 refers to mild endoscopic activity; 7 to 15 refers to moderate endoscopic activity, and > 15 refers to severe endoscopic activity.

TABLE 4. Drugs used in Crohn's disease treatment.

Drug	Induction dose	Maintenance dose
Corticosteroids	Budesonide (mild ileal and/or right colon commitment) 9 mg/day PO for 2–3 months Prednisolone 0.50 to 0.75 mg/kg PO with a maximum daily dose of 60 mg	Maintenance dose is not indicated. For prednisolone use, after 14 days of full dose, if patient with clinical improvement, consider tapering at 5 mg/week over an 8– to 12-week period
Immunosuppressants	Azathioprine: 1,5–2,5 mg/kg/day PO 6-mercaptopurine: 1–1.5 mg/kg/day PO	Azathioprine: 1,5–2,5 mg/kg/day PO 6-mercaptopurine: 1–1.5 mg/kg/day PO
	Methotrexate: 25 mg/week SC or IM for 12 weeks	Methotrexate: 15 mg/week SC or IM
Anti-TNF	Infliximab 10 mg/mL (10 mL/unit): 5 mg/kg IV at 0, 2, and 6 weeks or Infliximab 5 mg/kg IV at 0 and 2 weeks Adalimumab 40 mg (syringe or pen) or 80 mg (pen): 160 mg SC and then 80mg after 2 weeks Certolizumab pegol 200 mg/unit (syringe): 400 mg SC at weeks 0, 2 and 4	Infliximab 10 mg/mL (10 mL/unit): 5 mg/kg IV every 8 weeks or Infliximab 120 mg SC every 2 weeks from week 6 Optimized dose: 10 mg/kg every 8 weeks or 5 mg/kg every 4 weeks Adalimumab 40 mg (syringe or pen) or 80 mg: 40 mg SC every 2 weeks Optimized dose: 40 mg SC weekly or 80 mg SC every 2 weeks Certolizumab pegol 200 mg/unit (syringe): 400 mg SC every 4 weeks
Anti-integrin	Vedolizumab 300 mg/unit: 300 mg IV at weeks 0, 2 and 6 An additional dose at week 10 may be indicated in those patients with a suboptimal response	Vedolizumab 300 mg/unit: 300 mg IV every 8 weeks (vedolizumab): or 108 mg SC every 2 weeks starting after the second or third intravenous induction dose Optimized dose: 300 mg IV every 4 weeks or 108 mg SC weekly (off label)
Anti-interleukin	Ustekinumab 130 mg/26 mL 55 kg or less: 260 mg 55 kg to 85 kg: 390 mg more than 85 kg: 520 mg Risankizumab* 600 mg/unit: 600 mg IV at weeks 0, 4 and 8	Ustekinumab 90 mg/unit: 90mg SC every 8 or 12 weeks Optimized dose in patients with 90 mg every 12 weeks: 90 mg SC every 8 weeks (on-label) Optimized dose in patients with 90mg every 8 weeks: 90 mg SC every 4 weeks (off-label)Risankizumab* 360 mg/2.4 mL (syringe): 360 mg SC at week 12 and then every 8 weeks

PO: oral administration; IM: intramuscularly; SC: subcutaneous; IV: intravenous *(FDA approved).

curs during withdrawal, the corticosteroid dose may be increased to the same level as before the one that caused the relapse. In severe cases, inpatients may be given intravenous hydrocortisone or methylprednisolone followed by oral prednisone as soon as the patient can tolerate it.

Corticosteroid side effects are well known, primarily when used for prolonged periods, even at low doses. These side effects include appetite stimulation, increase in body weight, edema, insomnia, emotional lability, psychosis, acne, Cushing syndrome, osteoporosis, osteonecrosis, growth stunting, infections, myopathies, cataract, skin atrophy, striations, ecchymosis, fatty liver, diabetes, hypertension, glaucoma, and acute pancreatitis. Novel corticosteroids have been developed to reduce such effects[37]. For example, budesonide (which can be used in mild-to-moderate cases) undergoes a quick and effective (~90%) metabolization into inactive products after its first passage through the liver[39,40]. Some reports suggest that budesonide may be used for more extended periods (up to 6 months) when necessary. As soon as the patient presents signs of corticosteroid dependence (e.g., a corticosteroid is necessary to maintain remission) or refractoriness (non-responsive to a corticosteroid dose of 0.75–1 mg/kg/day, prednisone for 4–6 weeks), other alternatives must be instituted.

Immunosuppressants

Medical therapies for CD management heavily rely on suppressing an abnormally active intestinal immune system. For this reason, immunosuppressants are one of many available treatment options[10]. There are currently two medications of such kind for CD patients:

- Methotrexate (MTX), a folate antagonist with anti-inflammatory properties, is used to treat various inflammatory diseases, especially for alleviating signs and symptoms in patients with steroid dependence and maintaining remission[41].
- Thiopurines (azathioprine, AZA; and 6-mercaptopurine, 6-MP) are commonly used to maintain remission in steroid-dependent and steroid-refractory patients. They maintain long-term clinical remission and prevent relapses[42].

These medications are not without side-effects: thiopurines are associated with an increased risk of infection, myelosuppression, liver toxicity, pancreatitis, and malignancy, while MTX is associated with an increased risk of myelosuppression, pulmonary toxicity, liver toxicity, and congenital disabilities[43].

Other agents such as cyclosporine and tacrolimus share similar mechanisms of action and are valuable for patients with UC; however, such agents are ineffective for active CD treatment and thus should not be considered an option for these patients[44].

Biologic agents

The introduction of biologic agents for IBD has considerably modified the disease course[45,46]. Substantial improvements were made in outcomes with better symptom control, improved QoL, and control of inflammation, objectively judged through endoscopic, radiological, or biochemical measurements. Before initiating any biologic therapy, patients should be tested for latent tuberculosis and hepatitis B[18].

Currently, the available biologics for treatment of CD are anti-tumor necrosis factor alpha (anti-TNF-α), infliximab, adalimumab, certolizumab pegol, and the anti-integrin agent vedolizumab (a monoclonal antibody to the α4β7 integrin) and ustekinumab (an antibody that targets the p40 subunit of interleukins IL-12 and IL-23)[47]. Recently, phase III placebo-controlled studies (ADVANCE and MOTIVATE trials) demonstrated the efficacy of intravenous risankizumab for inducing and maintaining clinical remission (absolute risk difference, 20.7%; 95% confidence interval [CI]: 12.4 to 29.0; $P<0.001$) and endoscopic response[48]. Risankizumab is an IgG1 monoclonal antibody that selectively binds the unique p19 subunit of human IL-23. In a 12-week, phase 2 double-blind trial, intravenous guselkumab resulted in significantly greater rates of clinical remission and endoscopic response compared to placebo in moderately-to-severely active CD, with no safety concerns[49].

Probiotics

Probiotics are living microorganisms that, "when administered in adequate amounts, confer a health benefit on the host," according to the Food and Agriculture Organization[50]. Probiotics have long been proposed to improve human health; however, in recent years, there has been a growing interest in its use in IBD due to the role of microbiomes in disease pathogenesis[51,52]. Several studies evaluated the use of probiotic agents as adjuvant therapy in CD treatment; however, the literature is limited to few and small trials unable to provide evidence of clinical benefit in this patient population[53].

The objective of the consensus

This consensus aims to guide the most effective medical management of adults with CD. It is not intended to address the diagnostic evaluation. The question covered by this consensus is, "What is the best medical management for adults with CD according to the disease severity and treatment phase?"

METHODS

This consensus addresses the most relevant information to guide the decision-making process for the clinical management of CD. It synthesizes recommendations developed from evidence-based statements and state-of-the-art knowledge, although primary research was also reviewed. It does not intend to provide the full range of options for treatment available, nor does it cover all aspects of the condition. The consensus of experts, especially in health, can synthesize information ready for clinical assistance, management, research, and policy in health systems while maintaining diversity and independence of opinions, decentralization, and knowledge specialization.

The GEDIIB represents key Brazilian stakeholders who were involved in this consensus. The consensus targeted general practitioners and gastroenterologists interested in treating and managing adults with CD. This consensus also supports the decision-making of health insurance companies, institutional leaders, or administrators.

The rapid review approach[54] was the most appropriate as it is the highest quality method to provide the best and most recent evidence. The concern for timely decisions in health care and policies was the driving force for this consensus. Traditional systematic reviews can take years to complete; by contrast, a rapid review provides the same quality standards based on the principles of the Cochrane Collaboration. Therefore, the rapid systematic review approach was taken to support the recommendations/statements. According to its definition, the literature review was systematic but with some limitations such as database number, study design, and search period. High-quality guidelines or consensuses and level 1 evidence studies (systematic literature review) were eligible, identi-

fied, and synthesized to support the recommendations/statements in this document. To obtain the most recent evidence, the MEDLINE database search was limited to October 2016 to October 2021. The PICOS acronym was used to describe the questions to be answered, which are presented in detail in the supplementary material. Only publications in English were considered. Quality appraisal of the guidelines/consensuses was conducted using appropriate tools (additional methodologies data can be found in supplementary material: PICOS – TABLES S1 to S8; search strategy – TABLE S9; screening flowchart – FIGURES S1 and S2; and quality appraisal – TABLES S10 to S12). In addition to the studies identified and included through the systematic review, the recommendations were also endorsed by studies captured by a "snowballing search" starting from the reference list of the identified guidelines.

The quality appraisal of the included studies was conducted using the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II) and the Measurement Tool to Assess Systematic Reviews (AMSTAR 2). The AGREE II evaluates the quality of the guidelines or consensus included in the rapid literature review[55]. This instrument was developed to address the variability in the quality of practice guidelines. The AMSTAR 2 evaluates the quality of the evidence of the systematic literature review with meta-analysis[56]. Initially, the Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to investigate the methodological quality of systematic reviews. The AMSTAR 2 was developed for systematic reviews of randomized controlled trials. The overall confidence rate in the systematic review results is classified as high, moderate, low, or critically low.

Regarding the formulations of the recommendation/statements, the medical recommendations (pharmacological and non-pharmacological intervention) were structured and mapped according to the severity and treatment phase of the disease in three domains: management and treatment (drug and surgical interventions), criteria to evaluate medical treatment efficacy and patient follow-up/monitoring after initial treatment.

After structuring the recommendations/statements, the modified Delphi panel methodology was used to conduct the voting. This panel consisted of three rounds: two using a personalized and anonymous online voting platform and one face-to-face. Whenever participants disagreed with specific statements-recommendations, an option to explain was offered to enable free-text responses, allowing experts to elaborate or explain disagreement. The face-to-face consensus was held in Guarulhos, São Paulo, Brazil, in May 2022. It comprised 34 gastroenterologists and colorectal surgeons (members of GEDIIB). The consensus of recommendations/statements in each round was defined as ≥80% agreement[57].

MEDICAL MANAGEMENT OF CROHN'S DISEASE

Mild-to-moderate active CD
Induction Treatment

Salicylic acid derivatives

Recommendations

- We do not recommend oral mesalazine for induction of remission or promoting mucosal healing in patients with CD. **Agreement:** 94.5%[44,58].

