ORIGINAL ARTICLE

Second Brazilian consensus on the management of ulcerative colitis in adults: a consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

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ABSTRACT – **Background** – Inflammatory bowel diseases are immune-mediated disorders that include Crohn's disease (CD) and ulcerative colitis (UC). UC is a progressive disease that affects the colorectal mucosa causing debilitating symptoms leading to high morbidity and work disability. As a consequence of chronic colonic inflammation, UC is also associated with an increased risk of colorectal cancer. **Objective** – This consensus aims to provide guidance on the most effective medical management of adult patients with UC. **Methods** – A consensus statement was developed by stakeholders representing Brazilian gastroenterologists and colorectal surgeons (Brazilian Organization for Crohn's Disease and Colitis [GEDIIB]). A systematic review including the most recent evidence was conducted to support the recommendations and statements. All recommendations/statements were endorsed using a modified Delphi Panel by the stakeholders/experts in inflammatory bowel disease with at least 80% or greater consensus. **Results and conclusion** – The medical recommendations (pharmacological and non-pharmacological) were mapped according to the stage of treatment and severity of the disease onto 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 targeted general practitioners, gastroenterologists and surgeons who manage patients with UC, and supports decision-making processes by health insurance companies, regulatory agencies, health institutional leaders, and administrators.

Keywords – Colitis, ulcerative; 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 comprehensive, evidence-based medical recommendations on the management of Crohn's Disease (CD) and ulcerative colitis (UC) in acute and remission phases. This work aims to supplement a previously published Brazilian consensus in light of recently published therapeutic advances in UC that warrant an up-to-date review to inform clinical practice recommendations. It is critical to state that these recommendations are not meant to substitute for clinical judgment. Clinicians should consider the specific circumstances of each patient and the facilities in which they work.

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Ulcerative colitis

UC and CD are the two primary types of IBD. Although IBDs have unknown defined causes, their etiologies are associated with genetic factors, the intestinal microbiota, and mucosal immunoregulation[2-5]. UC and CD share overlapping epidemiological, clinical, and therapeutic characteristics; however, they are clearly distinguished by the fact that UC affects the rectum and colon (the rectum may be spared in fewer than 5% of adult patients with UC at diagnosis but may be seen in up to one-third of pediatric-onset colitis), whereas CD may occur in any part of the digestive tract, from the mouth to the anus. In addition, UC is more often characterized by symptoms of an inflamed rectum, like: tenesmus, urgency and bloody diarrhea than CD.

Disease extent

In patients with UC, the disease extent varies and may involve only the rectum, the left side of the colon to the splenic flexure, or the splenic flexure to the entire colon. It is best evaluated using colonoscopy. Below are the three major classifications of disease extension[6]:

- **Distal colitis:** involvement is limited to the rectum (i.e., the proximal extent of inflammation is distal to the rectosigmoid junction). Cases are usually mild and moderate, often with rectal bleeding, mucus and pus in stool, and tenesmus. Diarrhea occurs in 80% of cases; however, there may be constipation. Abdominal pain is usually crampy, preceding evacuations, and is not fully relieved after rectal emptying. Patients may complain of urgency, incontinence, and anorectal pain. Extraintestinal manifestations are less common.
- **Left-sided colitis:** the disease is distal to the splenic flexure. Patients usually suffer from moderate or severe forms of the disease; however, the fulminant form may also occur. Fever, asthenia, and weight loss with anorexia are common. Diarrhea with mucus, pus, blood, and tenesmus may also be present. Extraintestinal manifestations occur in 20–30% of cases (e.g., arthralgia, arthritis, sacroiliitis, oral aphthae, nodous erythema, episcleritis, and gangrenous pyoderma).
- **Extensive colitis (pancolitis):** involvement extends proximal to the splenic flexure with continuous inflammation beginning at the rectum. Upon presentation, pancolitis is found in 14–35% of patients, who may present with anorexia, bloody diarrhea, abdominal pain, and weight loss.

Disease severity

Ulcerative colitis may present with variable histological findings, ranging from minimal to evident ulceration and dysplasia.[7,8] Disease severity (i.e., intensity of the inflammatory process) may be clinically graded using patient-reported outcomes (PROs), inflammatory burden as measured by endoscopic assessment, markers of inflammation, or validated activity indices. The American Gastroenterology Association proposed an update of the activity indexes, encompassing laboratory markers and PROs (TABLE 1)[9,12]. The disease activity is graded as mild when all six criteria are satisfied, severe when criteria for frequency of bowel movement and ≥1 features of systemic disorder (bolded criteria) are satisfied, and moderate when variables fall between the criteria.

An alternative, simpler method to classify UC as severe is to consider the presence of ≥6 bloody stools/day with at least one of the following signs: a) fever (>37.8°C); b) tachycardia (>90 bpm); c) anemia (hemoglobin <10.5 g/dL); d) erythrocyte sedimentation rate (ESR) >30 mm/hour; or e) C-reactive protein (CRP) >30 mg/L[10].

Fulminant UC describes patients who present with severe UC complicated by high fevers, continuous bleeding, grossly elevated biochemical markers of inflammation or weight loss. Some patients also develop toxic megacolon. Although there is no universally agreed-upon distinction between severe and fulminant UC, most clinicians would agree that a flare of ulcerative colitis can be considered fulminant if associated with at least one of the following: high fever, tachycardia, anemia requiring transfusion, dehydration, low urine output, abdominal tenderness with distention, profound leukocytosis with left shift, severe malaise, or prostration[11]. In 2019, the American College of Gastroenterology proposed the following criteria for fulminant disease: a) >10 stools/day; (b) continuous blood in stools; (c) continuous urgency; (d) low levels of hemoglobin requiring transfusion; (e) erythrocyte sedimentation rate (ESR) >30; (f) elevated CRP; (g) fecal calprotectin >150–200 mg/g; (h) Mayo subscore of 3; or (i) Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score 7–8. The authors note that the disease does not need to present with all the factors to be considered fulminant[12].

Clinical response

There is large heterogeneity of definitions referring to clinical response, clinical remission and endoscopic remission in the literature[13]. The Mayo Score is one of the most employed scales, which can be applied to clinical practice to assess clinical response in UC based on symptom improvement and endoscopic findings (TABLE 2)[14]. The score of 0–12 includes a measure of stool frequency, rectal bleeding, a physician's global assessment and a measure of mucosal inflammation at endoscopy. The non-invasive components of the full score can be summed into the partial Mayo score, which correlates well to patient perceptions of response to therapy[15].

Endoscopic response

Endoscopy plays a central role in the care of IBD patients. Methods to describe UC endoscopic activity include some indexes of severity like the UCEIS (TABLE 3)[16] and the Mayo endoscopic subscore. Based on low quality of evidence, recent reports defined mucosal healing in UC as a Mayo endoscopic subscore of 0 (inactive disease) or 1 (mild disease) (TABLE 4)[12].

Although widely employed, none of the currently available methods to assess endoscopic response have been fully validated according to existing methodological norms. In addition, there is substantial variation in the interpretation of visual scores, which remains a significant limitation to these methods[18].

Clinical remission

Remission may be assessed using several definitions and scores. The US Food and Drug Administration recommends that clinical trials should assess remission as a Modified Mayo Score of 0 to 2, including the following three components[19]:

- Stool frequency subscore = 0 or 1
- Rectal bleeding subscore = 0
- Endoscopy subscore = 0 or 1 (score of 1 modified to exclude friability)

Alternative measures of remission include symptomatic

TABLE 1. Modified Truelove and Witt´s score proposed by the ACG[12].

	Remission	Mild	Moderate-severe	Fulminant
Stools (#/d)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75%	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/mL)	Normal	Elevated	Elevated	Elevated
FC (µg/mL)	<150–200	>150–200	>150–200	>150–200
Endoscopy (Mayo subscore)	0–1	1	2–3	3
UCEIS	0–1	2–4	5–8	7–8

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; UCEIS: Ulcerative Colitis Endoscopic Index Severity. Modified from[9].

TABLE 2. Mayo Score for ulcerative colitis. [derived from Lamb et al.[16]].

Mayo Index	0	1	2	3
Stool frequency	Normal	1–2 / day more than normal	3–4 / day more than normal	5 / day more than normal
Rectal bleeding	None	Streaks of blood with stool <50% of the time	Obvious blood with stool most of time	Blood passed without stool
Mucosa (endoscopic subscore)	Normal or inactive disease	Mild disease (erythema, decreased vascular pattern, mild friability)	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	Normal	Mild disease	Moderate disease	Severe disease

The Mayo score is the sum of scores for each of the four variables (maximum score 12).

Clinical response: reduction of baseline Mayo score by ≥3 points and a decrease of 30% from the baseline score with a decrease of at least one point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.

Clinical remission: defined as a Mayo score ≤2 and no individual subscore >1.

Mucosal healing: defined as a mucosa subscore of ≤1.

Disease activity: Mild 3–5; Moderate 6–10; Severe 11–12.

TABLE 3. Ulcerative Colitis Endoscopic Index of Severity [derived from Lamb et al.[16]].

Descriptor (score most severe lesions)	Likert scale	Definition
Vascular pattern*	Normal (1)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding*	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood or visible oozing from a hemorrhagic mucosa
Erosions and ulcers*	None (1)	Normal mucosa and no visible erosions or ulcers
	Erosions (2)	Tiny (≤5 mm) mucosa defects of a white or yellow color with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa that are discrete fibrin-covered ulcers when compared with erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge

UCEIS score: sum of all three descriptors in the worst affected area of the colon visible at endoscopy. Remission, score ≤1. *These three features account for 90% of variability in assessment of severity.

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TABLE 4. Modified Mayo Score (mMS)

mMS subscores by category	
Stool frequency*	
0	Normal number of stools
1	1–2 more stools than usual
2	3–4 more stools than usual
3	5 or more stools than usual
Rectal bleeding**	
0	No blood seen
1	Stool with streaks of blood
2	Stool with more than streaks of blood
3	Blood alone passed
Endoscopy	
0	Normal appearance of mucosa
1	Mild disease (erythema, decreased vascular pattern), no friability
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)

*The patient provides their own baseline against which to compare the degree of abnormality in stool frequency; **Represents the worst bleeding score for that day.

remission (through PROs, no rectal bleeding, and no urgency) and endoscopic evidence of mucosal healing. Remission refers to asymptomatic patients or those without inflammatory sequelae, including those who responded to medical or surgical intervention without evidence of residual disease[20].

Steroid-free clinical remission, endoscopic healing, and deep remission

Corticosteroids are effective at improving symptoms and providing a global sense of wellbeing; however, they are ineffective as a maintenance therapy, and toxicity can be significant[17]. For this reason, corticosteroid-free clinical remission has been used as an essential endpoint in clinical trials. Remission may be defined based on symptoms, endoscopic findings or disease impact without ongoing steroid use. While symptomatic remission refers to improvement in PROs, endoscopic healing (mucosal healing) is considered in the absence of mucosal friability. Deep remission is understood as a combination of symptomatic remission and endoscopic healing and is the preferred goal of treatment[12]. Disease activity indexes commonly used in clinical trials may be used to define steroid-free remission, including the Mayo score.

Sustained clinical remission

There is considerable variation among studies concerning the definition of sustained remission. Examples include broad definitions such as a stable, steroid-free clinical remission during a 1-year follow-up[21]. In clinical trials as a primary endpoint, sustained clinical remission has been evaluated using two definitions: (a) a partial Mayo Score of ≤2 with no subscore >1 and (b) a rectal bleeding subscore of 0 throughout weeks 14, 26, 38, and 52[22].

Quality of life (QoL) improvement

With advances in clinical trial designs and the influence of regulatory agencies seeking PROs as primary endpoints, QoL and related psychosocial measures are of growing significance in IBD research[23]. The IBDQ is the most widely used QoL instrument for patients with IBD[24]. The scale includes 32 items scored on a 7-point Likert scale, ranging from 1 (worst health) to 7 (best health).

Drug classes (TABLE 5)

We divide the treatment of UC into conventional and advanced therapy. We considered conventional therapy aminosalicylates, corticosteroids and immunomodulators. Regarding advanced therapy, we considered the classes of biologics (anti-TNF, anti-integrin, and anti-interleukin) and small molecules (JAK inhibitors and S1p inhibitors). In strictly selected cases, probiotic therapy may be used.

Aminosalicylates derivatives

In this group of drugs (also known as aminosalicylates), we included sulfasalazine (SSZ) and salicylic acid derivatives (5-ASA). SSZ is unfolded in the colon and acts by direct contact with colonic mucosa to suppress various pro-inflammatory pathways including cyclooxygenase- and lipoxygenase-derived products (e.g., prostaglandins and leukotrienes from arachidonic acid). More recently, it has been shown that a substantial part of 5-ASA activity is due to its ability to activate peroxisome proliferator-activated receptor-g[25].

Several types of mesalazine have been developed to be administered either orally, as suppositories, or enemas. Various oral formulations were designed to target the delivery of mesalazine to the diseased area of the bowel to provide local anti-inflammatory activity, achieving maximal drug release in different locations and timing[25]. Oral, unprotected mesalazine is readily absorbed from the stomach and proximal small bowel; however, a few preparations have been developed using either pro-drug or modified-release mechanisms to deliver it to the distal intestine[26]. The currently approved formulations in the Brazilian market are a) Eudragit-S (released at pH >7, mostly in the terminal ileum and colon); b) microgranule mesalazine (released throughout the intestinal tract in a time-dependent fashion); and c) Eudragit-S with multi-matrix

TABLE 5. Drugs used in ulcerative colitis treatment.