Evidence to support the efficacy of aminosalicylates as induction therapy for patients with CD is controversial. The meta-analysis of Coward et al. (2017) found that high doses of corticosteroids were more effective than high doses of mesalazine (OR=1.83 [95% credible interval [CrI] 1.16 to 2.88]). However, corticosteroids (odds ratio [OR] = 3.80 [95% CrI 2.48 to 5.66]), high-dose budesonide (OR=2.96 [95% CrI 2.06 to 4.30]), and high-dose mesalamine (OR=2.29 [95% CrI 1.58 to 3.33]) were superior to placebo; sulfasalazine was not significantly superior to any therapy including placebo[59]. In agreement with this evidence, Lim et al. (2016) found that low-dose mesalazine (1 to 2 g/day) was not superior to placebo for induction of remission (risk ratio [RR=1.46 [95%CI 0.89 to 2.40). High-dose delayed-release mesalazine (3 to 4.5 g/day) was also not superior to conventional corticosteroids (RR=1.04 [95%CI 0.79 to 1.36) or budesonide (RR=0.89 [95%CI 0.76 to 1.05)[60].

Corticosteroids

Recommendations

- Ileal-release budesonide (daily dose of 9 mg for eight weeks) can be used to induce remission in active ileocecal CD or disease limited to the ileum or ascending colon. If treatment is ineffective, systemic corticosteroids should be used. **Agreement:** 86.1%[18,44,58,61-63].

Budesonide 9 mg/day (and at higher doses [15 or 18 mg/day]), was superior to placebo for induction of remission [OR=2.93 [95% CrI 1.52 to 5.39] and OR=3.28 [CrI 1.46 to 7.55], respectively] and ranks at the top of the hierarchy of the competing treatments[64]. In a Cochrane review, budesonide was more effective than placebo for induction of remission in CD. Although the short-term efficacy of budesonide was inferior to conventional steroids (particularly in those with severe disease or more extensive colonic involvement), the likelihood of adverse events and adrenal suppression with budesonide was lower[65].

Immunosuppressants

Recommendations

- We recommend against using thiopurine monotherapy, cyclosporine, and tacrolimus to induce remission in patients with luminal CD. **Agreement:** 90%[1,66].

Expert opinion

- We suggest the early use of thiopurines or parenteral methotrexate in patients with mild-to-moderate CD receiving systemic glucocorticoids for induction of remission to spare long-term corticosteroid therapy. **Agreement:** 100%.

Current evidence does not support the use of thiopurine monotherapy in symptomatic remission rates for CD. Across five randomized controlled trials (RCTs), overall remission was achieved in 48% of patients receiving thiopurines compared to 37% of patients receiving placebo; however, the difference was not statistically significant (RR=1.23 [95%CI 0.97 to 1.55]). The assessment of clinical remission using AZA or 6-MP compared to placebo or other active therapy generated no statistically significant difference between therapies (RR=1.26, 95%CI 0.98 to 1.62)[42]. The combination of intramuscular MTX with prednisone was associated with clinical improvement and less need for prolonged corticosteroids.

Probiotics and symbiotics

Recommendations
- We do not recommend probiotics or symbiotics for induction of remission in patients with CD. **Agreement:** 86.1%[2,66].

Several systematic reviews with meta-analyses showed no benefit in favor of probiotics for patients with CD based on few and small clinical trials[67-70]. A recently published Cochrane meta-analysis found no evidence in favor of probiotics for the induction of remission (RR=1.06 [95%CI 0.65 to 1.71; two studies, 46 participants])[71]. The literature is currently limited and does not support the recommendation for probiotics in CD as induction treatment.

Maintenance treatment

Salicylic acid derivates

Recommendations
- The use of mesalazine is not recommended to maintain medically induced remission in CD. **Agreement:** 80.5%[2,18,61].

Based on high-quality studies and robust data, current evidence does not support the use of salicylic derivates in the maintenance of CD. In a meta-analysis of 11 RCTs (2014 participants) that compared oral 5-ASA agents to placebo during maintenance therapy, there was no evidence of a significant difference in relapse rates at 12 months (RR=0.98 [95%CI 0.91 to 1.07; moderate quality evidence])[72].

Corticosteroids

Recommendations
- We recommend against the use of corticosteroids for the maintenance of remission in CD. Systemic or locally acting corticosteroids such as budesonide should be avoided as maintenance therapy in CD due to toxicity and lack of efficacy. **Agreement:** 91.7%[2,18,61,63].

In a meta-analysis of three RCTs, there was no evidence of superiority vs placebo in favor of corticosteroids at 6, 12, or 24 months (RR at 6 months: 0.71 [95%CI 0.39 to 1.31; at 12 months: 0.82 [95%CI 0.47 to 1.43]; at 24 months: 0.72 [95%CI 0.38 to 1.35])[73]. Similarly, the meta-analysis by Kuenzig et al. (2014) found no efficacy of budesonide for maintenance of remission at three months (RR=1.25 [95%CI 1.00 to 1.58]), at 6 months (RR=1.15 [95%CI 0.95 to 1.39]), or at 12 months (RR=1.13 [95%CI 0.94 to 1.35])[74]. In addition to its well-known unwanted side effects, there is compelling evidence that corticosteroids are not disease-modifying agents, with several trials failing to provide evidence of their efficacy in maintaining remission, reducing flares, or disease recurrence[73,75].

Immunosuppressants

Recommendations
1. Thiopurines such as AZA or 6-MP may be used as monotherapy for the maintenance of remission in CD. These drugs are recommended for the maintenance of remission in steroid-dependent and steroid-refractory CD patients. **Agreement:** 88.9%[2,18,61,66,76,77].
2. Treatment with thiopurines should be continued in the long term despite achieving clinical remission to avoid the risk of relapse after its discontinuation. **Agreement:** 100%[2,18,61,66,76,77].
3. If parenteral MTX was used to induce remission, it may be used as maintenance therapy with a dose of at least 15 mg weekly. **Agreement:** 80.5%[18,61,76].
4. We do not recommend using either cyclosporine or tacrolimus for the maintenance of remission in patients with CD. **Agreement:** 97.3%[2].

For maintaining clinical remission, treatment with AZA or 6-MP is superior to placebo (OR=2.32 [95%CI 1.55 to 3.49]) and budesonide (OR=3.32 [95%CI 1.40 to 7.87])[42]. The continuous use of thiopurines during maintenance (after achieving clinical remission) is also associated with a reduced risk of relapse.

It is estimated that one in four patients undergoing treatment with thiopurines experiences adverse events, and withdrawal rates of AZA due to drug intolerance appear to be as high as 17%. The most frequent thiopurine-related side effect is nausea, followed by hepatotoxicity, pancreatitis, and leukopenia. Treatment may be switched from AZA to 6-MP (and vice-versa) in cases of nausea and vomiting before considering other therapies[78].

The assessment of clinical remission using MTX in a real-world setting demonstrated its efficacy as a second line immunomodulator in chronic active CD. The cumulative probabilities of maintaining remission using MTX at 6 months, 1, 2, and 3 years of treatment were 95.3%, 89.5%, 70.6%, and 62.8%, respectively. It should be noted that the use of MTX is limited by intolerable side effects in many patients[79]. In specific cases where patients have used this drug to induce remission and in patients who are intolerant or refractory to thiopurines, MTX may be effective in maintaining remission[18]. Parenteral MTX administration is recommended for the maintenance of remission in patients with steroid-dependent CD[58], and if remission has been achieved with systemic steroids, a thiopurine or MTX may be considered.

Thiopurines should also be avoided in patients with low thiopurine methyltransferase (TPMT) activity. The dose of thiopurine should be reduced to 50% in those with intermediate thiopurine activity. Daily dosage should also be reduced in patients with significant renal impairment. Low-dose thiopurines (25–33% of the usual dose) in combination with allopurinol 100 mg might be considered in patients with thiopurine hepatotoxicity, nausea, or flu-like symptoms, or those who are hyper-methylators[18]. However, in the Brazilian public health scenario, analytical methods for the measurement of TPMT genotype and phenotypic activity are not widely available.

Probiotics and symbiotics

Recommendations
- We do not recommend using probiotics or symbiotics to maintain remission in patients with CD. **Agreement:** 86.1%[2,66].

There is no compelling evidence to support the use of probiotics to maintain remission or postoperative recurrence in patients with CD. In a pooled analysis of four studies (289 participants), probiotics were not superior to placebo on the recurrence rate of CD (0.80 [95%CI 0.61 to 1.06][70]. Due to the sparsity of data and heterogeneity in treatment protocols, it is difficult to determine whether probiotics or symbiotics have a role in CD.

Moderate-to-severe active CD in adults

Induction treatment

Salicylic acid derivatives

Recommendations

- Mesalazine should not be used for induction of remission in CD. **Agreement:** 94.5%[18].

The evidence does not support the efficacy of mesalazine and the overall use of aminosalicylates for patients with CD. This also extends to moderate-to-severe CD in induction therapy.

Corticosteroids

Recommendations

- Systemic corticosteroids are recommended in the short term for alleviating symptoms. The early introduction of biologic therapy is suggested for those with poor prognostic features. **Agreement:** 97.3%[18,44].

Systemic corticosteroids (e.g., prednisone) have potent anti-inflammatory properties and are effective for induction of remission in moderate-to-severe cases of CD, independent of disease location[58,61,64,77,80]. However, not all corticosteroids are equally effective. In patients with severe disease, budesonide was inferior to conventional steroids (RR=0.52 [95%CI 0.28 to 0.95])[65]. In patients with a luminal CD of sufficient severity to require hospitalization, use of intravenous corticosteroids (e.g., methylprednisolone 40–60 mg/day or hydrocortisone 100 mg every 6 or 8 hours) is suggested to induce symptomatic remission[66].

Systemic corticosteroids should be tapered gradually according to disease severity and patient response, usually within eight weeks (complete weaning is recommended within eight to 12 weeks)[61,76]. Conventional corticosteroids are ineffective in achieving mucosal healing and should be used sparingly[44,77].

Immunosuppressants

Recommendations

- We do not recommend using thiopurine, cyclosporine, or tacrolimus monotherapy to induce remission in patients with CD. **Agreement:** 94.5%[2].

Several trials compared the use of thiopurines against placebo for induction of remission. In a meta-analysis of five studies (380 patients), no difference was found for clinical remission (RR=1.23 [95%CI 0.97 to 1.55]; moderate quality of evidence). These results are consistent with the rationale for avoiding thiopurines to induce remission due to their delayed onset of action (estimated time to response: 3.1 months)[42].

Systemic glucocorticoids in concomitant use with MTX may be effective in inducing CD remission. In the absence of poor prognostic features, intramuscular or subcutaneous MTX up to 25 mg once weekly may be a therapeutic alternative to induce remission of moderate-to-severe CD[44,58,61].

Biological agents

Recommendations

1. We recommend that patients refractory to immunomodulatory therapy or with complicated disease or poor prognostic features should be considered for early biologic therapy. The choice of specific therapy should be made on an individual basis. **Agreement:** 94.5%[18].
2. We suggest the early use of biologics within 2 years of diagnosis. Biologics improve clinical remission, promotes mucosal healing, and reduce relapse rates compared to late or conventional management. **Agreement:** 93.9%[81].

Expert opinion

- Patients with moderate-to-severe disease and safety-related risk factors (e.g., advanced age, relevant comorbidities, and previous serious infections) may be treated preferentially with vedolizumab or ustekinumab. **Agreement:** 94.5%[2,44,58,77,82].

Early use of biologics in patients with moderate-to-severe CD is statistically and clinically superior for inducing clinical remission (OR=2.10 [95%CI 1.69 to 2.60]; 2763 participants), reducing relapse (OR=0.31 [95%CI 0.14 to 0.68]; 596 participants), and inducing mucosal healing (OR=2.37 [95%CI 1.78 to 3.16]; 994 participants) compared to late or conventional treatment. It also improves clinical outcomes such as corticosteroid-free remission, hospitalization rate, complications, and surgeries and is cost-effective[81].

There is compelling evidence from six randomized trials in favor of vedolizumab's safety, which was associated with fewer infection events and similar rates of other adverse events compared to placebo. Trials and real-world data provide evidence of acceptable safety in favor of ustekinumab, with rates of infections and other adverse events comparable to placebo-treated patients[83]. Given these data and the gut-specificity of its receptor, vedolizumab and ustekinumab are considered safer biologic alternatives among the currently available therapeutic options for IBD[84].

Anti-TNF

Recommendations

1. Anti-TNF agents (e.g., infliximab, adalimumab, and certolizumab pegol) should be considered to treat moderate-to-severely active CD or refractory to conventional therapy or steroid-dependent patients. **Agreement:** 94.5%[2,44,58,77,82].
2. Combined infliximab and AZA induce better clinical outcomes than either one as monotherapy. **Agreement:** 91.7%[2,44,58,77,82].
3. It is recommended to use anti-TNF combined with thiopurines over anti-TNF monotherapy to induce remission in patients with moderate-to-severe CD when serum anti-drug antibodies are detected, or subtherapeutic drug concentrations are observed. **Agreement:** 88.9%[2,44,58,77,82].

Expert opinion

- We suggest using infliximab or adalimumab in patients with severe CD with a poor prognosis or hospitalized. **Agreement:** 83.4%[2,44,58,77,82].

Anti-TNF agents may induce remission of moderate-to-severe CD[61,82]. Real-world data demonstrate that after one year of treatment, almost half (48.6% [95%CI 32.8–64.7%]) of the patients with CD achieve deep remission (clinical and endoscopic) using anti-TNF[85]. Therapy with infliximab and immunomodulator was superior to infliximab monotherapy (RR=0.83 [95%CI 0.70 to 0.97])[86]. Infliximab monotherapy effectively induces remission in patients with moderate-to-severe CD refractory to conventional therapy[2] and may be administered to treat the fulminant cases of the disease[44]. Regarding adalimumab, the clinical benefit of its combination with thiopurine is uncertain for patients with moderate-to-severe CD[2,87].

Concerning the exposure to biologic therapy, in biologic-naïve patients with moderate-to-severe CD, infliximab monotherapy, infliximab combined with AZA, adalimumab, and ustekinumab were associated with significantly higher odds of inducing remission than certolizumab pegol[88,89]. In a systematic review and network meta-analysis comparing the efficacy of biologic therapies in moderate-to-severe CD, infliximab and AZA combination therapy were associated with significantly higher odds of inducing remission than vedolizumab. In patients previously exposed to biologic therapy, adalimumab after the loss of response to infliximab and risankizumab (not currently available in Brazil) were associated with higher odds of inducing remission than vedolizumab[89,90].

In case of objective evidence of active disease refractory to corticosteroids, an anti-TNF-based strategy may be considered among the appropriate therapeutic options, although surgical options should also be discussed early[63]. When the need for a switch from anti-TNF therapy to a different class of drugs in CD is identified, the choice to use anti-integrin or anti-interleukin can be made individually.

Anti-integrin

Recommendation

- We recommend using vedolizumab during induction in patients with moderate-to-severe CD and inadequate response to conventional or anti-TNF therapy. If a suboptimal response is seen after induction therapy (three doses), we suggest an additional dose at week ten. **Agreement:** 94.5%[2,18,44,58,66].

Vedolizumab was superior to placebo for the induction of remission at week 6 (14.5% vs 6.8%, respectively) and maintenance of remission at week 52 (39% vs 21.6%) for patients with moderately or severely active CD[91]. A second study (GEMINI 3) focused on patients in whom anti-TNF therapy had failed and resulted in favorable, clinically relevant effects on clinical remission between weeks 6 and 10 (remission rates were 15.2% and 26.6%, respectively, compared to 12.1% in placebo-treated patients at weeks 6 and 10)[92]. Long-term safety has been assessed in a more extensive study that provided favorable evidence with no unexpected or new concerns in 8 years of follow-up. There is compelling evidence that vedolizumab is effective in inducing remission in moderate-to-severe CD refractory to conventional therapy or anti-TNF agents[62]. Supplementary evidence from real-world data found that a third of patients achieved clinical remission and corticosteroid-free remission on vedolizumab in the short- and long-term (14 weeks and 12 months, respectively). Patients also present with improved long-term rates of mucosal healing (12 months: 63%)[93]. The currently available evidence does not suggest a benefit for the concomitant use of immunomodulators with vedolizumab; however, further studies are warranted[62].

Anti-interleukin

Recommendation

- We recommend ustekinumab for induction of remission in patients with moderate-to-severe CD and inadequate response to conventional or anti-TNF therapy. **Agreement:** 100%[2,18,58].

Pivotal trials (UNITI-1 and UNITI-2) provided compelling evidence in favor of intravenous ustekinumab for patients with moderately-to-severely active CD compared to placebo in induction therapy[94]. Similarly, during maintenance therapy after response to ustekinumab (IM-UNITI trial), the percentage of patients in remission at week 44 was more significant among those continuing to receive the drug relative to controls[94,95]. In a long-term extension study assessing the efficacy and safety of ustekinumab over five years, clinical remission rates remained consistent with no new safety concerns[96]. Thus, ustekinumab is considered an appropriate induction therapy for moderate-to-severe CD refractory to conventional therapy and/or anti-TNF agents. Based on current evidence, we cannot state that the concomitant use of an immunomodulator with ustekinumab is more effective than monotherapy with ustekinumab[62]. Ustekinumab real-world data showed that more than half of the patients achieved clinical response (56%), and more than one-third achieved clinical remission (34%) at 8 to 16 weeks of induction treatment[58,97]. It is noteworthy that most data derived from the real world scenario comprise of patients with previous exposure to anti-TNF agents[58,97].

Maintenance treatment

Salicylic acid derivatives

Recommendations

- Mesalazine should not be used for maintenance of remission in CD. **Agreement:** 91.7%[18].

The recommendation is against using 5-ASA to maintain medically induced remission in patients with moderate-to-severe CD and luminal CD of any severity[58,66].

Corticosteroids

Recommendations

- Corticosteroids are not recommended as maintenance of remission. Prolonged exposure to corticosteroid therapy is not beneficial and is associated with several adverse effects. **Agreement:** 100%[2,61,98].

Corticosteroids are effective as clinical induction but not maintenance therapy. There are significant concerns regarding the risk of adverse events (i.e., adrenocortical suppression), particularly when corticosteroids are used for long-term treatments (for example, beyond three months after induction of remission)[74]. Therefore, steroids should not be used to maintain remission[66,77].

Immunosuppressants

Recommendations

1. Azathioprine, 6-MP, and methotrexate may be considered for the maintenance of remission in patients without poor prognostic factors. **Agreement:** 86.2%[2,18,44,61,77].
2. Patients with moderate-to-severe CD responding to corticosteroids should receive early adjuvant maintenance therapy with thiopurines or methotrexate to reduce the risk of flare during or after weaning off steroids. **Agreement:** 80.6%[2,18,44,61,77].
3. There is no evidence to support the use of cyclosporine or tacrolimus for maintenance of remission in patients with active CD. **Agreement:** 97.3%[2].

Methotrexate may be used for the maintenance of remission of CD with a minimum dose of 15 mg weekly. Subcutaneous or intramuscular administration (up to 25 mg once weekly) has better bioavailability than oral (particularly at higher doses) and is effective in alleviating signs and symptoms in patients with steroid-dependent or resistant luminal CD[18,44,58,66,77]. Immunosuppressive agents may also be considered in cases of moderate CD with seemingly favorable prognostic factors.

MTX may be considered during maintenance therapy in cases of thiopurine intolerance, unresponsiveness, or contraindication. If intramuscular or subcutaneous MTX induced remission, the drug could be continued during maintenance[2,18,44,61,77].

Biologic agents

Anti-TNF

Recommendations

1. Anti-TNF agents should be continued during maintenance therapy in cases of anti-TNF-induced remission. **Agreement:** 100%[2,44,58,61,66,77].
2. Combination therapy of infliximab with azathioprine is recommended over infliximab or azathioprine monotherapy, especially in patients naïve to anti-TNF and thiopurine agents. There may be clinical benefits from a combination of adalimumab and azathioprine in patients with moderate-to-severe CD. **Agreement:** 94.5%[2,44,58,61,66,77].
3. If the therapeutic efficacy of infliximab or adalimumab is decreased or insufficient, we suggest shortening the interval or doubling its dose before considering a switch to another anti-TNF agent. In patients with primary non-response, we suggest changing the therapeutic class to an anti-integrin or anti-interleukin. **Agreement:** 91.7%[2,44,58,61,66,77].

Expert opinion

1. In cases of secondary loss of therapeutic response to anti-TNF, we suggest initially optimizing the same drug, preferably based on therapeutic drug monitoring (TDM). **Agreement:** 90.9%.
2. In the absence of response to anti-TNF optimization, we suggest switching to another anti-TNF, anti-integrin, or anti-interleukin, preferably guided by TDM. **Agreement:** 100%.

In terms of efficacy, a systematic review and network meta-analysis that compared the efficacy and safety of biologic therapies for moderate-to-severe CD suggested that adalimumab and infliximab are the highest-ranking alternatives for maintenance of remission (SUCRA: 0.97 and 0.68, respectively). Data from the SEAVEU trial, a study that examined 386 patients with CD comparing adalimumab to ustekinumab, found no between-group differences in clinical remission rates (61% vs 64.9%), clinical response (66.2% vs 72.3%) or corticosteroid-free remission (57.4% vs 60.7%). Discontinuation rates were lower (but not statistically significant) in patients treated with ustekinumab (15.2% vs 23.6%)[99].

The combination of infliximab with a thiopurine was more effective and reduced immunogenicity than monotherapy infliximab for the maintenance of remission[18,88]. Combination therapy of adalimumab or certolizumab pegol with an immunomodulator is not well established but may be superior in efficacy to therapy with anti-TNF alone, particularly given the immunogenicity related to anti-TNFs and the ability of immunomodulators to reduce the rate of antidrug antibody formation[44].