Drug	Induction dose	Maintenance dose
5-ASA	Topical: mesalazine suppositories: 500 mg to 1 g/day Mesalazine enema: 1–3 g/day Oral: mesalazine (granules or tablets) or sulfasalazine ≥ 3 g/day	Topical: Mesalazine suppositories 500 mg to 1g 3 times per week Oral: Mesalazine (granules or tablets) or sulfasalazine ≥2 g/day
Corticosteroids	Budesonide MMX: 9 mg/day 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
Cyclosporine	Intravenous cyclosporine (50 mg/mL) 2 mg/kg/day (with serum drug monitoring)	Oral cyclosporine (25 mg, 50 mg or 100 mg capsules 100 mg/mL solution) 5 mg/kg/day for up to 3 months
Immunosuppressants	Thiopurines: Azathioprine 1.5–2.5 mg/kg/day PO 6-mercaptopurine (6-MP): 1–1.5 mg/kg/day PO	Thiopurines: Azathioprine 1,5–2,5 mg/kg/day PO 6-mercaptopurine (6-MP): 1–1.5 mg/kg/day PO
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 80 mg after 2 weeks Golimumab 50 mg, 100 mg or 200 mg/dose (pen): 200 mg SC and then 100 mg SC after 2 weeks	Infliximab 10 mg/mL (10mL/unit): 5 mg/kg IV every 8 weeks or Infliximab 120mg SC every 2 weeks from week 6 Optimized dose: 10 mg/kg IV every 8 weeks or 5 mg/kg IV every 4 weeks Adalimumab 40 mg (syringe or pen) or 80 mg (pen): 40 mg SC every 2 weeks Optimized dose: 40 mg SC weekly or 80 mg SC every 2 weeks Golimumab 50 mg, 100 mg: 50 to 100 mg every 4 weeks
Anti-integrin	Vedolizumab 300 mg/unit 300 mg IV at weeks 0, 2 and 6	Vedolizumab 300 mg/unit: 300 mg IV every 8 weeks (vedolizumab): or 108 mg SC every 2 weeks starting after the second or third IV induction dose Optimized dose: 300 mg IV every 4 weeks or 108 mg SC weekly (off label)
Anti-interleukin	Ustekinumab 130 mg/ 26 mL or 90 mg/unit: 55 kg or less: 260 mg IV 55 kg to 85 kg: 390 mg IV more than 85 kg: 520 mg IV	Ustekinumab 90 mg/unit: 90 mg SC every 8 or 12 weeks Optimized dose: 90 mg SC every 4 weeks (off-label)
Jak inhibitors	Tofacinitib 5 mg and 10 mg 10 mg bid PO for 8 to 12 weeks Upadacitinib*: 45 mg PO once a day for 8 weeks Filgotinib**: 200 mg PO once a day for 10 weeks	Tofacinitib 5 mg 5 mg PO BID *if loss of response, consider new induction period for 8 weeks Upadacitinib*: 15 mg once a day Refractory, severe, or extensive disease: consider 30 mg q day Filgotinib**: 100 mg to 200 mg PO once a day
Sphingosine-1-phosphate (S1P) receptor modulator	Ozanimod 0.92 mg*: day 1–4: 0.23 mg PO q day Days 5–7: 0.46 mg PO q say	Ozanimod 0.92 mg*: day 8 and thereafter: 0.92 mg PO q day

PO: oral administration; IM: intramuscularly; SC: subcutaneous; IV: intravenous, bid: 2 times a day. *FDA (Food and Drug Administration) approved; **EMA (European Medicine Agency) approved.

system (MMX), which dissolves a hydrophilic matrix at pH >7 in the terminal ileum and colon, forming a viscous gel of slow diffusion and controlled release[27,28].

The granule and MMX formulations may be of special interest because they reduce pill burden and encourage adherence, potentially increasing tolerability and acceptability of treatment, as they can be taken once daily. Moreover, despite the lack of evidence adequate comparative trials, the specific release profiles are thought to be clinically important in terms of treatment efficacy to the point that clinicians often match these to the site and extent of inflammation to match the needs of their patients[25].

Most patients that are intolerant or allergic (80–90%) to SSZ tolerate mesalazine; however, some patients (10–20%) present SSZ-like side effects when using mesalazine. A Cochrane review showed that despite being less tolerated, SSZ was as effective in treating UC as the most recent formulations of mesalazine and were less costly[29]. For patients with mild-to-moderate left-sided UC or those with extensive involvement, a combination of oral (>2 g/day) and topical mesalazine is more effective than the use of each separately[30,31].

Side effects of SSZ are typically dose-dependent and related to sulphapyridine serum levels. Such effects occur in up to 45% of the patients with low genetic ability of hepatic acetylation of the drug. These side effects include abdominal pain, nausea, vomiting, anorexia, headache, hemolysis, and male infertility. Less frequently, SSZ side effects may occur due to hypersensitivity (allergy or idiosyncrasy), including fever, rash, lymphadenopathy, Stevens-Johnson syndrome, agranulocytosis, hepatitis, pancreatitis, and diarrhea.

Corticosteroids

Corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone, prednisolone) are the drugs of choice for moderate and severe cases of IBD; they induce clinical remission in 70% to 90% of cases after four to six weeks of treatment. The course of corticosteroids should be as short as possible, and prolonged treatment (i.e., for maintenance of UC remission) is not recommended given its well-known side effects[32].

In active UC, oral prednisone (0.75–1 mg/kg/day, up to a maximum 60 mg/day) is indicated to induce clinical remission but its use must be avoided for long periods (>2–3 months), even if administered at low doses. Corticosteroid weaning must be gradual, reducing 10 mg/week up to 20 mg/day, followed by 5 mg/week until total withdrawal is achieved. If a relapse occurs during withdrawal, the corticosteroid dose may be increased to the same level as the dose before the one that caused relapse. In severe cases, inpatients may be given 100 mg IV hydrocortisone every 6 or 8 hours or methylprednisolone 60 mg/daily for 7–10

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days, followed by oral prednisone (without exceeding 60 mg/day) as soon as the patient is recovered, stable and able to ingest it[1].

Corticosteroid side effects include appetite stimulation and increase in body weight, edema, insomnia, emotional lability, psychosis, acne, Cushing syndrome, osteoporosis, osteonecrosis, growth retardation, hypothalamus-hypophysis-adrenal axis suppression, infections, myopathies, cataract, skin atrophy, striations, ecchymosis, fatty liver, diabetes, hypertension, glaucoma, and acute pancreatitis[33-35]. Second-generation corticosteroids such as budesonide are associated with fewer systemic side effects, partly due to their first-pass metabolism in the liver. Oral budesonide (9 mg/day) produces similar adverse events (AEs) to placebo, except for "moon face," which is significantly more common with budesonide[36]. Compared to prednisone, budesonide also produces significantly fewer side effects[37]. While corticosteroids should not be used as maintenance drugs, budesonide can be used for more prolonged periods (up to 6 months) when necessary. As soon as patients present signs of corticosteroid dependence, defined as a patient who fails to taper steroids below 10 mg within 16 weeks from a starting dose of 0.75–1 mg/kg oral prednisone-equivalent, or who relapses within 12 weeks after steroid discontinuation, and steroid-refractory colitis is defined as patients who have active disease despite prednisolone up to 0.75 mg/kg/day over 4 weeks[38].

Immunomodulators

Thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) are commonly used for the maintenance of remission in steroid-dependent UC patients and for cases in which effective doses of aminosalicylates fail to maintain remission. These agents are considered effective for the maintenance of long-term clinical remission and relapse prevention[39].

Methotrexate (MTX), a folate antagonist, is an immunosuppressant with anti-inflammatory properties. It is used to treat inflammatory diseases including CD; however, it is not currently recommended either for induction or maintenance of UC as conclusive evidence is still lacking[40].

Cyclosporine is a macrolide immunosuppressant that inhibits the production of interleukin-2 activated by T-lymphocytes through a calcineurin-dependent pathway and the synthesis of other inflammatory cytokines[41]. It is considered a valid option to treat acute severe UC patients, especially those who do not respond to previous treatment with steroids or infliximab or as a bridge to other biological therapies[42]. Tacrolimus, a calcineurin inhibitor like cyclosporine, has a similar mechanism of action[43] and appears superior to placebo for promoting clinical remission and clinical improvement in corticosteroid-refractory colitis or proctitis[44].

Biological agents

Pharmacological treatment of UC aims to reduce the inflammatory process and maintain symptom remission[9]. Despite therapeutic progress, treatment options for moderately-to-severely active UC remain limited as only partial control is obtained with conventional therapies (aminosalicylates, corticosteroids and immunomodulators) in a substantial proportion of patients, in addition to the occurrence of drug-related AEs[45].

Biologic therapies are genetically engineered medications made from living organisms. They work by targeting specific cells in the gut involved in the inflammation process improving symptoms and QoL[46]. The anti-tumor necrosis factor alpha (anti-TNF-α) drugs bind and clear TNF and induce cytotoxicity in immune cells (including apoptosis). Anti-integrin is a monoclonal antibody specifically targeting extracellular integrins expressed by gut lymphocytes, thereby modulating gut inflammation. Anti-interleukin is a monoclonal antibody that blocks pro-inflammatory responses.

The drugs of choice for induction of remission in these patients are anti-TNF-α agents such as infliximab (IFX), adalimumab and golimumab, and the anti-integrin agent vedolizumab and anti-interleukin ustekinumab[8,39].

Janus Kinase (JAK) Inhibitors

JAK inhibitors have been incorporated into the management of immune-mediated diseases such as rheumatoid arthritis (in Brazil, since late 2014)[47]. They are a family of small molecules that block intracellular tyrosine kinases. Tofacitinib is an oral small-molecule drug which inhibits JAK1, JAK3, and (to a lesser extent) JAK2. This inhibition blocks signals for several inflammatory cytokines[48] involved in the pathogenesis of IBD and participates in many immune signaling routes including lymphocyte activation, function, and proliferation[49,50]. In March 2019, the drug was approved by Brazilian Health Regulatory Agency (ANVISA) for the treatment of moderate-to-severe UC[51]. Other drugs used are upadacitinib and filgotinib (both JAK1 inhibitors)[52].

Sphingosine 1-phosphate (SP) inhibitors

There is a new class of drugs that inhibits SP in the peripheral lymphocytes by binding to S1P1 and S1P15 receptors, thereby reducing inflammation. The novel drug ozanimod was approved for multiple sclerosis in 2020 and are now being tested for UC. According to the drug first approval, it demonstrated modest effect on UC[53].

Probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" according to the Food and Agriculture Organization[54]. The use of probiotics are thought to improve health; however, in recent years, there has been a growing interest in their use in IBD due to the role of the microbiome in the pathogenesis of this disease through inhibition of the growth of pathogenic bacteria, enhancement of the intestinal barrier function, and modulation of host immune responses[54].

The various treatment approaches for these conditions can be divided into treatment during the acute phase (induction therapy) and treatment for the long-term control of symptoms (maintenance therapy). High-quality clinical trials on the effects of probiotics in UC are scarce, especially in adults. Preliminary evidence in children shows that rectal enemas containing *Lactobacillus reuteri* and an oral formulation of VSL #3 may have a role in active UC for the induction and maintenance of remission, with a cautionary note against *Lactobacillus rhamnosus GG* in acute severe UC due to reported cases of bacteremia. In adults, probiotics may be useful for prevention and treatment of pouchitis in colectomized patients[55-57].

Objective of the consensus

This consensus aims to provide guidance concerning the most effective medical management of adult patients with UC. It is not intended to address the diagnostic evaluation. The question is "What is the best medical management for adult patients with UC according to the severity of the disease and phase of the treatment?"

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METHODS

This consensus addresses the most relevant information to guide decision-making for clinical management of UC. 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. Consensus with experts (especially regarding health matters) can synthesize information available for clinical assistance, management, research, and policy in health systems while maintaining diversity and independence of opinions, decentralization, and specialization of knowledge.

The GEDIIB represents the Brazilian key stakeholders that participated in this consensus. The consensus targeted general practitioners and gastroenterologists interested in the treatment and management of adult patients with UC. This consensus also supports the decision-making of health insurance companies, institutional leaders, and administrators.

The rapid review approach[58] was the most appropriate as it is the highest-quality method suited to the context of providing the best and most recent evidence. The concern for a timely decision on health care and policies was the driving force for this consensus. Additionally, traditional systematic reviews can take years to complete, and a rapid review provides the same quality standards based on the principles of the Cochrane Collaboration. Therefore, a adapted systematic review was performed to support the recommendations/statements. According to its definition, the literature review was systematic, however, with some limitations such as database number, study design, and search period. Existing high-quality guidelines or consensus and level 1 evidence studies (systematic literature review) were eligible, identified, 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 population, intervention, comparator, outcome and study design (PICOS) acronym was used to describe the questions to be answered. Only publications in the English language were considered. Quality appraisal of the guidelines/consensus was performed using appropriate tools (additional methodologies data can be found in supplementary material: PICOS—TABLES S1 to S7; search strategy—TABLE S8; screening flowchart—FIGURE S1 and S2; quality appraisal—TABLES S9 to S13). In addition to the studies identified and included through the systematic review, the recommendations were endorsed by studies captured by "snowballing search" starting from the reference list of the guidelines.

The quality appraisal of the included studies was performed 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[59]. This instrument was developed to address the issue of variability in the quality of practice guidelines. The AMSTAR 2 evaluates the quality of the evidence of the systematic literature review with meta-analysis[60]. Originally, the assessment of multiple systematic reviews (AMSTAR) tool was used for investigating the methodological quality of systematic reviews. The AMSTAR 2 was developed for systematic reviews of randomized controlled trials. The rate of overall confidence in the results of the systematic reviews 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. When 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 was composed of 34 gastroenterologists and colorectal surgeons who were members of the GEDIIB. The consensus of recommendations/statements in each round was considered to have been reached if there was ≥80% agreement[61].

MEDICAL MANAGEMENT OF UC

MILD-TO-MODERATE ACTIVE UC

Induction of remission treatment

Aminosalicylates derivatives

> **Recommendations**
> 1. The use of mesalazine or sulfasalazine induces global or clinical remission; however, mesalazine is associated with fewer AEs[12,16,62]. **Agreement:** 85.7%.
> 2. In patients with mildly active left-sided colitis, rectal 5-ASA enemas or combination therapy with oral 5-ASA are preferred for induction of remission[12,62,63]. **Agreement:** 85.7%.
> 3. In patients with mildly active proctitis, rectal 5-ASA suppository is recommended for induction of remission. When patients do not respond to 5-ASA suppository, it is recommended to consider combination therapy with oral 5-ASA[12,62,64]. **Agreement:** 82.9%.

For mild-to-moderate proctitis, rectal 5-ASA should be considered the topical therapy as the choice for disease management. Mesalamine foam (unavailable in Brazil) or enemas are an alternative; however, suppositories deliver the drug more effectively to the rectum and are better tolerated[63] (suppositories of 500 mg/day to 1000 mg/day for proctitis or enema of 1–3 g/day for distal colitis). Topical mesalazine is superior to rectal corticosteroids in inducing symptomatic improvement and remission (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.15 to 2.11; $P=0.004$ and 1.65 [95%CI 1.11 to 2.45; $P=0.01$], respectively)[12,16,62,64-68]. There were no differences in remission induction failure and rate of AEs when comparing a single daily dose to a conventional regimen or when comparing various formulations of 5-ASA. Therefore, treatment adherence is inconclusive when administered as a single dose instead of a conventional regimen[12,16,62,64,68,69].

For mild-to-moderate left-sided colitis, the evidence demonstrated that the first-line therapy should be the combination of oral and topical mesalazine. Combination therapy can be administered orally (>2 g/day) preferably combined with 5-ASA enema

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(if 5-ASA enema is unavailable, a suppository formulation can be used). Patients with moderate activity of the disease can benefit from an initial dose ≥4 g/day[12,62,63,66].

Specifically to the cases of extensive mild-moderate UC, an aminosalicylate enema of 1 g/day combined with oral mesalamine ≥4 g/day should be considered initial treatment. Nonresponsive patients may be prescribed a treatment regimen associated with systemic corticosteroids[12,63,64,68-73].

Corticosteroids

> **Recommendations**
> • Prednisone (or prednisolone) must be started in cases of rectal bleeding for more than two weeks despite the appropriate use of aminosalicylates[1,12,16,62,64]. **Agreement: 94.3%.**

The use of systemic corticosteroids in mild-to-moderately active UC to any extent is indicated for patients who are unresponsive to treatment with aminosalicylates at an adequate dose. Initiation of therapy is indicated in those patients with rectal bleeding or abdominal symptoms after 2 and 6 weeks of 5-ASA therapy, respectively, and in cases of worsening symptoms. The initial therapeutic dose may vary according to the patient's weight or from 40–60 mg of prednisone (or equivalent). Thereafter, a dose reduction of 5–10 mg/week must be performed until a daily dose of 20 mg is reached. From this point, the dose should be reduced to 2.5–5.0 mg/week[10,74].

Systemic corticosteroids and budesonide are superior to placebo and aminosalicylates for inducing remission of active UC. Budesonide is in a generation of corticosteroids with an ileal or colonic delivery mechanism, with low absorption and systemic concentration[74]. Two phase III, randomized, double-blind, double-dummy, placebo-controlled studies demonstrated the efficacy of budesonide-multimatrix (MMX). Sandborn et al. (2012) evaluated its efficacy for induction of remission in 509 patients with active, mild-to-moderate UC. Patients were randomly assigned to 9 mg or 6 mg of budesonide, 2.4 g of mesalazine as an active reference, and placebo for 8 weeks. Remission rates at week 8 among those using 9 mg or 6 mg budesonide-MMX or mesalamine were 17.9%, 13.2%, and 12.1%, respectively, compared with 7.4% for placebo (compared to placebo: $P=0143$, $P=1393$, and $P=2200$, respectively). Clinical improvement rates at week 8 for 9 mg or 6 mg budesonide-MMX or mesalamine were 33.3%, 30.6%, and 33.9%, respectively, compared with 24.8% for placebo ($P=1420$, $P=3146$, and $P=1189$, respectively). Endoscopic improvement rates at week 8 for 9 mg or 6 mg budesonide-MMX or mesalamine were 41.5%, 35.5%, and 33.1%, respectively, compared with 33.1% for placebo. Symptoms resolution rates at week 8 for 9 mg or 6 mg budesonide-MMX or mesalamine were 28.5%, 28.9%, and 25.0%, respectively, compared with 16.5% for placebo ($P=0258$, $P=0214$, and $P=1025$, respectively). Concerning the safety of budesonide-MMX, 12.4% of subjects in the placebo group experienced severe AEs (AEs) compared with 6.3% in the budesonide-MMX 9 mg group, 9.5% in the budesonide-MMX 6 mg group, and 5.5% in the mesalazine group. The study concluded that budesonide-MMX at 9 mg was safer and more effective than placebo in inducing remission in patients with active, mild-to-moderate UC[75]. The phase III, randomized, double-blind, double-dummy, placebo-controlled, parallel-group described in Travis et al. (2014) endorsed the evidence of Sandborn

et al. (2012). However, instead of mesalazine as a reference active group, Travis et al. (2014) used Entocort EC 9 mg (budesonide controlled ileal-release 3×3 mg capsules taken once daily in the morning). The study was conducted with 410 subjects with active, mild-to-moderate UC. The authors found that combined clinical and endoscopic remission rates with budesonide-MMX 9 mg, 6 mg, Entocort EC, and placebo were 17.4%, 8.3%, 12.6%, and 4.5%, respectively. There was a significant difference between budesonide-MMX 9 mg and placebo, in which the efficacy of budesonide was 4.5-fold more likely to be effective for this outcome (OR=4.49 [95%CI 1.47 to 13.72; $P=0.0047$]). Budesonide-MMX 9 mg was associated with numerically higher rates of clinical (42.2% vs 33.7%) and endoscopic improvement (42.2% vs 31.5%) versus placebo. The rate of histological healing (16.5% vs 6.7%; $P=0.0361$; OR=2.74 [1.04 to 7.22]) and proportion of patients with symptom resolution (23.9% vs 11.2%; $P=0.0220$; OR=2.47 [1.12 to 5.46]) with budesonide-MMX 9 mg were significantly higher than placebo. The percentage of treatment-emergent AEs was similar across groups, most common in the placebo, budesonide-MMX 9 mg and 6 mg, and Entocort EC groups for UC relapse (11.6%, 15.6%, 21.1%, and 12.7% respectively) and headache (6.2%, 16.4%, 15.6%, and 7.1%, respectively)[76].

Immunomodulators

> **Recommendations**
> 1. We recommend against the use of thiopurines for the induction of remission due to slow onset of action[62]. **Agreement: 88.6%.**
> 2. There is insufficient evidence to support the use of MTX to induce remission in patients with UC[62]. **Agreement: 88.6%.**

Thiopurines include AZA and 6-mercaptopurine. They inhibit cell growth, interfere with the synthesis of nucleic acids, and prevent the rapid cell proliferation that exacerbates most inflammatory processes. They are absorbed via the gastrointestinal tract and are characterized by low bioavailability and a short half-life, requiring 3–4 months to reach stable levels of 6-thioguanine (the final metabolite); for this reason, thiopurines are not effective in inducing remission.

A meta-analysis by Chande et al. (2014) compared oral MTX (15 mg/week) to placebo, 6-mercaptopurine (1.5 mg/kg/day), and 5-aminosalicylic acid (3 g/day). The authors found no benefit of MTX over placebo or any of these active comparators (risk ratio [RR] for placebo was 0.96 [95%CI 0.58 to 1.59] and for active comparators it was 0.74 [95%CI 0.43 to 1.29])[77]. A lack of efficacy was also observed by Khan et al. (2011) who compared AZA to placebo and found no difference between them concerning clinical remission (RR=0.85 [95%CI 0.71 to 1.01])[78].

A classical study by Jewel et al. (1974) demonstrated that, if a patient is being treated with corticosteroids for attacks of UC, the addition of AZA (2.5 mg/kg body weight) does not add any benefit. The same can be seen when the drug is used as a maintenance treatment during the year after the first attack. The use of AZA was effective in the treatment of patients who had relapses of established disease (reduced relapse rate)[79]. In addition, a one-year, randomized, placebo-controlled study of 83 patients (randomly assigned to the AZA combined with oral sulfasalazine [6–8 g/day], oral prednisolone (1 mg/kg/day) or oral AZA (2 mg/kg/day) and placebo group (oral sulfasalazine [6–8 g/day] or oral prednisolone

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[1 mg/kg/day] combined with placebo]) with severe UC who relapsed within two months on corticosteroids also demonstrated that AZA had no effect on remission, primarily when combined with prednisolone[80].

Probiotics

The probiotic VSL#3 can increase the response rates and clinical response and remission of active mild UC patients when compared to placebo (clinical response: OR=2.79 [95%CI 1.37 to 5.67; P=0.008]; clinical remission: OR=2.4 [95%CI 1.48 to 3.88; P=0.007])[81]. However, there is low-certainty evidence suggesting that probiotics may induce clinical remission compared to placebo. Regarding clinical remission compared to 5-ASA, there was little or no difference from using probiotics alone (KAUR, 2020). When combined probiotic with 5-ASA, there was superior efficacy in terms of clinical remission compared to 5-ASA alone (RR=1.40 [95%CI 1.27 to 1.53; P=0.000])[82].

Maintenance of remission treatment

Aminosalicylates derivatives

Recommendations
1. Mesalazine is the first-line maintenance treatment in patients responding to mesalamine or steroids[12,63,64,73]. **Agreement:** 100%.
2. 5-ASA combination therapy is more effective than oral or topical 5-ASA monotherapy. In case of recurrence with oral or topical 5-ASA monotherapy, combination therapy is recommended[16,62-64,73,83]. **Agreement:** 85.7%.
3. Topical 5-ASA is the first-line maintenance therapy in proctitis [suppository] or left-sided [enema] UC, although adherence may be a problem. A combination of oral and rectal mesalazine may be used as a second-line maintenance treatment[12,63,64,73]. **Agreement:** 100%.
4. For proctitis, the maintenance treatment may be carried out using mesalazine suppositories and may be discontinued after 1 year without relapses if patient monitoring is maintained[1,12,63,68,73]. **Agreement:** 100%.
5. It is recommended that UC patients on maintenance therapy with high-dose mesalazine, who required two or more courses of corticosteroids in the past year, or who become corticosteroid-dependent, or corticosteroid-refractory, should undergo treatment escalation with thiopurine or advanced therapy[16,62-64,73,83]. **Agreement:** 88.6%.

Mesalazine compounds are the first-line maintenance treatment in patients responding to mesalamine or steroids [oral or rectal][12,62,63,68,73]. Therefore, use of oral 5-ASA in a dose of 2 g or more should be considered. For mildly active left-sided UC, topical 5-ASA (suppository or enema) is the first-line maintenance therapy. A combination of oral and rectal mesalamine may be used as a second-line maintenance treatment[12,63,64,73]. In patients with extensive mild-moderate UC, the standard dose of mesalazine (2–3 grams/day) or diazo-bonded 5-ASA may be more effective than low dose mesalamine, sulfasalazine, or no treatment[12,68].

In patients with mild-moderate ulcerative proctitis, rectal therapy may be superior to oral therapy (the maintenance rate of symptomatic remission was 80% for rectal 5-ASA compared to 65% of patients in the oral 5-ASA group; RR=1.24 [95%CI

0.92 to 1.66]). For rectal 5-ASA, the dose of 1 g/d is effective to maintain remission, and lower doses may be used in some cases (e.g., 3 g per week)[12,62,63,68,73]. However, this information should be interpreted with caution due to the limited data and low quality of the evidence[84]. For proctitis and proctosigmoiditis UC, the maintenance treatment may be discontinued after 1 year without relapses. The combination of oral and rectal mesalamine may be used as second-line maintenance treatment[1,12,63,68,73].

There are few or no differences in the relapse rates and frequency of AEs in the comparison of various formulations of oral 5-ASA (sulfasalazine and mesalazine)[26,60]. Randomized controlled trials demonstrated that Pentasa had similar efficacy for induction and maintenance of remission compared to several 5-ASA formulations, and real-world data showed that Pentasa had significantly better efficacy in maintaining remission than Eudragit-S mesalazine and sulfasalazine[85]. There were no differences in efficacy or adherence to treatment between a 5-ASA daily dose (single total dose) and a conventional regimen (oral 5-ASA once daily vs. conventional dosing showed similar adherence [RR=0.72; 95%CI 0.46 to 1.13][69]. However, patients more often prefer dosing regimens that require taking medication fewer times per day. Therefore, dosing frequency can be determined according to the patient preferences, compliance, and costs[16,62-64,73,83].

Patients on maintenance therapy with high-dose mesalazine who required two or more courses of corticosteroids in the previous year, or who become corticosteroid-dependent or refractory, require treatment escalation with thiopurine, anti-TNF therapy, vedolizumab, ustekinumab, or tofacitinib. The choice of drug should be determined by clinical factors, patient choice, cost, likelihood of adherence, onset of action, and availability of infusion centers[16,62-64,73,83].

Corticosteroids

Recommendation
• Systemic corticosteroids are not recommended for maintenance of remission in patients with UC. Corticosteroids have no efficacy for maintenance of remission, and their long-term use can lead to AEs; therefore, they should not be used for maintenance of remission[12,64]. **Agreement:** 97.2%.

There is no robust evidence on the use of corticosteroids for maintenance of remission in patients with ulcerative colitis. Several authors discuss the risk-benefit ratio in cases where the risks associated with prolonged use (e.g., immunosuppression, glucose intolerance, slow wound healing, and osteoporosis) do not outweigh the benefits[8,76].