In treatment-naïve patients, if remission has been achieved with the combination of anti-TNF therapy and thiopurines, maintenance with the same regimen is recommended. If remission was achieved with anti-TNF monotherapy, treatment should be continued during maintenance[58,63].

In cases where the therapeutic efficacy of infliximab at a dose of 5 mg/kg is diminished or insufficient, consideration may be given to shortening the infusion interval or increasing the dose up to 10 mg/kg. If the same occurs for adalimumab at a biweekly dose of 40 mg, weekly administration or 80 mg biweekly of adalimumab may be considered before switching to another anti-TNF agent[61,66]. If a switch from anti-TNF therapy to a different drug class is required, the choice to use anti-integrin or anti-interleukin can be made individually. Patient preference, cost, likely adherence, safety data, availability, and speed of response to the drug should be considered during decision-making and the possibility of surgical procedures[18].

Anti-integrin

Recommendations

1. Vedolizumab is recommended for maintaining remission in patients with moderate-to-severe CD who achieved remission with vedolizumab. **Agreement:** 100%[18,58,66].
2. If the therapeutic efficacy of vedolizumab is decreased or insufficient, shortening the infusion interval can be considered. **Agreement:** 97.3%[18,58,66].

Based on previously discussed evidence of pivotal trials, patients with CD who have achieved symptomatic response with vedolizumab induction therapy are recommended to continue vedolizumab to achieve and maintain complete remission[18,58,62,63,66]. In cases when the therapeutic efficacy of vedolizumab is decreased or insufficient, shortening the infusion interval (every 4 weeks) can be considered[66]. Concerning combination therapy, the currently available evidence does not suggest a benefit for the concomitant use of immunomodulators with vedolizumab[62].

Anti-interleukin

Recommendation
- Ustekinumab is effective in maintaining remission of CD in patients with moderate-to-severe disease refractory to conventional therapy, including patients who do not respond to anti-TNF therapy. If the therapeutic efficacy of ustekinumab is decreased or insufficient, shortening its infusion interval can be considered. **Agreement:** 91.7%[2,18,44,58,66].

A meta-analysis including the previously described trials concluded that there is moderate-certainty evidence to suggest that ustekinumab is effective in maintaining clinical remission, and this agent is effective in patients with moderate-to-severe CD in remission (evidence from three studies: RR=0.53 [95%CI 0.36 to 0.79], RR=0.76 [95%CI 0.64 to 0.91], and RR=0.74 [95%CI 0.60 to 0.91])[100]. Real-world data demonstrated that more than half of the patients with CD achieved clinical and endoscopic responses (62% and 56%, respectively) using ustekinumab; however, 40% and 19% of the patients achieved clinical and endoscopic remission, respectively[97]. In cases where the therapeutic efficacy of ustekinumab is reduced or insufficient, the most appropriate course of action is to shorten the infusion interval. For patients receiving infusions every 8 weeks, the dose should be reduced to every 4 weeks (off label); for those receiving infusions every 12 weeks, the dose should be reduced to every 8 weeks. The currently available evidence does not suggest a benefit for the concomitant use of immunomodulators with ustekinumab[62].

Treatment of perianal CD

Antibiotics

Recommendations
- For symptomatic simple perianal fistulas, we recommend metronidazole or ciprofloxacin. **Agreement:** 86.2%[61].

For perianal CD fistulas, there were three trials evaluating 123 patients using either ciprofloxacin or metronidazole. Therapy was given for 4–12 weeks, and the authors found a statistically significant effect in reducing fistula drainage (RR=0.8 [95%CI 0.66 to 0.98)[101]. Supporting this evidence, Su et al. (2015) demonstrated in their meta-analysis the significant clinical benefits in patients with perianal fistulas using ciprofloxacin (500 mg twice a day for ≥4 weeks; RR=1.54 [95%CI 1.06 to 2.23, *P*=0.02]) compared to no treatment. It is essential to mention that these patients also used concomitant therapy with ciprofloxacin, including infliximab, budesonide, prednisone, and adalimumab[102]. The studies demonstrated the beneficial effects of antibiotics in perianal fistulas; however, the evidence remains inconclusive regarding confounders (e.g., concomitant use of other therapies).

Corticosteroids

Recommendations
- Corticosteroids are not effective in treating patients with perianal CD. **Agreement:** 97.3%[2].

Therapy goals in patients with perianal CD are to achieve complete fistula closure and avoid complications, typically involving anti-inflammatory treatment[103]. The requirement for corticosteroids in initial treatment, in addition to its well-known side effects, is an independent predictor of disabling CD 5 years after initial diagnosis (OR=2.42 [95%CI 1.87 to 3.11])[104]. Moreover, steroid-sparing therapy is associated with a 59% reduction in perianal fistula complications and less need for ostomies among those who developed complications after undergoing steroid-sparing therapy[105]. The current evidence supports the recommendation against using corticosteroids for active perianal CD as there is convincing evidence of considerable harm and little to no evidence of therapeutic benefit.

Immunosuppressants

Recommendations
- We do not recommend thiopurine monotherapy in patients with CD and complex perianal fistulae. **Agreement:** 88.9%[58].

Monotherapy with thiopurines is not indicated to achieve fistula closure or to treat complex perianal fistulae[58] except for tacrolimus, which can be administered for short-term treatment of perianal and cutaneous fistulas[44] and perianal penetrating CD refractory to anti-TNF therapy[2]. Thiopurine monotherapy is suggested only in the case of single, superficial, limited anal ulcerations of CD with few symptoms and in the absence of proctitis and requires careful monitoring[106].

A systematic review with meta-analysis demonstrated that more than one-third of patients receiving tacrolimus achieved remission and partial response (32% and 42.9%, respectively), with tacrolimus trough levels (the serum concentration reached by the drug immediately before the next dose is administered) varying from 5 to 20 ng/mL across studies. Such between-study variability is likely due to a lack of standardized optimal trough level for remission induction in active CD patients, as no RCT or dose escalation study has been performed to date. In addition, caution must be taken regarding the frequency of critical adverse events (65.5%) while using the therapy[107].

Biological agents – anti-TNF

Recommendations
1. For active perianal fistulae, infliximab is recommended over no treatment for the induction and maintenance of fistula remission. Infliximab should be used as the first-line biologic therapy for complex perianal fistula, starting as soon as sepsis has been adequately drained. **Agreement:** 86.2%[18,44,58,77,108,109].
2. Surgical or percutaneous drainage of abscesses should be performed before a course of anti-TNF in fistulizing CD. **Agreement:** 97.2%[18,44,58,77,108,109].
3. Infliximab should be considered for patients with enterocutaneous and rectovaginal fistulas and CD. **Agreement:** 86.2%[18,44,58,77,108,109].
4. Adalimumab should be considered for patients with perianal fistulas and CD. **Agreement:** 96.88%[18,44,58,77,108,109].
5. In patients with active perianal fistula absent of perianal abscess, we recommended that patients receive biologic agents combined with an antibiotic instead of a biologic alone to induce fistula remission. **Agreement:** 94.5%[18,44,58,77,108,109].
6. Patients with evidence of fistulizing disease should be continued on anti-TNF therapy if the symptomatic response has been achieved to induce and maintain complete remission. **Agreement:** 100%[18,44,58,77,108,109].

Expert opinion
- Despite limited evidence, we suggest vedolizumab or ustekinumab in patients with the fistulizing perianal disease in whom anti-TNF therapy fails. **Agreement:** 90.9%.

Although drug treatment for complex fistulas healing does not demonstrate a high level of evidence[58], treatment with biological therapy, especially TNF antagonists, is more effective than no treatment. Infliximab is the most studied drug for this purpose. Adalimumab and Certolizumab pegol are other options for TNF antagonists.[18,44,58,77,108,109].

A systematic review with the meta-analysis by Attauabi et al. (2021) demonstrated a "green light" in favor of ustekinumab for fistulizing perianal CD. At weeks 8, 24, and 52, the pooled response rates were 41.0%, 39.7%, and 55.9%, respectively. For fistula remission at weeks 8, 24, and 52, the pooled proportion of patients achieving this target was almost a quarter (17.1%, 17.7%, and 16.7%, respectively)[110]. Real-world data demonstrated similar findings, supporting the evidence that ustekinumab is safe and effective for perianal CD treatment[111]. Positive findings of sustained improvements in fistulizing CD were also demonstrated in favor of vedolizumab (ENTERPRISE study), which included patients with moderately-to-severely active CD and 1–3 active perianal fistulae[112].

Anti-TNF therapy is typically insufficient to completely heal enterocutaneous fistulae, especially postoperatively. In such cases, it is typically prudent to institute an initial conservative treatment consisting of nutritional status optimization, replacement of fluid and electrolytes, and sepsis control prior to an operative correction, if indicated[113,114]. For cases where the purpose is to increase the effectiveness of the biologic therapy, AZA may be used as a combination therapy with anti-TNF[2]. However, evidence to recommend the addition of immunomodulators to anti-TNF therapy in fistula healing is also insufficient[115].

Criteria to evaluate treatment efficacy for active CD

Clinical response

Expert opinion
- The clinical response may be evaluated by at least 50% improvement in PROs such as PRO-2 (abdominal pain ≤1 and stool frequency ≤3). The response may also be evaluated by the CDAI (reduction by ≥100 points) or the HBI (reduction by ≥3 points). **Agreement:** 91.7%[18,63,98].

Clinical remission

Expert opinion
1. Clinical remission should be evaluated using PRO-2, HBI <5, or CDAI <150, provided the patient is off steroids. **Agreement:** 91.7%[18,21,63,98,109].
2. Clinical remission in patients with the fistulizing perianal disease is the absence of pain and spontaneous drainage from the fistula tract. **Agreement:** 91.7%[18,21,63,98,107].

The most common definition of clinical response endorsed by the FDA is a decrease in CDAI scores by ≥100 points or HBI ≥3 points. Clinical remission has been typically defined as having a CDAI score of <150 or HBI <5. PROs are strongly correlated with overall well-being and health-related QoL, which is why it has been considered a critical outcome for decision-making across many medical conditions. Indeed, regulatory authorities have already incorporated PROs as fundamental efficacy outcomes in clinical trials for drug development in CD, highlighting the importance of these measures[116]. Accordingly, the International Organization for the Study of Inflammatory Bowel Diseases has recently issued guidelines on 'treat-to-target' strategies that incorporate normalization of health-related QoL and absence of disability along with objective measures of disease activity in the assessment of therapeutic targets throughout the disease course[21].

The most used PRO measurement in adult CD patients is the PRO-2, which correlates reasonably well with CDAI-defined outcomes and is responsive to effective therapy[117]. It is calculated as the sum of the weighted daily stool frequency and abdominal pain items from the CDAI. Measurements of gastrointestinal PROs reflect treatment targets such as the absence of abdominal pain and normalization of bowel habits. The absence of abdominal pain is defined as ≤1 event in seven days, and the target number of bowel movements in seven days can be a specific number or 1–2 more than expected[118].

Endoscopic response

Expert opinion
- An endoscopic response is a reduction of >50% in SES-CD or CDEIS scores. **Agreement:** 80.6%[21].

Endoscopic remission

Expert opinion
- Endoscopic remission is defined as the absence of ulcerations with CDEIS or SES-CD <3 points. **Agreement:** 100%.

Endoscopic scores are the gold standard for measuring CD activity and are used in clinical trials to measure pharmacological effectiveness in inducing and maintaining mucosal healing. The CDEIS and SES-CD are the most common tools for CD patients without bowel resection (GAJENDRAN, 2018). Complete mucosal healing in newly diagnosed CD predicts sustained, steroid-free remission for up to 4 years[119]. Achievement of endoscopic remission is also associated with an increased likelihood of favorable long-term outcomes, which provides further support to the treat-to-target algorithm and its efficacy in inducing endoscopic remission itself[120,121].

When using biologic therapy, the endoscopic mucosal inflammation may be assessed, as mucosal healing has been correlated with reduced hospitalization and surgeries, even if symptom control is maintained[63]. Endoscopy or colonoscopy is performed to confirm the diagnosis of CD, evaluate the severity of the disease, determine the effectiveness of treatment, and conduct surveillance for carcinogenesis[62,122].

Histological remission

Expert opinion
- Histological remission is not considered a target for treatment in CD. Further studies are necessary to demonstrate its role as an outcome measure. **Agreement:** 97.3%.

Histological healing can be defined as normal mucosa or the disappearance of inflammation. There is no standardized histological scoring system for assessing disease activity in IBD, and most supporting data are retrospective and based on endoscopic assessment. Thus, assessing histological remission is a fragile measure and, therefore, should not be considered a target of treatment efficacy[123].

Corticosteroid-free remission

Expert opinion

- Steroid-free clinical remission is the disappearance of symptoms without systemic steroids for 3 months (or low-bioavailability steroids for 3–6 months). **Agreement:** 86.2%[98].

Corticosteroid-free clinical remission (CSF-CR) has been used as an endpoint in several clinical trials assessing CD maintenance, as avoidance of corticosteroids is an essential patient- and physician-preferred treatment target due to short-term side effects and long-term adverse events[26]. As rates of CSF-CR are typically 20 to 25% lower than overall remission, it is considered a more stringent or "difficult" endpoint. There is, however, no universal consensus on its precise definition, and it is often not described in detail by the authors of original reports. The most debatable aspect of CSF-CR definition is the period during which patients are required to persist consistently off steroids to be classified as a case of CSF-CR. Overall, the minimum time under clinical remission without systematic steroids has been around 12 to 14 weeks of follow-up, with few studies following patients for as long as 54 weeks (also defined as "sustained CSF-CR"). To provide an endpoint definition that is feasible to assess in a reasonably short amount of time in clinical practice and clinically predictive of better outcomes, we based our recommendation on 3 months of clinical remission in the absence of systemic corticosteroid use or a more extended period (up to 6 months) for patients using low-bioavailability steroids. It should be noted that there is no minimum safe period for CSF-CR, and some experts believe that at least 1–2 years is a reasonable time frame[18].

Improvement in QoL

Expert opinion

- We recommend that health-related QoL and absence of disability should be considered essential long-term outcomes. **Agreement:** 97.3%[21].

The QoL of adult CD patients is consistently determined by markers of active disease, including fatigue, professional productivity, work disability, number of relapses, biologic treatment, hospitalization rate, and the feeling of having a normal life. Importantly, disease activity accounts for 37% of QoL impairment. Therefore, these features can be refined during the CD treatment[124].

The typical time frame for achieving these targets of QoL improvement is 4–6 months after the start of treatment. This time frame should not be adjusted based on the therapeutic class[122]. Additionally, physical and mental QoL are essential indicators of patient-reported outcomes. Of particular interest to the mental QoL; there is a high prevalence of patients with IBD (especially men) suffering from anxiety (one-third of patients) and depressive symptoms (a quarter of patients). This evidence must encourage gastroenterologists to screen and investigate these disorders, aiming to improve treatment outcomes[125].

Patient management pre- and post-treatment for active CD

Postoperative management

Recommendations

- Patients should have an endoscopic activity assessment with colonoscopy six months following ileocolonic resection for CD. **Agreement:** 100%[18].

Assessment of endoscopic recurrence is used frequently in clinical trials as it provides the prognosis for the course of the disease and, therefore, can guide additional therapy earlier. Endoscopic recurrence was observed in up to 60% of patients undergoing ileocolonic resection at 6 months. A meta-analysis of placebo groups of postoperative maintenance trials showed an endoscopic recurrence rate of 58% (95%CI: 51% to 65%) at a median of 1 year after surgery[126]. These findings underscore the recommendation for assessment of endoscopic activity with colonoscopy 6 months after surgery. Smoking was associated with a 2.5-fold increased risk of endoscopic recurrence and a two-fold increased risk of clinical recurrence[127]. A randomized, multicenter, controlled trial has studied the optimal strategy to prevent postoperative disease recurrence. Patients treated according to the clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, had more favorable outcomes than conventional drug therapy alone. The management of CD after intestinal resection should consider the risk of recurrence, timing and efficacy of medications, the value of endoscopic assessment with a structured response for recurrence, and disease progression in the early postoperative period[128].

Calprotectin

Recommendations

1. Fecal calprotectin is a validated biomarker for endoscopic disease activity and may inform treatment escalation or de-escalation decisions. **Agreement:** 97.3%[18].
2. Fecal calprotectin or cross-sectional imaging may be used if ileocolonoscopy is not possible or acceptable, although it may lack sensitivity to detect localized inflammation. **Agreement:** 86.2%[18].
3. Patients whose biologic therapy is withdrawn should be observed for evidence of relapse. A rise in fecal calprotectin levels may be an early predictor of clinical relapse. **Agreement:** 100%[18].
4. We recommend that fecal calprotectin should be measured to search for evidence of mucosal inflammation in uncertainty about whether symptom etiology is ongoing inflammation or something else (e.g., bile acid malabsorption, functional bowel disorder, or short bowel syndrome). **Agreement:** 94.5%[18].

Fecal calprotectin is used as a marker of the activity of inflammation and helps guide treatment and short-term follow-up and predict clinical relapse in CD[77,129]. The treatment target for fecal calprotectin is <250 µg/g in a non-postoperative situation and

<100 µg/g in a postoperative situation[21,120,128]. The time frame for reaching these targets is 3–4 months, irrespective of the therapeutic class of the undergoing medical treatments[122]. Notably, fecal calprotectin may be adjunctive in monitoring disease activity[44].

Imaging (exams/consultation frequency)

Recommendations

1. Patients with confirmed bowel patency may use small bowel capsule endoscopy interchangeably with CT enterography (CTE) or magnetic resonance enterography (MRE) for assessing small bowel disease activity or postoperative recurrence. **Agreement:** 86.2%[62].
2. We recommend MRE to monitor intestinal disease activity and evaluate mucosal healing, extraluminal disease, and treatment responses. **Agreement:** 83.4%[62].
3. We recommend performing cross-sectional imaging (MRI, CT, and bowel ultrasound) over conventional barium fluoroscopic and nuclear medicine techniques. **Agreement:** 94.5%[18,62].
4. Pelvic MRI should be used as an adjunct to clinical assessment and examination under anesthesia (by an experienced surgeon) to evaluate fistulizing perianal CD. Depending on local availability and expertise, endoanal ultrasound may also be used. **Agreement:** 94.5%[18].

A meta-analysis evaluating the diagnostic accuracy of MRI in assessing the activity of CD in the small bowel showed high sensitivity and specificity[130,131]. Balloon-assisted enteroscopy or small bowel capsule endoscopy might be helpful for the close examination and follow-up of small bowel lesions in CD[62,80]. Endoscopic reassessment should be considered in cases of relapse, refractoriness, new symptoms, or when surgery is considered[80].

Imaging studies (in particular MRI or CT enterography) can be used for monitoring the treatment response of CD, as they showed comparably high accurate grading estimates in a per-patient analysis (P=0.8)[132]. Periodic cross-sectional imaging (i.e., CTE, MRE) might be considered in monitoring response to therapy in certain patients with small bowel CD[80]; however, CTE exposes patients to non-negligible levels of ionizing radiation weighs in favor of refraining from routinely performing the procedure. Bowel ultrasound (or intestinal echography) is a non-invasive, low-cost, accessible method that allows real-time assessment of the disease and its inflammatory activity[133]. A meta-analysis of prospective studies comparing its accuracy to other cross-sectional imaging methods showed high sensitivity and specificity (as high as 93.0% and 95.6%, respectively, depending on the comparator) for diagnosing IBD[134]. The STARDUST trial provides compelling evidence in favor of bowel ultrasound as an effective method for monitoring patients with IBD, given its positive findings for the early assessment of treatment response and predicting clinical and endoscopic responses[135]. Extramural or extraluminal complications (e.g., stenosis, fistulae, and abscesses) might also be reliably assessed by the technique.

Transmural healing (assessed by CTE, MRE, or bowel ultrasound) is not a treatment target in CD. Nevertheless, it should be used as an adjunct to endoscopic remission to represent a deeper level of healing[21].

Therapeutic failure

Recommendations

- Laparoscopic resection should be considered in localized ileocecal CD for those failing or relapsing after initial medical therapy or for those who prefer surgery over drug therapy. **Agreement:** 88.9%[18].

The laparoscopic surgery technique for recurrent CD (complex or simple) is safe, effective, and associated with shorter hospital stays. The procedure does not appear to increase the risk of postoperative complications compared to the open approach[136,137].

TDM

Recommendations

1. Treatment options after failure of initial anti-TNF therapy (i.e., increased dose, shortened dosage interval, and switching to alternative anti-TNF different drug classes) should be informed by the overall clinical context and by measurement of serum drug and anti-drug antibody concentrations. **Agreement:** 94.5%.
2. Patients with secondary loss of response to anti-TNF therapy should have their serum drug and anti-drug antibody concentrations measured to inform appropriate changes in treatment. **Agreement:** 100%[18].

In cases of primary non-response or secondary loss of response to anti-TNF, re-evaluation of disease activity and treatment change might be necessary[61]. When available, serum anti-TNF trough levels and anti-drug antibodies could be measured to guide optimization strategy[63].

Antidrug antibodies predict loss of response and adverse events. The best time for measuring drug levels is before the subsequent dose (trough levels). Thresholds for adequate drug levels depend on the anti-TNF agent. Reactive TDM of biologics has been proven more cost-effective than empiric anti-TNF therapy optimization. This approach should be performed in patients with confirmed primary non-response or secondary loss of response to anti-TNF therapy.

Currently, the evidence is insufficient to recommend proactive TDM to improve clinical outcomes compared to routine care in patients in clinical remission on anti-TNF treatment[58]. Proactive TDM of biologics might be performed after induction and at least once during maintenance therapy for patients treated with anti-TNF therapy. This should also be performed after reactive TDM of anti-TNF therapy in more severely active patients and patients with higher drug clearance. Increased anti-TNF clearance is associated with anti-drug antibodies, male gender, low albumin, high baseline CRP, and high BMI[138,139].