Immunomodulators

Recommendations
1. Thiopurines (AZA/6-MP) can be used to maintain remission in patients who do not maintain remission despite adequate 5-ASA therapy and those who are steroid-dependent[62-64,73,86]. **Agreement:** 90.9%.
2. In patients with UC who showed clinical remission with a corticosteroid, thiopurine therapy can be used to maintain steroid-free remission[62-64,73,86]. **Agreement:** 91.4%.

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Thiopurines are effective in patients who have experienced early or frequent relapse while taking mesalazine at an optimal dose or who are intolerant to mesalazine, patients who are steroid-dependent, and patients responding to cyclosporine or tacrolimus. In patients who showed clinical remission with a corticosteroid, thiopurine therapy can be used to maintain remission without corticosteroids[62-64,73,86]. There is insufficient evidence to support the use of oral MTX in the maintenance of remission[62-64,73,86]. The meta-analysis of Khan et al. (2011) suggested a trend toward benefit of AZA in two randomized controlled trials with 130 active UC patients; however, it did not show statistical significance (RR=0.85 [95%CI 0.71 to 1.01]). In quiescent UC, the use of AZA resulted in a statistically significant benefit in preventing relapse (RR=0.60 [95%CI 0.37 to 0.95])[78].

Probiotics

The probiotic VSL#3 can increase the response rates and clinical remission of active mild UC. Some probiotics, especially *Escherichia coli* Nissle 1917, can be as effective as 5-ASA derivatives for the maintenance of clinical remission in patients with UC in remission[62]. However, the meta-analysis of Iheozor-Ejiofor et al. (2020) found that there is no difference in clinical relapses when treating patients with active UC with probiotics compared to placebo or 5-ASA[87]. These findings suggest that there is insufficient evidence to draw conclusions about the efficacy of probiotics for the maintenance of remission in UC due to the small number of patients and events and the poor quality of the evidence.

MODERATE-TO-SEVERE ACTIVE UC

Induction of remission treatment

> **Expert opinions**
> 1. We suggest that patients with moderate-to-severe UC should be promptly evaluated for the need of hospital admission **Agreement:** 94.3%.
> 2. Patients with severe UC should be promptly admitted and periodically evaluated for severe acute colitis and toxic megacolon criteria. **Agreement:** 100%.

It is essential to evaluate the severity of UC and criteria of severity to manage the induction of remission treatment. UC is classified as mild, moderate, severe, or fulminant. To evaluate these criteria, the most commonly used tool is the Trulove and Witt, which includes several items, including stool number, blood in stool, and hemoglobin. It is critical to understand classification to best evaluate the patient and their needs.

Aminosalicylates derivatives

> **Expert opinion**
> 1. There is no evidence to support the use of 5-ASA in inducing remission in moderate-to-severe UC. **Agreement:** 88.6%.

Evidence suggests that the use of 5-ASA is not recommended for inducing remission in patients with moderate to severe disease if better therapy is available[29]. Despite this conclusion, it is still unclear whether 5-ASA can benefit moderate and severe cases (in combination therapy), and the question remains open.

Corticosteroids

> **Recommendations**
> 1. It is recommended that moderate-to-severe UC should be treated with oral or intravenous corticosteroids depending on the severity of the disease[12,16,62,73]. **Agreement:** 91.5%.
> 2. Long-term therapy with systemic steroids is not indicated[12,16,62,73]. **Agreement:** 94.3%.

Corticosteroids have potent anti-inflammatory properties and are effective for induction of remission in UC[64,83]; however, long-term use can lead to steroid-dependent or steroid-refractory colitis.

Oral or intravenous corticosteroids such as prednisolone (40–60 mg with daily weaning until significant clinical improvement is noted) delivers a clinical response within approximately 2 weeks and total use for up to 8 weeks. After that a dose reduction of 5–10 mg/week must be performed until a daily dose of 20 mg is reached. From this point, the dose should be reduced to 2.5–5.0 mg/week. There is no evidence to support the use of doses greater than 60 mg/day of prednisolone or equivalent[12,16,62,73].

Immunomodulators

> **Recommendations**
> 1. In patients with moderately-to-severely active UC, we recommend against monotherapy with thiopurines for induction of remission[12]. **Agreement:** 88.6%.
> 2. Patients with severe corticosteroid-refractory UC and no surgical indications are candidates for rescue therapy with cyclosporine or infliximab. There is no clear evidence of an advantage of using cyclosporine over infliximab[62]. **Agreement:** 94.3%.

The efficacy of cyclosporine 2 mg/kg/day continuous infusion is equivalent to that of cyclosporine 4 mg/kg/day; however, AEs at 4 mg are more frequent. There is no clear evidence of the advantage of using cyclosporine over infliximab, and both drugs can be used in severe cases of corticosteroid-refractory UC[62].

The use of intravenous cyclosporine requires close monitoring due to risks such as nephrotoxicity, hypertension, neurotoxicity, metabolic derangements, and infection. The monitoring takes place using serum dosage of the drug. At the end of venous therapy, if the patient responds, they are discharged with oral AZA[88].

The meta-analysis of Liu et al. (2018) suggested that tacrolimus and infliximab were safe and effective for the rescue therapy of moderate-to-severe active UC and steroid-refractory UC (clinical remission: OR=1.08 [95%CI 0.77 to 1.49, P=0.67]; clinical response: OR=0.92 [95%CI 0.63 to 1.34, P=0.66]). These findings suggest that tacrolimus is another choice for these patients[89]. As described for mild-to-moderate UC, there is no evidence to support the use of these medications in inducing remission, primarily because of the late onset of action of AZA/6-MP in the treatment of UC.

Biologic agents and small molecules

> **Recommendations**
> 1. We recommend that patients refractory to immunomodulatory therapy or with complicated disease or poor prognostic features should be considered for advanced therapy. The choice between anti-TNFs, anti-integrin, anti-interleukin, or

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JAK inhibitor should be made on an individual basis, considering patient preference, cost, likely adherence, safety, speed of action, and availability of the drug[16]. **Agreement:** 82.9%.

2. We suggest using infliximab or vedolizumab for induction of remission in adult outpatients with moderate-to-severe UC who are naïve to biologic agents[90]. **Agreement:** 91.5%.

3. For patients with prior exposure to TNF antagonists, ustekinumab and tofacitinib may be better options as second-line therapy[91]. **Agreement:** 93.5%.

Expert opinion

4. Patients with moderate-to-severe disease and safety-related risk factors (e.g., advanced age, previous severe infections, relevant comorbidities, and previous malignancy) may be treated preferentially with vedolizumab or ustekinumab. **Agreement:** 85.7%.

Infliximab and vedolizumab are intravenous medications that in clinical trials showed better induction of remission in patients with moderate-to-severe UC. The trials used network meta-analysis, and the authors suggested that could be a comparative effect with optimal concentrations of infliximab, adalimumab and golimumab[90]. The VARSITY study group performed a phase 3 clinical trial and concluded that vedolizumab was superior to adalimumab and should be used in moderate-to-severe UC[92].

Anti-TNF

Recommendations

1. We recommend treating adult outpatients with moderate-to-severe UC with infliximab, adalimumab, or golimumab, over no treatment for the induction and maintenance of remission[90]. **Agreement:** 88.6%.

2. Patients with severe corticosteroid-refractory UC and no surgical indications are candidates for rescue therapy with infliximab. There is no clear evidence of the advantage of using cyclosporine over infliximab, and both can be used in severe cases of corticosteroid-refractory UC[62]. **Agreement:** 88.6%.

3. In patients with loss of response to anti-TNF even after dose optimization, switching to the same or other classes is recommended, preferably guided by monitoring drug levels and anti-drug antibodies[73]. **Agreement:** 93.9%.

Expert opinion

4. We recommend treatment with anti-TNF for the induction of remission in patients with moderate-to-severe active UC who have inadequate response or intolerance to conventional therapy. **Agreement:** 91.4%.

Anti-TNF drugs bind and clear TNF and induce cytotoxicity in immune cells (e.g., apoptosis). There are six studies that demonstrated the safety and efficacy of infliximab, adalimumab, and golimumab in the treatment and maintenance of remission of patients with moderate-to-severe UC. Infliximab was studied in the ACT-1 and -2 studies for long-term use (3 years)[93]. The authors evaluated the safety and efficacy and concluded that the drug should be used to maintain remission because of its well tol-

erability and maintain clinical benefits. Adalimumab was studied in two clinical trials (ULTRA-1 and -2) and was found to be safe and effective; it maintained clinical remission better than placebo or when the treatment with corticosteroids or immunosuppressants failed[94,95]. The studies were conducted in North America and Europe. The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT) studied golimumab as treatment for moderate-to-severe UC and found that it was effective for clinical response and remission[96,97]. One review compared all these studies above and concluded that all medications could be used as alternatives; the authors also stated that this decision should be patient-related and individualized, considering other factors such as cost-effectiveness[98].

The network meta-analysis of Bonovas et al. (2016) included 14,590 adults with IBD and determined whether biologic agents (i.e., adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, and vedolizumab) world affect the risk of infection or malignancy. Overall, patients with IBD exposed to biologics had moderately higher risks of any infection and opportunistic infections compared to placebo (OR=1.19 [95%CI 1.10 to 1.29] and OR=1.90 [95%CI 1.21 to 3.01], respectively). The latter outcome was not statistically significant in patients with UC (OR=1.32 [95%CI 0.64 to 2.72]) and the subgroup difference did not reach statistical significance (P=0.21). The risk of developing severe infections was not increased in patients treated with biologics (OR=0.89 [95%CI 0.71 to 1.12]). Conversely, in the studies with low risk of bias, biologics appeared to significantly reduce risk of severe infections (OR=0.56 [95%CI 0.35 to 0.90]). Finally, there was no increased risk of malignancy with use of biologic agents (OR=0.90 [95%CI 0.54 to 1.50])[99].

Anti-integrins

Recommendations

1. In patients with moderately-to-severely active UC, we recommend vedolizumab for induction of remission[63,73]. **Agreement:** 94.3%.

Expert opinion

2. We recommend treatment with vedolizumab for the induction of remission in patients with moderate-to-severe active UC who have inadequate response or intolerance to conventional therapy. **Agreement:** 94.3%.

Anti-integrin is a monoclonal antibody targeting extracellular integrins expressed by gut lymphocytes, thereby modulating gut inflammation. Vedolizumab was subject of analysis in the GEMINI study. Long-term vedolizumab showed low immunogenicity and its interruption induced an increase in anti-drug antibody rates. This rate decreased when the patient was retreated[100].

A phase 3b, double-blind, double-dummy, randomized trial of 769 patients compared vedolizumab (N=383) to adalimumab (N=386) in adults with moderately-to-severely active UC. Twenty-five percent of the patients had previous exposure to an anti-TNF agent other than adalimumab. The patients were assigned to receive infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). At week 52, a higher percentage

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of patients achieved clinical remission and endoscopic improvement with vedolizumab than adalimumab (31.3% vs 22.5%, P=0.006; 39.7% vs 27.7%, P<0.001, respectively). Conversely, corticosteroid-free clinical remission was numerically higher in the adalimumab group than in vedolizumab group (21.8% vs 12.6%, P=0.4). The exposure-adjusted incidence rates of infection were 23.4 and 34.6 events per 100 patient-years with vedolizumab and adalimumab, respectively, and the corresponding rates for severe infection were 1.6 and 2.2 events per 100 patient-year, respectively[92].

Anti-interleukins

> **Recommendations**
> 1. It is recommended treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC[86]. **Agreement:** 94.3%.
>
> **Expert opinion**
> 2. We recommend treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC who have inadequate response or intolerance to conventional therapy. **Agreement:** 94.3%.

Anti-interleukin is a monoclonal antibody that blocks pro-inflammatory responses. The UNIFI study compared the use of ustekinumab vs. placebo for induction of remission in patients with moderate-to-severe UC. The study enrolled 961 patients and showed after 44 weeks that the drug was effective for inducing and maintaining remission[101].

Another study using the same patients found that the drug improved symptoms after a short time and had better Mayo scores. The efficacy was demonstrated by patient-reported data (e.g. stool frequency), clinical scores (e.g., Mayo score), and biomarkers (e.g., CRP)[102].

Small molecules — JAK inhibitors

> **Recommendations**
> 1. We recommend treatment with tofacitinib to induce remission in patients with moderate-to-severe UC[16,62,86]. **Agreement:** 97.2%.
>
> **Expert opinions**
> 2. We recommend treatment with tofacitinib for the induction of remission in patients with moderately-to-severely active UC who have inadequate response or intolerance to conventional therapy. **Agreement:** 91.5%.
> 3. Tofacitinib should be used with caution in patients with a history or risk factors for thromboembolic events. **Agreement:** 97.2%.

JAK inhibitors are a family of small molecules that block intra-cellular tyrosine kinases. The OCTAVE study investigated tofacitinib therapy in patients with UC[103]. They enrolled 1207 patients divided into induction and sustain trials. The results showed that the induction of remission occurred after 8 weeks was greater than in the placebo group in both trials; mucosal healing was also. The doses were 10 and 5 mg. Nevertheless, caution should be taken in patients with a history or risk factors for thromboembolic events and those at risk of infectious complications, especially herpes zoster infections[83].

Combination therapy with immunomodulators and biological agents

> **Recommendations**
> 1. Patients with moderate-to-severe colitis refractory to thiopurines with an indication for anti-TNF therapy should be evaluated for combined use with thiopurines, at least for infliximab[63,83]. **Agreement:** 94.3%.
>
> **Expert opinion**
> 2. The currently available evidence does not suggest a benefit for the concomitant use of immunomodulators with golimumab, vedolizumab, or ustekinumab; however, further studies are warranted. **Agreement:** 97.2%.

Probiotics in pouchitis UC

The meta-analysis of Poo et al. (2022) compared the efficacy and tolerability of treatments in the management and prevention of acute and chronic pouchitis. They found that antimicrobial therapy remains the mainstay of treatment and adds weight to current guideline recommendations. The results of this study demonstrated that probiotics may deserve a more prominent role. For chronic pouchitis, metronidazole followed by probiotics had a significant effect on inducing remission and probiotics proved to be superior to placebo in the prevention of pouchitis[104].

Maintenance of remission treatment

Corticosteroids

> **Recommendation**
> • We recommend against systemic corticosteroids for maintenance of remission in patients with UC[12]. **Agreement:** 94.3%.

Corticosteroids have no efficacy for maintenance of remission, and their long-term use can lead to AEs. Additionally, the use of corticosteroids at the time of surgery in patients with IBD is associated with a higher risk of total postoperative complications and infectious disease[62,64,83].

Immunomodulators

> **Recommendations**
> 1. AZA and 6-MP are effective for preventing relapse in UC patients in remission, and therefore are effective for maintenance of remission, especially in patients who are steroid-dependent or unable to maintain remission with 5-ASA preparations[1,64]. **Agreement:** 97.2%
> 2. Thiopurines should be used to maintain remission; however, a therapeutic response may not occur within three months[1,64]. **Agreement:** 91.5%.

For patients with previously moderately-to-severely active UC who are in remission due to corticosteroid induction, thiopurines for maintenance of remission are a better option than no treatment or corticosteroids[12]. IBD patients in prolonged remission on thiopurines who show mucosal healing may stop the drug after discussing the risks and benefits and considering patient preference. Reintroduction if relapse occurs is usually successful[16].

Caution must be taken when using thiopurines. Their intro-

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duction as maintenance therapy should be carefully followed. Assessment of myelotoxicity (AZA or 6MP) or hepatotoxicity (AZA) especially in the first few weeks of therapy. Patients requiring concomitant use of allopurinol should have their AZA dose reduced to one-third or one-half of the usual dose[105]. In patients over 65 years of age, the use of thiopurines should be discouraged both because of the conditions mentioned above and the higher risk of neoplasms and infections. Currently, there is insufficient evidence to support the use of oral MTX in the maintenance of remission in patients with UC[1,64].

Biological agents

> **Recommendations**
> 1. We recommend anti-TNF agents [infliximab, adalimumab, or golimumab] for the maintenance of remission in patients with UC who responded to induction therapy with the same drug[83,86]. **Agreement:** 100%.
> 2. We recommend vedolizumab for maintenance of remission in patients with UC who responded to induction therapy with vedolizumab[12,16,83,86]. **Agreement:** 100%.
> 3. We recommend ustekinumab for the maintenance of remission in patients with UC who responded to induction therapy with ustekinumab[83,86]. **Agreement:** 100%.

Anti-TNF

Long-term administration of anti-TNF agents is effective as remission maintenance therapy for moderate-to-severe UC patients who achieved remission with anti-TNF agents. Maintenance of remission with anti-TNF agents provides a higher likelihood of avoiding colectomy[64].

Infliximab was the first biologic agent approved for the use in UC in 2005 that binds to TNF-α, neutralizing its activity and reducing the inflammatory response. The doses studied were 5 and 10 mg and approval were granted after the ACT-1 and ACT-2 trials. Infliximab is administered intravenously, and the maintenance interval is every 8 weeks with interval changes of 4 weeks[106].

Adalimumab was investigated in the ULTRA 1 study. It is a monoclonal antibody that acts against TNF-α and reduces inflammation. The induction dose is 160/80 mg, and the maintenance dose is 40 mg with an interval of every 2 weeks and interval changes every week. The dose is administrated subcutaneously[106]. The VARSITY direct comparison trial between adalimumab and vedolizumab demonstrated that (at 52 weeks) the primary outcome of clinical remission and mucosal healing was significantly higher in patients using vedolizumab than adalimumab (clinical remission: 31.3% vs 22.5% [P=0.006], respectively; mucosal healing: 39.7% vs 27.7% [P<0.001], respectively). Corticosteroid-free remission rates in patients who received steroids at baseline were not significantly different between groups. These data suggest that vedolizumab may be an option for first-line treatment for UC in patients who have failed conventional therapy[92].

Golimumab is also administrated subcutaneously at 200 mg and 100 mg with a maintenance interval of every 4 weeks and no interval changes. It is a monoclonal antibody that was effective in reducing the inflammatory response and the mucosal healing, as shown in the PURSUIT study[106]. Secondary loss of response is a common event for anti-TNFs, varying according to the pharmacokinetic and structural characteristics of the drug. In the presence of secondary loss of response, it is recommended to monitor the serum levels of the drug and the presence of anti-drug antibodies. It is suggested that, in the absence of availability of these tests or (with low serum drug levels in the absence of anti-drug antibodies) the dose should be increased or the interval between doses should be increased.

Anti-integrins

In patients responding to vedolizumab, maintenance therapy with vedolizumab is appropriate[63]. The phase 3, randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in patients with moderate-to-severe UC (GEMINI 1) demonstrated that (at week 52) patients who were randomly assigned to continue receiving vedolizumab were more likely to have clinical remission than were those randomly assigned to switch to placebo (vedolizumab every 8 weeks = 41.8%; vedolizumab every 4 weeks = 44.8%; placebo = 15.9%). Rates of durable clinical response (vedolizumab every 8 weeks = 56.6%; vedolizumab every 4 weeks = 52%; placebo = 23.8%), durable clinical remission (vedolizumab every 8 weeks = 20.5%; vedolizumab every 4 weeks = 24%; placebo = 8.7%), mucosal healing (vedolizumab every 8 weeks = 51.6%; vedolizumab every 4 weeks = 56%; placebo = 19.8%), and glucocorticoid-free remission (vedolizumab every 8 weeks = 31.4%; vedolizumab every 4 weeks = 45.2%; placebo = 13.9%) were higher among patients assigned to the vedolizumab regimens than among those assigned to placebo. The risk of uncommon AEs, rates of severe, opportunistic, or enteric infections with vedolizumab did not differ significantly from the rates with placebo, and no dose-response relationship was observed[107].

A post hoc analysis of data from the GEMINI 1 study patients who had an inadequate response, loss of response, or intolerance to anti-TNF antagonists demonstrated that the use of vedolizumab was effective in maintaining clinical remission (RR=6.6 [95%CI 1.7 to 26.5]), durable clinical response (RR=2.6 (95%CI 1.2 to 5.7]), and mucosal healing (RR=5.4 [95%CI 1.8 to 16.3]) compared to placebo at week 52[108].

The VARSITY study enrolled 769 patients to compare vedolizumab and adalimumab. The results showed that vedolizumab was superior in clinical remission and endoscopic improvement in moderate-to-severe UC[92]. The comparison was at 52 weeks of remission using the Mayo scale, patient QoL, histological remission, and clinical response.

In case of secondary loss of therapeutic response, due to lack of robust data on adequate serum level of vedolizumab in the maintenance phase and the low formation of anti-vedolizumab antibodies, it is recommended to reduce the dosing interval to four weeks.

Anti-Interleukins

The UNIFI study evaluated the efficacy and safety of ustekinumab for induction and maintenance of remission. Regarding the maintenance therapy, patients receiving ustekinumab had higher rates of clinical response than placebo (90 mg of ustekinumab every 12 weeks [Uq12w] = 38.4%; every 8 weeks [Uq8w] = 43.8%; placebo group = 24.0%; [P=0.002 and P<0.001, respectively, for the comparison with placebo]). The percentages of patients with maintenance of clinical response (Uq8w = 71%; Uq12w = 68%; placebo = 44.6) through week 44, endoscopic improvement response (Uq8w = 51.1%; Uq12w = 43.6%; placebo = 28.6) at week 44, or corticosteroid-free clinical remission response (Uq8w = 72%; Uq12w = 37.8%; placebo = 23.4) at week 44 were significantly higher in both ustekinumab groups than in the placebo group. Among patients

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using corticosteroids at baseline, 67% of Uq12w, 77% of Uq8w, and 44% of the placebo group discontinued corticosteroid use at least 90 days before week 44. Through week 44 in the maintenance trial, the percentages of patients who reported at least one AE in the Uq12w, Uq8w and placebo were 69.2%, 77.3%, and 78.9%, respectively. The percentages of patients with at least one severe AE were 7.6%, 8.5%, and 9.7%, respectively; and the percentages of patients with a severe infection were 3.5%, 1.7%, and 2.3%, respectively[101].

Panaccione et al. (2020) evaluated the efficacy (through week 92) and safety (through week 96) of ustekinumab during the long-term extension of the UNIFI study. Patients were responders to intravenous ustekinumab induction, randomized to maintenance therapy and were treated in the long-term extension (115 received subcutaneous placebo, 141 received Uq12w, and 143 received Uq8w). Among all patients randomized in maintenance, symptomatic remission rates at week 92 were 64.5% for Uq12w and 67.6% for Uq8w. Among randomized patients treated only in the long-term extension, rates of symptomatic remission at week 92 were 78.7% for Uq12w and 83.2% for Uq8w. More than 95% of patients in symptomatic remission at week 92 were corticosteroid-free. Ustekinumab groups maintained efficacy through week 92. From weeks 44 to 96, AEs per hundred patient-years of follow-up for combined ustekinumab vs placebo were as follows: 255.68 vs 267.93; severe AEs, 9.34 vs 12.69; malignancies (including non-melanoma skin cancers), 0.93 vs 1.49; and severe infections, 2.33 vs 2.99. One patient with multiple comorbidities who received one ustekinumab dose after dose-adjusting from placebo experienced a fatal cardiac arrest[109]. Abreu et al. (2022) demonstrated data from the UNIFI study on the efficacy and safety of 90 mg subcutaneous ustekinumab over three years of maintenance therapy. Among patients randomized to the Uq12w and Uq8w groups at baseline maintenance, 54.1% and 56.3% achieved symptomatic remission at week 152, respectively. Of these, 94.6% in the Uq12w group and 98.0% were in the Uq12w group were also corticosteroid-free. Corticosteroid-free symptomatic remission rates in the ustekinumab q12w and q8w groups were 51.2% and 55.1% at week 152, respectively. Overall, 20% of patients discontinued ustekinumab, 10% were naïve to biologic therapy, and 30% were exposed to a biological agent. Remission rates were higher for biologic-naïve patients than those with a history of biologic failure. Biochemical evidence of response was demonstrated by stable, decreased CRP and fecal calprotectin over 3 years. From weeks 96 to 156, there were no deaths, major adverse cardiovascular events, or tuberculosis. Nasopharyngitis, UC, and upper respiratory tract infections were reported more frequently. One ustekinumab-treated patient with a history of basal cell carcinoma reported two new tumors. One patient in the ustekinumab q8w group who was receiving concomitant 6-mercaptopurine experienced severe AEs of neutropenic sepsis and oral herpes[110]. In case of secondary loss of therapeutic response, with the absence of robust data on the adequate serum level of ustekinumab in the maintenance phase and the low formation of anti-ustekinumab antibodies, it is recommended to reduce the interval from 12 to 8 weeks or 8 to 4 weeks.

Small molecules — JAK inhibitors

> **Recommendation**
> * We recommend tofacitinib for maintaining remission in patients with UC who responded to induction therapy with tofacitinib[16,86,90]. **Agreement: 100%.**

There are few studies indirectly comparing tofacitinib to other therapies and direct comparisons are lacking. Specifically compared to no treatment for the maintenance of remission, tofacitinib was superior in terms of clinical remission and mucosal healing, regardless of previous exposure to anti-TNF agents[62].

The OCTAVE study compared the use of tofacitinib with placebo in patients with moderate-to-severe UC. The remission period studied was 8 and 52 weeks, using 5 and 10 mg; in both arms, the drug reduced inflammation and was effective as induction and maintenance therapy. The trial was divided into three parts (OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain trial); even when using anti-TNF, the treatment was effective[103].

Davis et al. (2020) demonstrated that there is high-certainty evidence that tofacitinib is superior to placebo for maintenance of clinical and endoscopic remission at 52 weeks in participants with moderate-to-severe UC in remission and no increased risk of AEs with tofacitinib compared to placebo. Evidence from real-world UC patients also reported that tofacitinib is a safe and effective maintenance therapy[111,112].

In a meta-analysis by Bonovas et al. (2018), the efficacy of tofacitinib in patients not previously exposed to TNF antagonists did not differ from other approved biological therapies, although tofacitinib appeared "slightly below average" of infliximab and vedolizumab at both treatment phases (induction and maintenance). However, tofacitinib can be integrated into clinical practice given the advantage of oral administration, which may favor adherence and improve the QoL in patients distressed by the need for long-term injections or infusions[113]. The meta-analysis also reported that caution should be taken when using tofacitinib because of its potential to cause AEs. Tofacitinib exposes patients to the risk of herpes zoster and other infections, decreasing adherence[112,114,115].

If a patient experiences a secondary loss of response, after the therapeutic dose has been reduced from 10 to 5mg or during the maintenance phase, an increase in the dose to 10 mg every 12 hours can be performed, considering the risks of AEs, especially venous thromboembolism events (VTE).

Combination therapy

> **Recommendation**
> * We recommend evaluating the long-term combination of anti-TNF agents and immunomodulators from the viewpoint of usefulness and safety[83]. **Agreement:** 85.7%.

Currently, it is debated whether the combined use of immunomodulators such as AZA, 6-MP, and MTX with biologics can contribute to the therapeutic efficacy of patients with IBD. To answer this question, Chen et al. (2021) conducted a meta-analysis to compare the efficacy and safety of combinations of biologics and immunosuppressants with biological monotherapy in IBD. The authors demonstrated a benefit for combination treatment over biologic monotherapy (infliximab or adalimumab) (inducing the remission and preventing the relapse) (RR=0.89 [95%CI 0.80 to 0.98]), and this was more evident in a subgroup treated with infliximab (RR=0.83 [95%CI 0.70 to 0.97]) and in patients with CD[116].