Corticosteroids

Recommendations

- Patients starting corticosteroids should be assessed for risk of osteoporosis. Those at high risk should receive bisphosphonate therapy as an adjunct to corticosteroids, in addition to supplementing with 800–1000 mg/day of calcium and 800 IU/day of vitamin D. **Agreement:** 86.2%[18].

Expert opinion

- Patients on long-term corticosteroid therapy should have a tapering course if discontinuing. These patients should also have monitored blood pressure, glycemic control, and serum potassium and receive the same vaccination recommendations as those on immunomodulatory therapy. **Agreement:** 86.2%[18].

The efficacy and risks of corticosteroid use need to be monitored. Evaluation for symptomatic response must determine the need to modify therapy: prednisone between 2 and 4 weeks, intravenous methylprednisolone within 1 week, and budesonide between 4 and 8 weeks[66]. Prolonged use of corticosteroids is a risk factor for osteoporosis in IBD. General risk factors should also be tracked and corrected, including vitamin D, calcium, possibly vitamin K and other nutrients, inflammatory cytokines, smoking, and lack of weight training. Bisphosphonates are beneficial in reducing the risk of vertebral fractures, with data extending up to 24 months of use. Bisphosphonates are beneficial in preventing and treating corticosteroid-induced bone loss in the lumbar spine and femoral neck[140]. Another approach to preventing osteoporosis or osteopenia in patients with CD is the intake of 800–1000 mg/day of calcium and 800 IU/day of vitamin D. Lifestyle modification advice should also be provided, including regular physical exercise and smoking cessation[18].

Patients making long-term use of corticosteroids are at risk of adrenal suppression and, therefore, should undergo weaning if the option is to discontinue. These patients should be informed of possible steroid withdrawal syndrome, including non-specific symptoms such as weakness, nausea, and arthralgia[18].

Biological agents

Expert opinion

- Patients receiving immunomodulators or biologics should undergo an annual review for treatment continuation, optimization, or cessation. The anti-TNF response should be monitored 2 to 4 weeks after induction for dose optimization based on clinical response and laboratory information (e.g., serum drug and anti-drug antibody concentrations, inflammatory blood markers, fecal biomarkers, or endoscopy). **Agreement:** 80.5%[18].

Patients with luminal CD should be evaluated for symptomatic responses after induction to determine the need to modify therapy[66]. There is insufficient evidence to recommend withdrawing anti-TNF therapy in CD patients after achieving long-term remission. Therefore, the decision to continue anti-TNF therapy should be individualized, and the patient should always discuss potential consequences (risks and benefits)[58].

Diet (nutritional therapy)

Recommendations

- Patients who are malnourished or at risk of malnutrition should undergo screening and assessment of macronutrient and micronutrient deficiencies (e.g., iron storages, vitamin B12, folate, vitamins A, C, D, and E, potassium, calcium, magnesium, phosphate, zinc, and selenium). **Agreement:** 100%[18].

Expert opinion

1. Patients should be encouraged to eat a balanced diet that meets their energy, macro-, and micronutrient requirements. Patients at risk of malnutrition should have access to dietitian assistance for proper nutritional assessment, and where nutritional requirements cannot be met, supplementation with oral, enteral, or parenteral nutrition is indicated. **Agreement:** 86.2%[18].
2. Patients should undergo a complete nutritional assessment and screening for evidence of recent weight loss or risk of malnutrition at each clinic appointment and on hospital admissions. **Agreement:** 97.3%[18].

Patients with IBD (primarily CD) are deficient in the absorption of micronutrients, as IBD affects the small intestine. Therefore, these patients may be at risk for vitamin B12 and folate insufficiency. In addition, CD patients had lower serum concentrations of 25(OH)D than their healthy controls, and more than half of them had hypovitaminosis D[141]. Patients with CD should be referred to a nutritionist with experience in IBD.

Smoking

Recommendations

- Smoking in CD should be discouraged as a matter of policy. **Agreement:** 97.2%[77].

Patients who smoke have a 2.5-fold increased risk of endoscopic recurrence and a two-fold increased risk of clinical recurrence[127]. Compared with nonsmokers, CD patients who were smokers were more likely to have an exacerbation of disease activity (OR=1.56 [95%CI 1.21 to 2.01]), exacerbation after surgery (OR=1.97 [95%CI 1.36 to 2.85]), need for first surgery (OR=1.68 [95%CI 1.33 to 2.12]) and need for the second surgery (OR=2.17 [95%CI 1.63 to 2.89]). Ex-smokers' odds of these outcomes decreased after smoking cessation, with similar outcomes to non-smokers. In the case of a flare or second surgery, former smokers had significantly lower odds than smokers. Therefore, smokers present a more complicated disease course, and smoking cessation may improve these outcomes[142]. Additionally, smoking is significantly associated with a reduction in the ability of infliximab or adalimumab to induce short-term clinical responses and remission[143]. Policies to advise patients of the harmful effects of smoking should be carried out in addition to smoking cessation counseling to reduce the disease burden and costs in these patients.

Special situations

Pregnancy and lactation

Recommendations

- We recommend that most patients on thiopurines, anti-TNF, vedolizumab, and ustekinumab should continue therapy during pregnancy. However, MTX is contraindicated during pregnancy and lactation and should also be discontinued 3 to 6 months before conception. **Agreement:** 100%[77].

Patients and their physicians should discuss an individual approach, select the best treatment during pregnancy and lactation, and consider the benefits and harms[62]. Modifying treatment for IBD is usually unnecessary in pregnant patients, except for MTX,

which is contraindicated in pregnancy[129]. Due to MTX's teratogenic and embryotoxic effects, women should discontinue MTX for 3 to 6 months before conception. If patients become pregnant and take MTX, the drug should be discontinued, and high-dose folic acid (15 mg daily) should be taken for at least 6 weeks. For men who are using MTX, there is no need to withhold or discontinue treatment before conception[18]. During pregnancy, although corticosteroids are indicated in cases of disease flares, the increased risk of gestational diabetes due to chronic immunosuppression is likely to outweigh its benefits during maintenance treatment. It is worth mentioning that the safety of vedolizumab and ustekinumab for pregnant women, lactating women, women attempting to conceive, and children have not been sufficiently established[62]. However, data from the PIANO registry, which assessed the outcomes of 1490 pregnancies and 1431 live births, demonstrated that exposure to biologics and immunomodulators during pregnancy did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infections during the first year of life[144]. For breastfeeding, 5-ASA, corticosteroids, and AZA are considered safe. MTX and cyclosporine are contraindicated in lactating women. The mother is advised to consult a pediatrician regarding breastfeeding premature babies[129]. For infants (and if indicated), Bacille Calmette-Guerin vaccination is withheld until at least six months after birth. Rotavirus vaccine should not be given to babies exposed to mothers treated with biologic therapies. Non-live vaccines can be administered according to standard vaccination schedules[18].

Older adults

Recommendations

- Treatment of older adults should be like that of younger patients, with particular care to the appropriate timing of surgery for those with severe disease as a delay in diagnosis or surgery is associated with worse outcomes. **Agreement:** 80.5%[77].

The treatment of older adult patients with IBD is identical to that of younger patients. Because of adverse events, especially the increased risk of malignancies, immunomodulatory therapy in older adults has been discouraged. In cases where an immunosuppressant is deemed necessary, MTX may be more appropriate than thiopurines[145]. It is also suggested to avoid combined therapy (immunomodulator plus biologic therapy) in older adults due to the increased risk of infections in this population.

Anti-integrin and anti-interleukin drugs have shown a better safety profile and should be considered in the absence of strict indication of other therapies[91,94].

Infections/vaccines

Recommendations

1. It is recommended that all patients with IBD who will receive immunosuppressive therapy also receive empirical treatment for intestinal parasites due to the high risk of associated complications. **Agreement:** 97%[18].
2. IBD patients should receive standard vaccination advice; however, live vaccination is proscribed for those on immunosuppressive therapy unless treatment has been discontinued at least three months in advance. **Agreement:** 94.5%[18].
3. It is recommended that vaccinations remain up to date for all patients with CD before initiating immunomodulators or biologics. Live vaccinations may be given ≥4 weeks before starting or at least three months after stopping immunosuppressive therapy. **Agreement:** 88.9%[18].
4. Patients on immunomodulators or biologics should be vaccinated for influenza each autumn and receive pneumococcal vaccination with a booster after 5 years. **Agreement:** 97.2%[18].

Infections/HIV, tuberculosis, and hepatitis

Recommendations

1. Before treatment with biologic agents, especially anti-TNF therapy, patients should be screened for tuberculosis with a combination of clinical risk stratification, chest x-ray, interferon-gamma release assays, or tuberculin skin test. The differential diagnosis for tuberculosis should be considered in patients with suspected ileocecal CD, particularly in patients born or who have lived for extended periods in endemic areas or present with other risk factors for infection. **Agreement:** 97.3%[18].
2. We recommend routine screening for HIV and hepatitis B and C before immunosuppressive therapy (including vedolizumab and ustekinumab). **Agreement:** 91.7%[18].

Expert opinion

- In patients currently or previously infected with HBV, the risk of developing hepatitis B due to HBV reactivation should be considered after initiating immunosuppressive drugs. **Agreement:** 97.3%[62].

Patients with CD are at increased risk of opportunistic infections. A meta-analysis conducted with 216,552 participants with IBD and 790 events of herpes zoster among these participants demonstrated a pooled incidence of 10.41 per 1,000 person-years. Patients with IBD have a 1.68-fold higher risk of developing herpes zoster than individuals without IBD. This evidence suggests that vaccination should be considered when diagnosing IBD[146]. Regarding the HBV vaccination, only three of five IBD patients will show a serological response to HBV vaccination (pooled response rate: 61%). Young age and vaccination during disease remission were positively associated with the response to vaccination. Furthermore, no immunosuppressive therapy predicted an immune response compared with immunomodulator or anti-TNF therapy. Vaccination should be performed during IBD diagnosis, during disease remission, or before starting immunosuppressive therapy[147]. Before, during, and at least 12 months after immunomodulatory treatment, patients who are HbsAg-positive should receive potent anti-viral agents (nucleoside/nucleotide analogs with a high barrier to resistance) regardless of the degree of viremia to avoid a hepatitis B flare[62].

Colon cancer screening – malignancies – clinical management

Recommendations

1. We recommend that ileo-colonoscopy should be offered to patients with colonic disease eight years after the onset of symptoms for cancer screening, assessment of disease extent, and provision of information regarding the frequency of subsequent monitoring. **Agreement:** 86.2%[18].

2. Patients with colonic or anastomotic strictures should be evaluated with endoscopy and biopsy to rule out cancer as long as the stricture is accessible, and the procedures are considered safe. **Agreement:** 94.5%[18].

Expert opinion

1. In patients with CD of the colon, it is recommended to start annual screening for colorectal cancer from the diagnosis of primary sclerosing cholangitis. **Agreement:** 100%.

Patients with CD have a two-fold and 22-fold increased incidence of colorectal and small bowel cancer, respectively, compared to the general population[148]. CD patients are also at increased risk for small bowel, colon, extraintestinal, and lymphoma cancers[149-151]. Cancer surveillance is required for CD patients. CD patients whose disease affects more than one-third of the large intestine should have a screening colonoscopy eight years after disease onset[1,77].

Intestinal strictures (commonly colonic or anastomotic) are a common complication of CD, and their risk factors can be clinical, environmental, genetic, or endoscopic parameters (e.g., age, smoking, and deep mucosal ulcerations)[152]. Endoscopy plays an essential role in cancer surveillance in patients with long-term IBD. Endoscopy also offers therapeutic potential for treating IBD, especially with dilatation of strictures and treatment of bleeding.

Oncological patients (medication association)

Recommendations

1. Treatment with thiopurines is associated with increased risk of lymphoma, non-melanoma skin cancers, and cervical dysplasia, whereas anti-TNF agents increase the risk of melanomas. Therefore, patients should undergo annual dermoscopy, and (for female patients) national cervical screening programs should also be incentivized. **Agreement:** 86.2%[18,63].
2. There is currently insufficient data to confirm that anti-TNF alone increases the risk of lymphoproliferative disorders or solid tumors, although their combination with thiopurines significantly increases the risk of lymphoproliferative disorders. Nevertheless, the absolute rates of these malignancies remain low, and risks should always be carefully weighed against the substantial benefits associated with these treatments and discussed with the patient. **Agreement:** 86.2%[18,63].

Future perspectives in therapeutics

Risankizumab

Risankizumab, an anti-interleukin 23 antibody directed against its p19 subunit, has been recently approved by the US Food and Drug Administration based on data from several trials[48,153]. Compared to placebo, risankizumab resulted in higher rates of clinical remission of as much as 20% absolute risk difference and greater rates of sustained remission over 52 weeks of as much as 14% absolute risk difference. The induction dosing protocol is established as 600 mg intravenously at 0, 4, and 8 weeks, while maintenance dosing is a subcutaneous injection of 360 mg at week 12 and every 8 subsequent weeks. Risankizumab has since been proposed as an alternative to other first-line biologic therapies.

Guselkumab

Guselkumab is a human IgG1 monoclonal antibody directed against the p19 subunit of IL-23, which ultimately inhibits specific intracellular signaling and subsequent activation of cytokine production. Currently, the drug is approved for inflammatory diseases such as plaque psoriasis but not for CD. In a 12-week, phase 2 double-blind trial, intravenous guselkumab resulted in significantly greater rates of clinical remission (absolute risk difference of as much as 41%) and endoscopic response compared to placebo in moderately-to-severely active CD, with no safety concerns[49]. Further trials for induction and maintenance might provide definitive evidence of its role in CD management. Approved drugs with respective doses are better described in TABLE 4.

ACKNOWLEDGMENTS

We would like to express our gratitude and deepest appreciation to Dr Fábio Vieira Teixeira, Dr Idblan Carvalho de Albuquerque and Dr Mauro Bafutto for scientifically supporting this consensus.

Authors' contribution

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Imbrizi M, Baima JP, Azevedo MFC, Andrade AR, Queiroz NSF, Chebli JMF, Chebli LA, Argollo MC, Sassaki LY, Parra RS, Quaresma AB, Vieira A, Damião AOMC, Moraes ACS, Flores C, Zaltman C, Vilela EG, Morsoletto EM, Gonçalves Filho FA, Penna FGC, Santana GO, Zabot GP, Parente JML, Costa MHM, Zerôncio MA, Machado MB, Cassol OS, Fróes RSB, Miszputen SJ, Ambrogini Junior O, Kotze PG, Saad-Hossne R, Coy CSR. Segundo Consenso Brasileiro de Manejo da Doença de Crohn em adultos: um consenso da Organização Brasileira de Doença de Crohn e Colite (GEDIIB). Arq Gastroenterol. 2022;59(Suppl 1):20-50.

RESUMO – Contexto – A doença inflamatória intestinal (DII) é uma doença imunomediada que inclui a doença de Crohn (DC) e a retocolite ulcerativa. A DC é caracterizada por um envolvimento intestinal transmural da boca ao ânus com sintomas recorrentes e remitentes que podem levar a danos intestinais progressivos e incapacidade ao longo do tempo. **Objetivo –** Orientar os tratamentos médicos mais seguros e eficazes de adultos com DC. **Métodos –** Este consenso foi desenvolvido por autores que representam gastroenterologistas e cirurgiões brasileiros especialistas em doenças colorretais (GEDIIB, Organização Brasileira de Doença de Crohn e Colite). Uma revisão sistemática das evidências mais recentes foi realizada para apoiar as recomendações/declarações. Todas as recomendações e declarações incluídas foram endossadas em um painel Delphi modificado pelas partes interessadas e especialistas em DII com uma concordância de pelo menos 80% ou mais. **Resultados e conclusão –** As recomendações médicas (intervenções farmacológicas e não farmacológicas) foram mapeadas de acordo com o estágio de tratamento e gravidade da doença em três domínios: manejo e tratamento (intervenções medicamentosas e cirúrgicas), critérios para avaliar a eficácia do tratamento médico, e acompanhamento/monitoramento do paciente após o tratamento inicial. O consenso é direcionado a clínicos gerais, gastroenterologistas e cirurgiões interessados em tratar e gerenciar adultos com DC e apoia a tomada de decisões de companhias de seguro de saúde, agências reguladoras e líderes ou administradores de instituições de saúde.

Palavras-chave – Doença de Crohn; adultos; doenças inflamatórias intestinais; terapia medicamentosa; manejo de doenças.

Supplementary material of the second Brazilian Consensus on the Management of Crohn's Disease in Adults: a consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

Defining the question to be answered in the pragmatic literature review

The acronym PICO-S (patient, intervention, comparator, outcome, and study design) indicated in TABLES S1-S7 describes the question to be answered regarding Crohn's disease (CD) in adults.

TABLE S1. PICO strategy on the induction treatment of mild to moderate active CD.

P	Adults (≥18 years) with mild to moderate active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Not applicable
Type of study	Consensus and/or guidelines limited to the 2016–2021

Question: What are the recommended induction treatments for mild to moderate active CD, according to the international guidelines and/or consensus?

TABLE S2. PICO strategy on the induction treatment of moderate to severe active CD.

P	Adults (≥18 years) with moderate to severe active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended induction treatments for moderate to severe active CD, according to the international guidelines and/or consensus?

TABLE S3. PICO strategy on the maintenance treatment of mild to moderate active CD.

P	Adults (≥18 years) with mild to moderate active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended maintenance treatments for mild to moderate active CD, according to the international guidelines and/or consensus?

TABLE S4. PICO strategy on the maintenance treatment of moderate to severe active CD.

P	Adults (≥18 years) with moderate to severe active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended maintenance treatments for moderate to severe active CD, according to the international guidelines and/or consensus?

TABLE S5. PICO strategy on the clinical treatment of perianal CD.

P	Adults (≥18 years) with perianal CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended treatments for perianal CD, according to the international guidelines and/or consensus?

TABLE S6. PICO strategy on criteria for evaluating the efficacy of treatment of CD.

P	Adults (≥18years) with active CD
I	Not applicable
C	Not applicable
O	Criteria used to assess the efficacy of treatment: • Clinical response • Clinical remission • Endoscopic response • Endoscopic remission • Histological remission • Corticosteroid-free clinical remission • Improves quality of life • Adverse events • Others found in the literature
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended criteria to evaluate the efficacy of treatment of adults with CD, according to the international guidelines and/or consensus?

TABLE S7. PICO strategy on patient follow-up after initial treatment of CD.

P	Adults (≥18years) with active CD
I	Not applicable
C	Not applicable
O	Follow-up of the patient after initial treatment (e.g., clinical value, calprotectin, PCR, colonoscopy, imaging [periodicity of examinations and consultation], therapeutic failure, treatment drug monitoring (TDM), screening of cancer and others)
Type of study	Consensus and/or guidelines limited to 2016–2021

Question: What are the recommended approaches and factors to follow-up/monitoring adult patients with CD after initial treatment, according to the international guidelines and/or consensus?

TABLE S8. PICO strategy on the efficacy of clinical treatments for CD in adults.

P	Adults (≥18years) with active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab and etrolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	• Not applicable
O	All efficacy outcomes considered in the published studies (i.e., clinical response and remission, endoscopic response and remission, mucosal healing, etc.)
Type of study	Systematic reviews with meta-analysis

Question: What is the efficacy of the clinical treatment for adults with CD, according to the systematic reviews with meta-analysis?

Eligibility criteria

Inclusion criteria

- International guidelines and/or consensus for adults (≥18 years) with CD;
- Guidelines and/or consensus in English;
- Guidelines and/or consensus published in the last 5 years (from November 2016 until December 2021);
- Systematic reviews with meta-analysis that evaluate the efficacy of nutritional approaches, specific classes of drugs, and/or medications for the pediatric population with CD.

Exclusion criteria:

- Guidelines and/or consensus on drug use or specific drug classes recommended to pediatric patients;
- Guidelines and/or consensus published before November 2016;
- Reviews of guidelines and/or consensus;
- Systematic reviews with meta-analysis with overlapped results (in these cases, we considered the most recent review);
- Publication in languages other than English;
- Systematic reviews without meta-analysis.

Search Strategy

The search strategy was conducted on MEDLINE (National Library of Medicine of the United States and Medical Database of the National Institutes of Health, using the PubMed interface). TABLE S9 describes the search strategy used in the search for the electronic database. The total number of articles found may vary depending on the search date.

TABLE S9. Search strategy.

Databases	Search strategy	Results (titles)
Pubmed	("inflammatory bowel disease" [Title] OR "IBD" [Title] OR "crohn" [Title]) AND ("treatment" [Title/Abstract] OR "management" [Title/Abstract] OR "monitoring" [Title/Abstract]) AND ("consensus" [Title] OR "guidelines" [Title]) AND ((y_5[Filter]) AND (english [Filter]))	85
Systematic Literature Reviews with meta-analysis	((("inflammatory bowel disease" [Title] OR "IBD" [Title] OR "crohn" [Title]) AND ("treatment" [Title/Abstract] OR "management" [Title/Abstract] OR "monitoring" [Title/Abstract])) AND ((meta-analysis [Filter]) AND (english [Filter]))	318

Search conducted on November 11, 2021.

Screening of studies

The selection of title and abstract according to eligibility criteria was carried out through the f Rayyan® Platform. It is a tool specifically developed to speed up the initial screening of abstracts and titles using a semi-automatic process. The selected publications were evaluated in full text based on the inclusion and exclusion criteria. Two independent researchers screened the studies in a blinded fashion way, and, in case of divergence, the decision was made with a third reviewer. The screening flowchart can be found in FIGURES S1 AND S2.