The SUCCESS trial compared infliximab combined with AZA (2.0–2.5 mg/kg/day) with infliximab monotherapy in moderate-to-severe UC patients, showing that there was no significant benefit of combined therapy over IFX monotherapy (RR=0.82 [95%CI 0.56 to 1.19])[117]. Another trial compared infliximab combined with

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AZA with IFX monotherapy in quiescent UC and CD patients and demonstrated that there was no significant benefit of combination therapy over infliximab monotherapy in maintaining UC remission (RR=0.61 [95%CI 0.12 to 3.00])[118].

Concerning safety, a meta-analysis demonstrated that the risk of severe infection increased by 1.19-fold with the combination of anti-TNF and an immunosuppressive agent compared with anti-TNF monotherapy (RR=1.19 [95%CI 1.03 to 1.37])[119]. Additionally, the combined therapy with immunomodulator and anti-TNF was associated with reduced risk of formation of antibodies against anti-TNF in patients with IBD[120].

The appropriate dose of AZA in combination therapy remains uncertain. Doses of less than 2 mg/kg are believed to be effective. Magro et al. (2020) showed no difference between 50 mg per day and the standard calculated by the patient's weight[121].

Acute severe UC

> **Recommendations**
> 1. Acute severe extensive colitis is an indication for hospital admission for intensive treatment[12,63,64,68,73]. **Agreement:** 96.9%.
> 2. Patients with severe and fulminant UC should be admitted to undergo intensive treatment. The treatment of choice is parenteral corticosteroids[1]. **Agreement:** 100%.
> 3. All patients hospitalized with severe UC should be assessed to confirm the diagnosis and exclude concomitant infection with *Clostridium difficile* or cytomegalovirus[62]. **Agreement:** 96.7%.
> 4. Fulminant cases with or without toxic megacolon must be clinically and radiologically evaluated and supervised by a colorectal surgeon[1]. **Agreement:** 89.7%.
> 5. Patients with severe UC should receive prophylactic low-molecular-weight heparin[16]. **Agreement**: 84.8%.
>
> **Expert opinions**
> 6. Surveillance of abdominal radiography is helpful for patients with acute severe colitis. **Agreement:** 85.7%.

Antibiotics

The indication of antibiotic therapy in the treatment of severe acute colitis is not consensual. However, antibiotics should be used when infection is suspected and immediately before surgery. Clinical trials evaluating the use of ciprofloxacin and/or metronidazole as therapy for acute colitis have not demonstrated superior benefit over standard therapy[122].

Corticosteroids

> **Recommendations**
> 1. Patients with severe UC who have systemic toxic symptoms need to be admitted and treated with intravenous corticosteroids (methylprednisolone 40−60 mg/day or hydrocortisone 300−400 mg/day)[73]. **Agreement:** 87.9%.
> 2. The absence of improvement after 3–5 days of intravenous steroids is an indication to initiate rescue therapy[62]. **Agreement:** 90.9%.

Patients with severe and fulminant UC face a risk of death and should be admitted to undergo intensive treatment.

The choice treatment may be parenteral corticosteroids (e.g., methylprednisolone 60 mg daily or hydrocortisone, 100 mg IV, 3–4 times/day) added to prophylactic low-molecular-weight heparin[1,17]. The response to intravenous corticosteroid is best assessed objectively between three and seven days, and rescue or surgical treatment is indicated in case of therapeutic failure[1]. Additionally, biologic agents (especially infliximab) or cyclosporine may be appropriate as second-line therapy in patients not responding to intravenous corticosteroids[63,123]. Colectomy is effective if there is no improvement following 4–7 days of salvage therapy[63]. Cases of cytomegalovirus infection must be verified in severe UC that do not respond to intravenous corticosteroids. If infection is found, antiviral treatment is recommended (ganciclovir, 5.0−7.5 mg/kg/12 hour)[73].

Rescue therapies

> **Recommendation**
> • We recommend that patients with acute severe UC failing to respond by day 3, as judged by a suitable scoring system, should be treated with rescue therapy in the form of intravenous infliximab or cyclosporine for patients who have not previously failed thiopurine therapy[16]. **Agreement:** 87.9%.

Patients with severe corticosteroid-refractory UC and no surgical indications are candidates for rescue therapy with cyclosporine or infliximab. A meta-analysis conducted with seven randomized controlled trials containing 534 patients [415 patients in head-to-head trials of cyclosporine vs infliximab] demonstrated that the risk of colectomy at ≤1 month was reduced significantly with both treatments, compared with placebo. In terms of colectomy between >1 month and <1 year, both drugs ranked equally, and neither treatment was more effective than the placebo in reducing the risk of colectomy at ≥1 year[124].

It is important to note that both therapies [infliximab or cyclosporine] are efficient and have advantages and disadvantages. The advantages of cyclosporine in patients at imminent risk of colectomy are its rapid onset of action and short half-life. Even though cyclosporine (and probably infliximab as well) only postpone colectomy in at least half of patients, elective colectomy at a later stage of the disease may lead to better outcomes[88].

Patients responding to infliximab should continue infliximab with or without thiopurines. When used as rescue therapy in patients with severe acute or fulminant colitis, infliximab is effective in the short term (three months) and long term (three years) to reduce the need for colectomy[62].

Monotherapy with intravenous cyclosporine is an alternative, especially in cases of severe AEs due to steroids. The previous use of AZA results in lower response rates to cyclosporine. In thiopurine-naïve patients with severe colitis responding to steroids, cyclosporine, tacrolimus, or (especially) thiopurines are appropriate to maintain remission[63]. The association with AZA as a maintenance treatment after the induction of remission with cyclosporine intravenous reduces the colectomy rate by 40–50%[62].

Criteria to evaluate treatment efficacy and monitor the treatment

> **Recommendations**
> 1. Response to treatment in active UC should be determined by a combination of clinical parameters, laboratory markers such as CRP, fecal calprotectin, and endoscopy[12]. **Agreement:** 94.3%.

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Clinical response

> **Expert opinion**
> • Disease activity can be assessed using the Mayo Score for UC, which is widely used in clinical trials and may be applied to clinical practice as a composite clinical and endoscopic tool. Other scores such as Truelove and Witts or PROs can be used to assess clinical response[16]. **Agreement: 91.4%.**

The Mayo score includes a measure of stool frequency, rectal bleeding, a physician's global assessment, and a measure of mucosal inflammation at endoscopy. The partial Mayo score uses the non-invasive components of the full score and correlates well to patient perceptions of response to therapy[16]. In addition to these parameters, general patient-experience outcomes, gastrointestinal PROs, endoscopic healing, and levels of biological markers of inflammation are measures that can be used to assess treatment efficacy. When the option is gastrointestinal PROs, some specific details must be evaluated, including normalization of bowel habit (0 extra stools), absence of blood in stools, and absence of urgency and incontinence. Bowel habits and blood in stools should be evaluated over seven days[125]. The STRIDE-II study recommends that clinical response be an immediate and short-term target of treatment and should be considered when there is evidence of at least a 50% decrease in PROs (rectal bleeding and stool frequency)[126].

Clinical remission

> **Recommendation**
> 1. Clinical remission is defined as stool frequency ≤3/day with no rectal bleeding[10]. **Agreement: 88.9%.**
>
> **Expert opinion**
> 2. Clinical remission should be considered as two-item PROs (PRO2) (rectal bleeding = 0 and stool frequency = 0) or partial Mayo (<3 and no subscore >1)[126]. **Agreement: 100%.**
> 3. Treatment targets are normalization of bowel habit (0 extra bowel movements), absence of blood in stools, and absence of urgency and incontinence[16]. **Agreement: 82.9%.**

The standardization of disease activity measurement remains uncertain and directly impacts the definition of clinical remission of the disease. Definitions of remission in UC vary by users, settings, and the purpose of monitoring disease activity. The definition of remission used in clinical practice and by the patient often differs from that used in clinical trials.

Given the diverse evidence in the literature on the concept of clinical remission in patients with UC, this consensus supported the recommendation in classical definitions, such as the Truelove and Witts Severity Index, PRO2, and partial Mayo score[127]. In adults, PRO2 has become the current standard for evaluating symptoms in UC. It includes the two subjective items of the Mayo score (frequency of bowel movements and rectal bleeding). Its correlation with endoscopic healing is moderate to high and, therefore, should be used in conjunction with an objective measure of inflammation[128-130].

The total Mayo score includes clinical parameters (evacuation frequency, rectal bleeding, and global medical assessment) and endoscopic parameters (where each parameter scores between 0 and 3).

The Mayo partial score considers only the clinical parameters described, and clinical remission is the sum <3 and no subscore >1.

Insurance companies, governments, and patient organizations demand registration of patient-reported outcome measures as efficacy endpoints of interventions in routine care. In addition, the use of patients' perspectives on the effectiveness of therapies in clinical trials is strongly recommended by the US food and drug administration[131].

Fecal calprotectin

> **Recommendations**
> 1. Fecal calprotectin can be considered as a laboratory monitoring option between endoscopic examinations to suggest disease activity[16]. **Agreement: 91.4%.**
> 2. In IBD patients where it is unclear if symptoms are due to ongoing inflammation or other non-inflammatory causes (such as bile acid malabsorption, functional bowel disorder, or short bowel), fecal calprotectin measurement may be used to provide evidence of mucosal inflammation[16]. **Agreement: 97.2%.**
> 3. Patients in whom therapy is withdrawn should be observed for evidence of relapse. Monitoring of fecal calprotectin may be helpful because levels may rise before clinical relapse occurs[16]. **Agreement: 94.3%.**

Fecal calprotectin is the primary laboratory marker for the follow-up of patients with UC, being more sensitive and specific than serum markers such as CRP or ESR. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) proposed targets for UC treatment. Fecal calprotectin was found to be the easiest and least expensive noninvasive biomarker to predict endoscopic and histological activity/indices[126]. The study supported a fecal calprotectin cut-off value of 150 μg/g to identify endoscopic healing; the authors suggested that the range of 100 to 250 is a gray zone and values <600 could indicate inflammation.

A meta-analysis by Rokkas et al. (2018) aimed to determine the diagnostic performance of fecal calprotectin in assessing IBD endoscopic activity in adults. They found that this laboratory test is reliable for assessing endoscopic activity with a pooled sensitivity of 85% and specificity of 75%. The subgroup analysis showed that this reliability is more accurate in UC patients (pooled sensitivity for CD was 82.4% and for UC was 87.3%; specificity for CD was 72.1% and for UC was 77.1%), possibly due to the extent and severity of the colonic lesions in the two disease groups[132].

Many studies determined the best cut-off value for defining normal FC levels in IBD patients; nevertheless, to date, there is no strong evidence indicating that values between 50 and 250 mcg/g determine endoscopic disease activity. For patients aged 16–40 years who present in primary care with chronic diarrhea and symptoms that may be consistent with either IBD or IBS, fecal calprotectin is a useful screening tool with a high negative predictive value. If significantly elevated, patients should be further investigated to rule out superinfections, such as cytomegalovirus and *C. difficile*[16].

CRP

CRP indicates acute phase responses and is used as a marker of inflammation and disease activity in IBD. Under normal conditions, low CRP levels are produced by hepatocytes; however in situations of systemic inflammation under the influence of

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interleukin-6, TNF-α and interleukin 1β, these rates increase rapidly. After inflammation resolves, CRP levels also decline rapidly due to the short half-life of 19 h. CRP is correlated with markers of clinical, endoscopic, radiological, and cross-sectional activity in IBD (especially in CD)[133]. The CRP could be helpful during the patient evaluation. Use of CRP changes with disease presentation: for proctitis, biological markers of inflammation should not be used; for left-sided and pancolitis, CRP should be a measure of treatment efficacy.

Despite the low specificity of CRP in relation to the endoscopic activity of UC, this marker continues to be indicated for patient evaluations in inducing remission and in maintenance. STRIDE-II determined that CRP reduction is a target to be achieved in the short to medium term.

Endoscopic remission

> **Recommendation**
> 1. Endoscopic remission predicts good outcomes. Endoscopic reassessment is appropriate at relapse, for steroid-dependent or refractory UC, or when considering colectomy. **Agreement: 88.6%**[10].
>
> **Expert opinions**
> 2. Colonoscopy is used to confirm the diagnosis of UC and evaluate the severity of the disease, determine the effectiveness of treatment, and conduct surveillance for carcinogenesis[83,134]. **Agreement: 91.4%.**
> 3. To evaluate the endoscopic healing, the treatment target is a Mayo endoscopic subscore <1 on colonoscopy[83,134]. **Agreement: 100%.**

When performing a colonoscopic examination to assess remission, it is suggested to perform biopsies of colon segments for histological evaluation of the disease, although this is not a formal target to be achieved. STRIDE-II recommends that histologic remission should not be a treatment target but it could be used with endoscopic remission to represent a deeper level of healing[126]. The Mayo and UCEIS scores can be found in TABLES 1 and 3, respectively.

Improvement in QoL

> **Expert opinions**
> • The absence of disability and normalized health-related QoL are long-term treatment targets and are general patient-experience outcomes expressed by improvement of multidimensional aspects of life (fatigue, QoL, professional productivity, and the feeling of having a normal life)[16,126,134]. **Agreement: 97.2%.**

The QoL (physical and mental) is an essential indicator of PROs. In active UC patients, QoL is impaired compared to quiescent UC patients and healthy individuals[135]. Regarding the mental QoL, there is a high prevalence of patients with IBD suffering from anxiety (one-third of patients) and depressive (a quarter of patients) symptoms. This evidence must encourage the gastroenterologists to screen and investigate these disorders, aiming to improve outcomes[136] Adequate treatment has the potential to improve the QoL of UC patients[46].

Histological remission

> **Recommendation**
> • Histologic remission is not official treatment target in UC. Nevertheless, it could be used as an adjunct to endoscopic remission to represent a deeper level of healing[16,126]. **Agreement: 88.6%.**

In 2021, the International Organization for the Study of IBD pointed out for the first time the increase in data on histological activity in the UC, scoring it as a possible (but informal) long-term therapeutic target. Despite being related to endoscopic healing and colorectal cancer (CRC) prevention, histological remission is still achieved in only one-third of the cases that achieved mucosal healing; these parameters are not completely defined[126]. The histopathological evaluation should preferably be performed with the classification of the disease using validated scores such as the Robert's Histological Index or the Geboes Score[137].