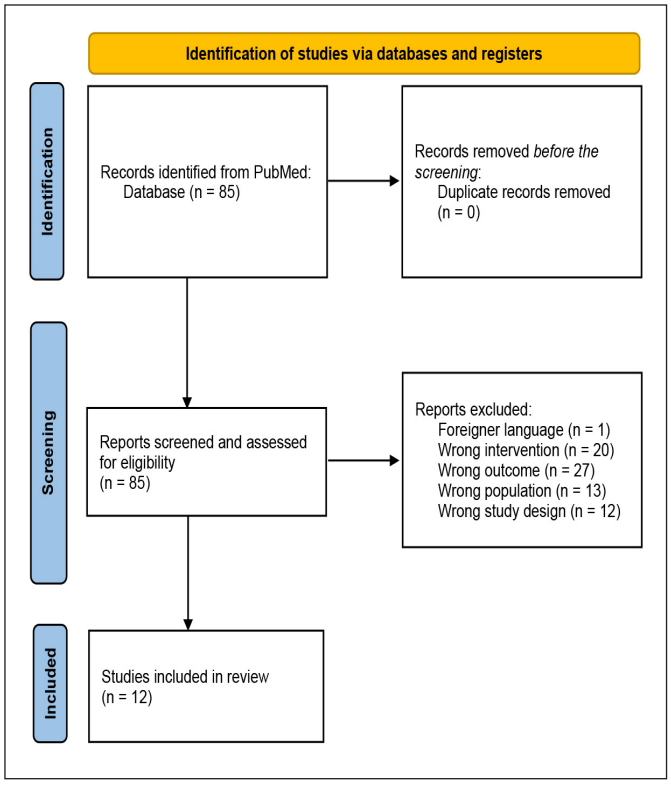

FIGURE S1. Screening flowchart of Consensus and/or Guidelines.

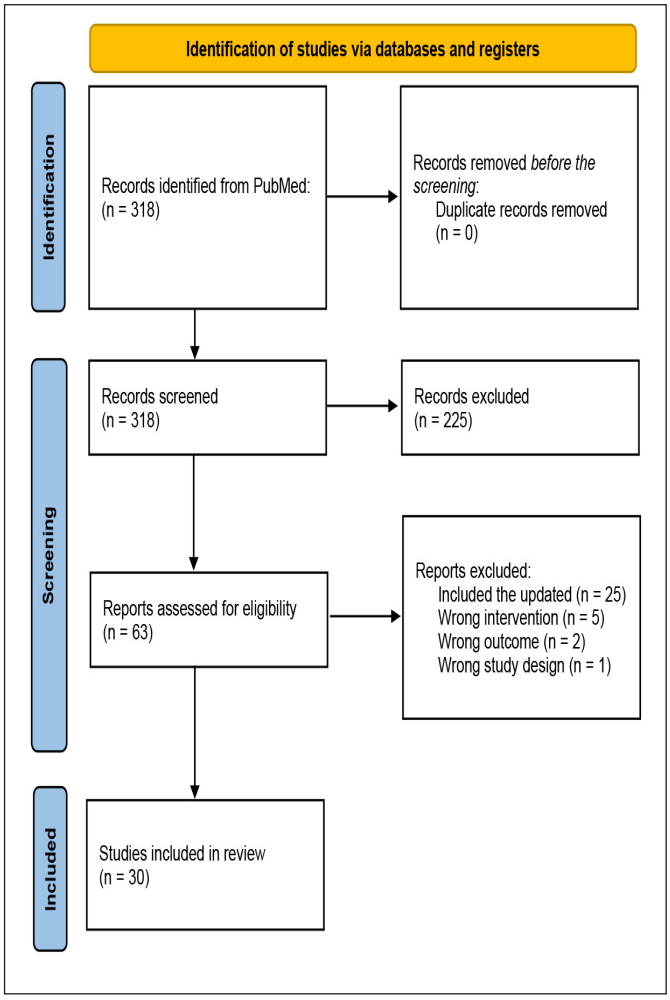

FIGURE S2. Screening flowchart (PRISMA) of the efficacy of treatment for adults with CD.

Data recovery and extraction

The guidelines and/or consensus that met all the inclusion criteria and did not meet any of the exclusion criteria were retrieved electronically via the journal's website or appropriate database. The description of the studies includes the following data:

- Author, year;
- Recommendation according to the eligible variable;
- Quality of the evidence;
- Instrument used for the quality appraisal

Regarding the systematic literature review with meta-analysis, the data extracted from the studies include:

- Author, year;
- Study site;
- Evaluated technology;
- Sample size;
- Characteristics of the population;
- Intervention protocol of the evaluated technology;
- Outcome of interest;
- Results;
- Effect size;
- Effect direction.

Imbrizi M, Baima JP, Azevedo MFC, Andrade AR, Queiroz NSF, Chebli JMF, Chebli LA, Argollo MC, Sassaki LY, Parra RS, Quaresma AB, Vieira A, Damião AOMC, Moraes ACS, Flores C, Zaltman C, Vilela EG, Morsoletto EM, Gonçalves Filho FA, Penna FGC, Santana GO, Zabot GP, Parente JML, Costa MHM, Zerôncio MA, Machado MB, Cassol OS, Fróes RSB, Miszputen SJ, Ambrogini Junior O, Kotze PG, Coy CSR. Second Brazilian Consensus on the Management of Crohn's disease in adults: a consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

TABLE S10. Quality assessment of the Guidelines/Consensus by the AGREE-II Tool.

Authors, year	Title	Domain 1 score	Domain 2 score	Domain 3 score	Domain 4 score	Domain 5 score	Domain 6 score	Overall assessment
Amiot et al., 2021	Clinical guidelines for the management of inflammatory bowel disease: update of a French national consensus.	16.7	55.6	35.4	38.9	41.7	50.0	39.7
Bonnaud et al., 2020	Monitoring of inflammatory bowel disease in 2019: A French consensus for clinical practice.	61.1	72.2	45.8	77.8	58.3	58.3	62.3
Bouchard et al., 2019	How to manage anal ulcerations and anorectal stenosis in Crohn's disease: algorithm-based decision making: French National Working Group Consensus 2018.	33.3	27.8	39.6	83.3	54.2	83.3	53.6
Cheifetz et al., 2021	A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease.	100.0	88.9	62.5	88.9	62.5	75.0	79.6
Clarke et al., 2019	Colorectal cancer surveillance in inflammatory bowel disease: Practice guidelines and recent developments.	77.8	0.0	20.8	66.7	41.7	91.7	49.8
Feuerstein et al., 2021	AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease.	94.4	72.2	58.3	83.3	20.8	100.0	71.5
Gomollon et al., 2017	3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management.	61.1	50.0	54.2	83.3	62.5	58.3	61.6
Greuter et al., 2020	Therapeutic Drug Monitoring to Guide Clinical Decision Making in Inflammatory Bowel Disease Patients with Loss of Response to Anti-TNF: A Delphi Technique-Based Consensus.	72.2	61.1	47.9	83.3	54.2	83.3	67.0
Khan et al., 2019	New Zealand Society of Gastroenterology Guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease.	66.7	50.0	43.8	83.3	62.5	66.7	62.2
Lamb et al., 2019	British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults.	100.0	100.0	100.0	100.0	95.8	100.0	99.3
Matsuoka et al., 2018	Evidence-based clinical practice guidelines for inflammatory bowel disease.	83.3	61.1	66.7	83.3	50.0	66.7	68.5
Nakase et al., 2021	Evidence-based clinical practice guidelines for inflammatory bowel disease 2020.	83.3	72.2	81.3	83.3	50.0	66.7	72.8
Papamichael et al., 2019	Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients with Inflammatory Bowel Diseases.	83.3	72.2	60.4	77.8	58.3	58.3	68.4
Park et al., 2017	Second Korean guidelines for the management of Crohn's disease.	88.9	72.2	85.4	88.9	58.3	58.3	75.3
Qian et al., 2021	Chinese consensus on diagnosis and treatment in inflammatory bowel disease (2018, Beijing).	72.2	61.1	56.3	50.0	41.7	50.0	55.2
Steinhart et al., 2019	Clinical Practice Guideline for the Medical Management of Perianal Fistulizing Crohn's Disease: The Toronto Consensus.	77.8	72.2	79.2	72.2	66.7	83.3	75.2
Torres et al., 2020	ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment.	83.3	94.4	85.4	83.3	62.5	75.0	80.7
Wei et al., 2017	Management of Crohn's disease in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease.	55.6	38.9	25.0	61.1	37.5	8.3	37.7
Syal et al., 2021	Health Maintenance Consensus for Adults with Inflammatory Bowel Disease.	66.7	50.0	56.3	61.1	37.5	58.3	55.0
Lichtenstein et al., 2018	ACG Clinical Guideline: Management of Crohn's Disease in Adults.	55.6	16.7	56.3	83.3	37.5	66.7	52.7
Panaccione et al., 2019	Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Luminal Crohn's Disease.	83.3	72.2	95.8	100.0	66.7	100.0	86.3
Turner et al., 2021	STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD.	61.1	72.2	64.6	61.1	50.0	91.7	66.8
Gionchetti et al., 2017	Use of corticosteroids and immunosuppressive drugs in inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease.	55.6	61.1	60.4	83.3	45.8	66.7	62.2
Ran et al., 2021	Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology practice recommendations for medical management and monitoring of inflammatory bowel disease in Asia.	22.2	38.9	16.7	61.1	29.2	50.0	36.3

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TABLE S11. Quality Assessment of the Systematic Literature Review by the AMSTAR 2 tool.

Author	Alipour	Attauabi	Chandar	Chande	Chande	Chande	Chen	Cholapranee	Coward	Da	Davies	Hazlewood	Kawalec	Kopylov
Year	2021	2021	2015	2016	2015	2013	2021	2017	2017	2013	2019	2015	2016	2014
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
*2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
*4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
*7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes
*9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Partial	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	No
*11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
*13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
*15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial
Rating overall	Low	Critically Low	Low	High	High	High	Low	Critically Low	Critically Low	Critically Low	High	Critically Low	Critically Low	Low

Imbrizi M, Baima JP, Azevedo MFC, Andrade AR, Queiroz NSF, Chebli JMF, Chebli LA, Argollo MC, Sassaki LY, Parra RS, Quaresma AB, Vieira A, Damião AOMC, Moraes ACS, Flores C, Zaltman C, Vilela EG, Morsoletto EM, Gonçalves Filho FA, Penna FGC, Santana GO, Zabot GP, Parente JML, Costa MHM, Zerôncio MA, Machado MB, Cassol OS, Fróes RSB, Miszputen SJ, Ambrogini Junior O, Kotze PG, Coy CSR. Second Brazilian Consensus on the Management of Crohn's disease in adults: a consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

TABLE S12. Quality Assessment of the Systematic Literature Review by the AMSTAR 2 tool.

Author	Kuenzig	Lim	Limketkai	Macaluso	Miligkos	Moja	Patel	Rezaie	Rolfe	Schreiber	Singh	Singh	Singh
Year	2014	2016	2020	2020	2016	2015	2014	2015	2006	2018	2014	2018	2021
1. Did the research questions and inclusion criteria for the review include the components of pico?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Partial	Partial	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
*4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
*7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Partial
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial
*9. Did the review authors use a satisfactory technique for assessing the risk of bias (rob) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
*11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of rob in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
*13. Did the review authors account for rob in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
*15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rating overall	High	High	High	Low	Critically low	High	High	High	High	Critically low	Critically low	Low	Low

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