Therapeutic failure

> **Expert opinions**
> 1. We suggest changing the therapeutic class when there is a primary therapeutic failure[16]. **Agreement: 85.7%.**
> 2. We suggest switching medication within or outside the therapeutic class when secondary failure occurs. This approach is best indicated with the use of reactive therapeutic drug monitoring (TDM)[16]. **Agreement: 88.6%.**

Therapeutic failure is common to any therapy and occurs primarily in two modes: (1) primary therapeutic failure, where there is no clinical response to therapy with adequate induction doses, and (2) secondary loss of response in patients who had a therapeutic response but the disease subsequently relapsed[138].

The rate of primary non-responders and loss of secondary response varies depending on the drug chosen. In general, the anti-TNF class shows greater loss of secondary response than anti-integrins, anti-interleukins, and JAK inhibitors. Even so, it should not be equated to a class effect, because molecular differences determine greater loss of response to infliximab (a chimeric monoclonal antibody that provides greater immunogenic potential) than to adalimumab or golimumab (fully human monoclonal antibodies)[138].

It is possible that a patient who primarily fails a certain therapeutic class will respond to a drug of the same class; however, studies show that the response rate is small. It is assumed that another inflammatory pathway is determinant in the etiology of the patient's disease. Thus, it is suggested that changing the therapeutic class is a preferable option. Patients who do not respond to two or more drugs of different therapeutic classes should be followed up by a coloproctologist, who should consider surgery as a therapeutic option[139].

Treatment drug monitoring

> **Recommendations**
> 1. Treatment options for the failure of initial anti-TNF therapy (increase dose, shorten dosage interval, switch to alternative anti-TNF, or switch to different drug classes) may be guided by the clinical context and by measurement of serum drug and anti-drug antibody concentrations[12,16]. **Agreement: 97.2%.**

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2. Patients with secondary loss of response to anti-TNF therapy may have serum drug and anti-drug antibody concentrations measured to guide appropriate changes in treatment[12,17]. **Agreement:** 97.2%.
3. Drug level monitoring is mandatory during treatment with calcineurin inhibitors[12,17]. **Agreement:** 91.5%.

Patient compliance and differences in drug metabolism are likely to cause significant inter-individual variability in drug efficacy and risk of toxicity. TDM is defined as the assessment of the concentration of drugs and anti-drug antibodies. This practice during the treatment of patients with UC is effective in optimizing anti-TNF maintenance therapy[138,139].

Reactive TDM can be used to manage loss of response, in addition to being more cost-effective when compared to empirical dose escalation. Reactive TDM of biologicals should be performed in patients with confirmed primary nonresponse or secondary loss of response to anti-TNF therapy[138,139].

Proactive TDM applied to patients with clinical benefit is associated with prolonged treatment with infliximab, less need for rescue therapy, and an increased likelihood of maintaining infliximab concentrations in the therapeutic window compared with standard care. These findings suggest that proactive TDM impacts positively when performed at least once during maintenance therapy for patients treated with anti-TNF therapy and after reactive TDM of anti-TNF therapy[138,139].

Endoscopic surveillance

Recommendations
1. Surveillance colonoscopy is recommended for patients with extensive and left-sided UC starting at eight years after the onset of UC[10,83]. **Agreement:** 91.5%.
2. Targeted biopsy is recommended for UC-associated CRC surveillance[10,83]. **Agreement:** 97.2%.
3. Chromoendoscopy with targeted biopsies increases the dysplasia detection rate. Alternatively, random biopsies (quadrantic biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed if white light endoscopy is used. High-definition endoscopy should be used if available[10,83]. **Agreement:** 91.5%.
4. Colonoscopic surveillance is best performed when UC is in remission because it is otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies[10,83]. **Agreement:** 94.3%.

Cancer screening

Recommendations
1. The risk of CRC in UC is greater than in the general population. The risk is associated with disease duration, extent, and severe or persistent inflammatory activity[10,16,64]. **Agreement:** 94.3%.
2. When disease activity is limited to the rectum without evidence of previous or current endoscopic or microscopic inflammation proximal to the rectum, inclusion in a regular surveillance colonoscopy program is not necessary[10,16,64]. **Agreement:** 94.3%.

3. Concomitant primary sclerosing cholangitis confer an additional risk for CRC. In patients with concurrent primary sclerosing cholangitis, an annual surveillance colonoscopy should be performed following the diagnosis of primary sclerosing cholangitis, irrespective of disease activity, extent, and duration[10,16,64]. **Agreement:** 94.3%.
4. Patients with other high-risk features (e.g., stricture or dysplasia and extensive colitis with severe active inflammation) should also have their next surveillance colonoscopy scheduled for 1 year[10,16,64]. **Agreement:** 94.3%.
5. Patients with intermediate risk factors should have their next surveillance scheduled for 2 to 3 years later. Intermediate risk factors include extensive colitis with mild or moderate active inflammation, many inflammatory polyps, or a family history of CRC in a first-degree relative diagnosed at age 50 years and above. Patients with neither intermediate nor high-risk features should have their next surveillance colonoscopy scheduled for 5 years later[10,16,64]. **Agreement:** 91.5%.

Long-term patients with UC have an increased risk of CRC and colonoscopic surveillance may reduce the development of both CRC and the rate of CRC-associated death through early detection[140,141]. The meta-analysis of Subramanian included six studies and 1,277 patients. The authors found that the pooled incremental yield of chromoendoscopy over standard white light endoscopy for the detection of any grade of dysplasia on a per patient basis was 7% (95%CI 3.2–11.3) (number needed to treat = 14.3). The pooled increase in targeted dysplastic lesion detection of chromoendoscopy over standard white light endoscopy was 44% (95%CI 28.6–59.1), and the pooled increase in flat dysplastic lesion detection was 27% (95%CI 11.2–41.9). The absolute difference in lesions detected by targeted biopsies was 44% [95%CI: 28.6–59.1], and flat lesions were 27% [95%CI 11.2–41.9][142].

Chromoendoscopy is preferable to standard white light endoscopy for dysplasia detection during surveillance endoscopies of patients with colonic IBD. This finding implies that chromoendoscopy can detect dysplastic lesions able to be ressected by endoscopic techniques and reduce the need for colectomy. Endorsing this evidence, Wu et al. (2012) showed that chromoendoscopy has medium to high sensitivity (pooled sensitivity of 83.3%) and high diagnostic accuracy (specificity of 91.3%) for dysplastic lesions in UC[143]. Finally, the meta-analysis of Resende et al. (2020) of 17 randomized controlled trials and 2,457 patients reported that dye-spraying chromoendoscopy detected more patients and dysplastic lesions than standard white light endoscopy[144].

Infections/vaccines

Recommendations
1. UC patients at risk of opportunistic infections are those treated with immunomodulators, especially in combination therapy, and those with malnutrition. Comorbidities and a history of severe infections should be considered[10]. **Agreement:** 91.5%.
2. Reactivation of latent tuberculosis in patients treated with anti-TNF is increased and is more severe than in the general population. Latent tuberculosis should be diagnosed using a combination of patient history, chest X-ray, tuberculin skin

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test, and interferon-gamma release assays. Screening should be considered at diagnosis and always be performed before immunosuppressive therapy[10]. **Agreement:** 85.7%.

3. All UC patients should be tested for hepatitis B virus (HBV) [HBsAg, anti-HBAbs, anti-HBcAb] at diagnosis. In patients with positive HBsAg, viremia (HBV-DNA) should also be quantified. HBV vaccination is recommended in all anti-HBsAb seronegative patients with UC[10]. **Agreement:** 85.7%.

4. Efficacy of HBV immunization is impaired in IBD, probably by the disease itself and by the immunosuppressive drugs. Anti-HBV responses should be measured after vaccination[10]. **Agreement:** 85.7%.

5. In patients infected with HBV (carriers and those previously infected), the risk of developing HBV due to reactivation after the initiation of immunosuppressive drugs should be considered[83]. **Agreement:** 91.5%.

6. Prophylactic treatment for *Pneumocystis jiroveci (carinii)* infection is recommended during triple immunosuppressive therapy[62]. **Agreement:** 95.8%.

IBD is associated with an 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 increased risk of developing herpes zoster compared to individuals without IBD. Specifically, UC patients have a 1.49-fold risk of developing this infection. This evidence suggests that vaccination should be considered at the time of IBD being diagnosed[145]. Regarding HBV vaccination, only three in five IBD patients show a serological response to HBV vaccination (pooled response rate: 61%). Factors positively associated with the response to vaccination were young age and vaccination during disease remission. Furthermore, no immunosuppressive therapy predicted an immune response compared with immunomodulator or anti-TNF therapy. Vaccination should be performed at the time of IBD diagnosis, during disease remission, or before starting immunosuppressive therapy[146]. Before, during, and for at least 12 months after immunomodulatory treatment has ceased, 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 hepatitis B flare[83].

Adverse events

Recommendations

1. Patients starting corticosteroids should be assessed for risk of osteoporosis. Those at high risk should be started on bisphosphonate therapy at the onset of corticosteroid therapy. All patients receiving a course of corticosteroids for a disease flare should receive 800–1000 mg/day of calcium and 800 IU/day of vitamin D[10,16,83]. **Agreement:** 94.3%.

Expert opinions

2. Corticosteroids are the therapeutic class with the highest frequency of AEs among UC therapies[16]. **Agreement:** 94.3%.

Medical treatment of IBD is linked to AEs ranging from mild nuisance symptoms to potentially life-threatening complications including infections and malignancies[147]. Sulfasalazine therapy is accompanied by a relatively high incidence of side effects related to intolerance. Side effects of 5-aminosalicylates are typically not severe; however, they can be the cause of drug interruption[148]. The toxic effects of corticosteroids are related to the dose and duration of treatment[35]. An updated discussion on AEs associated with IBD treatment options can be summarized as follows[149]:

- Thiopurines are associated with an increased risk of infection, myelosuppression, liver toxicity, pancreatitis, and malignancy.
- MTX is associated with an increased risk of myelosuppression, pulmonary toxicity, liver toxicity, and birth defects.
- Anti-TNF-α agents are associated with an increased risk of infection, autoimmunity, demyelinating disease, congestive heart failure, and malignancy.
- Vedolizumab and ustekinumab has been shown to be safe and comparable to placebo in a pooled data analysis including six phase 2/3 trials, with up to 1 year of follow-up[150].
- JAK inhibitors are associated with increased risk of herpes zoster infection[48].

Thiopurines:

Treatment with AZA/6-MP is associated with a potential risk of lymphoma, with a positive correlation between lymphoma and Epstein-Barr virus infection[62]. There is an increased association of the use of thiopurines with non-melanoma skin cancer, high-grade cervical dysplasia or cancer, and urinary tract cancer[62]. A higher incidence of myelosuppression occurs in the first eight weeks of thiopurine therapy and may justify more frequent monitoring during this period[62].

Tofacitinib:

There was an increased risk of infections (particularly herpes zoster virus) seen in tofacitinib-treated patients during induction and maintenance phases[16]. Tofacitinib should be used with caution in patients with a history or risk factors for thromboembolic events.

IBD has been associated with an increased risk of nonmelanoma skin cancer, particularly in patients treated with thiopurines. The meta-analysis of Singh et al. (2014) did not find this association; however, these data must be interpreted with caution due to the limited number of studies included in the analysis (two studies)[151]. Concerning CRC, it is unclear whether the use of thiopurines protects patients with IBD from the risk of developing this neoplasia, particularly among UC patients[152,153]. A meta-analysis performed with population-based studies from referral centers reported that IBD patients had a lower but significantly increased risk of lymphoma among patients taking thiopurines. The increased risk does not appear to persist after discontinuation of therapy. Furthermore, patients aged over 50 years had the highest absolute risk of lymphoma per year on thiopurines (1:354 cases per patient-year, with a relative risk of 4.78), while men under 30 may also be a high-risk group (pooled standardized incidence ratio: 6.99 [95%CI 2.99 to 16.4][154]. On the other hand, patients receiving AZA were at a significantly higher risk of withdrawing the treatment due to AEs than control patients. AEs related to the use of AZA include acute pancreatitis and significant bone marrow suppression[155].

A prospective study found that, among the four patients having myelotoxicity, one had intermediate basal thiopurine-methyltransferase (TPMT) levels, and three had high levels; however, no patient had low levels. Therefore, it was not possible to determine whether

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the choice of AZA/6-MP dose based on TPMT activity prevents myelotoxicity in patients with IBD[156]. The strategy of determining TPMT activity in patients prior to initiating treatment with AZA could help minimize the risk of myelotoxicity, as patients with intermediate TPMT activity had 4-fold greater risk than high TPMT activity patients[156]. Especially in Brazilian patients, the prevalence of TPMT genotypes was high. Two variant genes (TPMT 2 [C238G], 3.6%) and 3C (TPMT 3C [A719G], 7.7%) might be associated with AZA pancreatic toxicity in an southeastern Brazilian IBD population[157].

Two meta-analyses highlighted the potential of tofacitinib in causing AEs. Trigo-Vicente et al. (2018) demonstrated that tofacitinib ranked the worst for the rate of infections compared to those therapies[114]. Taxonera et al. (2022) reported an incidence rate of severe AEs of 8.9 per 100 patient-years and an incidence rate of herpes zoster of 6.9 per 100 patient-years[112]. Macaluso et al. (2022) reported a pooled estimate of the incidence rate of AEs of 53 per 100 person-years, while the pooled estimate of the incidence rate of withdrawal due to AEs was 9.3 per 100 person-years, with a pooled rate of infections of 17.6 per 100 person-years[115].

Other recommendations

Recommendations

1. Thromboprophylaxis in hospitalized IBD patients should be considered with an understanding of the increased risk of bleeding associated with the intervention[10,16,83]. **Agreement:** 88.6%.
2. Risk factors for osteoporosis in IBD include prolonged corticosteroid use; however, general risk factors should also be screened for and corrected, including malnutrition, inflammation, smoking, and lack of weight-bearing exercise[16]. **Agreement:** 94.3%.

CLINICAL TREATMENT FOR SPECIAL SITUATIONS

Pregnant women and newborns care

Recommendations

1. Ultrasound and abdominal MRI without intravenous gadolinium are the safest techniques to examine pregnant women in whom IBD is known or suspected, regardless of trimester[12]. **Agreement:** 97.2%.
2. Endoscopy is generally considered to be safe in pregnancy; however, procedures should only be performed when there is a strong indication and clear clinical benefit[12]. **Agreement:** 97.2%.
3. Bacille Calmette-Guerin and rotavirus vaccines (if indicated) should be withheld until at least 6 months after birth to infants exposed in utero to biological therapies[10,16,64]. **Agreement:** 97.2%.
4. Non-live vaccinations may be given according to standard vaccination schedules[10,16,64]. **Agreement:** 94.3%.

Expert opinions

5. We recommend choosing treatment during pregnancy in IBD patients via adequate discussion between physicians and patients in consideration of the risks and benefits of each patient[10]. **Agreement:** 94.3%.

6. We recommend continuing treatment with aminosalicylates, thiopurines, anti-TNF, vedolizumab, and ustekinumab because the benefits of treatment exceed the risks of drugs in most patients. MTX is formally contraindicated during pregnancy and lactation. It is recommended to suspend MTX 3 to 6 months before conception[64]. **Agreement:** 92%.
7. In cases where sulfasalazine cannot be substituted, it should be implemented in parallel with high-dose folic acid supplementation[10]. **Agreement:** 82.9%.

Patients and their physicians should discuss treatments for patients with IBD during pregnancy and lactation, considering treatment benefits and harms individually[83]. The present consensus guidelines consider disease remission during pregnancy the most important isolated factor for a complication-free pregnancy for the mother and unborn child. Disease activity at conception or during pregnancy is associated with early pregnancy loss, preterm birth, and low birth weight. Compared to control pregnant women, women with UC are 1.77-fold more likely to have preterm birth at less than 37 weeks of gestation (OR=1.77 [95%CI 1.53 to 2.04]). Additionally, women with IBD are 1.36-fold, 1.29-fold, and 1.57-fold more likely to experience births complicated with small gestational birth weight, congenital anomalies, and stillbirth, respectively[158].

Corticosteroids to treat UC in pregnancy was studied in the PIANO registry. The results showed worse outcomes (i.e., low birth weight and preterm birth) in women that needed the drug. The authors emphasize that it is important to control the disease activity before and during pregnancy with steroid-sparing therapy[159].

Therapies with thiopurines in pregnant IBD women were more significantly associated with congenital abnormalities than a control group, suggesting that a risk-benefit ratio should be considered in prescribing or continuing medicinal therapy during pregnancy in IBD patients[160].

Regarding biological therapies in pregnancies with IBD, the meta-analysis by Nielsen et al. (2022) demonstrated that this treatment was associated with a pooled prevalence of 8% for early pregnancy loss, 9% for preterm birth, 0% for stillbirth, 8% for low birth weight, and 1% for congenital malformations. Subgroup analyses demonstrated a higher prevalence of early pregnancy loss and preterm birth in women using vedolizumab than in anti-TNF users. Continued TNF inhibitor use during the third trimester was not associated with the risk of preterm birth, low birth weight, or congenital malformations[161]. Furthermore, biological therapy during pregnancy was not associated with an increased risk of infantile infections (infantile antibiotic use or infection-related hospitalizations), except for infantile upper respiratory infections[161].

For patients with active disease or a high risk of relapse, it may be advisable to continue drug therapy, while for those with the inactive disease who wish to discontinue therapy, it may be reasonable to stop at the start of the third trimester[10,16,64].

Vaccination is recommended; however, there are some caveats. Live vaccination is not recommended for patients using biologic treatment. For example, offspring exposed to biologics (i.e., in women that used anti-TNF drugs during pregnancy) should receive inactivated vaccines and wait until after 6 months old to be vaccinated[16].

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Older adult care

Recommendations
1. Treatments for older adult UC patients are largely the same as those for younger patients[64]. **Agreement: 82.9%.**

Expert opinion
2. In patients over the age of 65, MTX in combination therapy is more appropriate than AZA[83,125]. **Agreement: 82.6%.**

About 10–15% of IBD cases are diagnosed in patients >60 years of age, and 10–30% of the population with IBD are >60 years of age. The clinical features of IBD in older patients are distinct, tend to have less of a disease trajectory, and a broader differential diagnosis. Left-sided proctitis and UC are common in patients >60 years of age. Infections are age-associated and account for significant mortality in patients with IBD[162-163].

The treatment of IBD in the older adult is like that of young patients; however, the therapeutic approach should be started slowly. Gisbert et al. (2004) reported lower responses and higher AEs in older adults using anti-TNF therapy than in young patients[164]. On the other hand, and regarding the response to anti-TNF therapy, Cheng et al. (2021) found no significant difference in the efficacy of anti-TNF therapy in inducing or maintaining remission between these two groups (older adults vs. young patients). However, their analysis demonstrated that a higher proportions of older adult patients receiving anti-TNF therapy had severe AEs (20%) and hospitalizations (14.4%), compared with younger patients (10.2% had severe AEs and 5.2% were hospitalized)[165].

With age-related waning immunity, frailty and comorbidities, older patients are more susceptible to severe infections and malignancy with immunosuppressive therapy. Immunomodulatory therapies are associated with an increased risk of infections and malignancies, and caution must be taken especially in older adult patients with IBD.

A meta-analysis of 14 cohort studies of immune-mediated inflammatory diseases, including IBD, showed that exposure to biological agents (mainly adalimumab and infliximab) was associated with a 2.3-fold increase in the likelihood of severe infections in older patients compared to younger patients. Among older patients only, the exposure to biologics (vs no exposure) was associated with a 3.6-fold increase in severe infections in older adult patients compared with older adult patients with untreated IBD[166].

A cohort study comparing efficacy and safety of vedolizumab in young and older adult patients with IBD found significantly more infections involving the nasopharynx, urinary tract, skin, and vulva, as well as *C. difficile* infections in the older adult patients than in young patients (12% vs 2%, P=0.002), none of which were fatal. Treatment was discontinued due to urinary sepsis in only one older adult patient[167].

Due to their mechanism of action, vedolizumab and ustekinumab may be less immunosuppressive and therefore safer in older adult patients. However, in a retrospective cohort study of 234 older adult patients biologically treated with IBD, Adar and colleagues (2019) found no significant difference in the risk of severe infections between patients treated with TNF-α antagonists versus patients treated with vedolizumab (1 year: 20 % vs 17%, P=0.54)[168]. Older adult frailty is a critical measure of age-related decline. Adding this measure to the assessment of older adult patients helps to identify those who may be more vulnerable to adverse health outcomes[169].

Infections and vaccines

Recommendations
1. Patients with infections should not receive biological therapy until the infection is controlled[16]. **Agreement: 88.6%.**

2. Latent infections such as tuberculosis, hepatitis B, and human immunodeficiency virus must be excluded or treated before starting biological therapy[16]. **Agreement: 94.3%.**

3. Patients inoculated with live vaccines should not receive biological therapy for three months[73]. **Agreement: 85.7%.**

FUTURE PERSPECTIVES

JAK inhibitors
Upadacitinib
In patients with moderately-to-severely active UC (possibly having pancolitis and disease refractory to biologic therapy), eight weeks of treatment with upadacitinib (7.5 mg, 15 mg, 30 mg, or 45 mg extended-release once daily) is more effective in inducing clinical remission and response, endoscopic and histologic improvement than placebo[170]. In patients with moderately-to-severely active UC with previous inadequate response to, loss of response to, or intolerance to corticosteroids, immunosuppressants, or biologic therapies, therapy with upadacitinib (especially at 45 mg once daily) reduces bowel urgency and abdominal pain compared to placebo, supporting its use to monitor disease severity[171]. In patients with moderate-to-severe active UC previously exposed to anti-TNF-α therapies or naïve to these drugs, upadacitinib (especially 45 mg once daily) as induction treatment is effective in achieving clinical response and remission and endoscopic improvement (in 6 to 14 weeks) compared to other biologics and small molecules drugs. However, it is important to be aware of its AEs[172,173].

Filgotinib
Oral filgotinib 200 mg once daily for 10 weeks was effective in inducing and maintaining clinical remission compared to placebo for patients with moderately-to-severely active UC who were biologic-naïve or biologic-experienced[174].

S1P Inhibitors
Ozanimod
The meta-analysis of Trigo-Vicente et al. (2018) found that ozanimod is not superior for induction of remission (6–8 weeks) when compared to placebo[114]. Randomized controlled trial demonstrated that, in patients with moderate-to-severe UC, long-term (up to 4 years) treatment with oral ozanimod hydrochloride at a dose of 1 mg once daily is effective in maintaining clinical, endoscopic, histological, and biomarker measures and was more effective than placebo as maintenance (52 weeks) therapy. Nevertheless, it is essential to be aware of its AEs[175].

ACKNOWLEDGMENTS

Authors' contribution

Baima JP, Imbrizi M, Andrade AR, Chebli JMF, Chebli LA, Argollo MC, Queiroz NSF, Azevedo MFC, Vieira A, Costa MHM, Fróes RSB, Penna FGC, Saad-Hossne R: methodology, literature review, recommendations decision making, writing and review. Coy CSR, Ambrogini O, Kotze PG: final review of the manuscript. Quaresma AB, Damião AOMC, Moraes ACS, Carlos Santos CHM, Flores C, Zaltman C, Vilela EG, Morsoletto E, Gonçalves Filho FA, Santana GO, Zabot GP, Parente JML, Sassaki LY Zerôncio MA, Machado MB, Cassol OS, Parra RS, Miszputen SJ: recommendations decision making.

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RESUMO – **Contexto** – As doenças inflamatórias intestinais são doenças imunomediadas que incluem a doença de Crohn (DC) e a retocolite ulcerativa (RCU). A RCU é uma doença progressiva que acomete a mucosa colorretal causando sintomas debilitantes levando a alta morbidade e incapacidade laboral. Como consequência da inflamação crônica do cólon, a RCU também está associada a um risco aumentado de câncer colorretal. **Objetivo** – Este consenso visa fornecer orientações sobre o manejo médico mais eficaz de pacientes adultos com RCU. **Métodos** – As recomendações do consenso foram desenvolvidas por gastroenterologistas e cirurgiões colorretais referências no Brasil (membros da Organização Brasileira para Doença de Crohn e Colite [GEDIIB]). Uma revisão sistemática, incluindo as evidências mais recentes, foi conduzida para apoiar as recomendações. Todas as recomendações foram endossadas pelas partes interessadas/especialistas em doença inflamatória intestinal usando um Painel Delphi modificado. O nível de concordância para alcançar consenso foi de 80% ou mais. **Resultados e conclus**ão – As recomendações médicas (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 foi direcionado a clínicos gerais, gastroenterologistas e cirurgiões que tratam pacientes com RCU e apoia os processos de tomada de decisão por companhias de seguro de saúde, agências reguladoras, líderes institucionais de saúde e administradores.

Palavras-chave – Colite ulcerativa; adultos; doenças inflamatórias intestinais; terapia medicamentosa; manejo de doenças.

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

Supplementary Material of the Brazilian Consensus on the Management of Ulcerative Colitis in Adult Patients: Medical Treatment

Defining the question to be answered

The acronym PICOS (patient, intervention, comparator, outcome, and study design) indicated in Tables **S1–S7** describes the question regarding the treatment of adults with ulcerative colitis (UC).

TABLE S1. PICO strategy on the induction treatment of mild-to-moderately active UC.

P	Adults (≥18 years) with mild-to-moderately active ulcerative colitis
I	• Corticosteroids (*budesonide MMX* + all traditional) • Salicylates (sulfasalazine, mesalazine, mesalazine MMX, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, cyclosporine, tacrolimus) • Biological ◆ Anti-TNF (infliximab, golimumab, adalimumab) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab) • JAK inhibitors (tofacitinib, upadacitinib) • S1P receptor modulators (ozanimod)
C	Not applicable
O	Not applicable
Type of study	Consensus or guidelines limited to 2016–2021.

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

TABLE S2. PICO strategy for the induction treatment of moderate-to-severe active UC.

P	Adults (≥ 18 years) with moderate-to-severe active UC
I	• Corticosteroids (budesonide MMX + all traditional) • Salicylates (sulfasalazine, mesalazine, mesalazine MMX, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, cyclosporine, tacrolimus) • Biological ◆ Anti-TNF (infliximab, golimumab, adalimumab) ◆ Anti-integrin (vedolizumab) ◆ Anti-interleukin (ustekinumab) • JAK inhibitors (tofacitinib, upadacitinib) • S1P receptor modulators (ozanimod)
C	Not applicable
O	Consensus or guideline recommendation
Type of study	Consensus or guidelines limited to 2016–2021.

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

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

P	Adults (≥18 years) with mild-to-moderate active UC
I	• Corticosteroids (budesonide MMX + all traditional) • Salicylates (sulfasalazine, mesalazine, mesalazine MMX, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, cyclosporine, tacrolimus) • Biological ◆ Anti-TNF (infliximab, golimumab, adalimumab) ◆ Anti-integrin (vedolizumab) ◆ Anti-interleukin (ustekinumab) • JAK inhibitors (tofacitinib, upadacitinib) • S1P receptor modulators (ozanimod)
C	Not applicable
O	Consensus or guideline recommendation
Type of study	Consensus or guidelines limited to 2016–2021.

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

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

P	Adults (≥ 18 years) with moderate-to-severe active UC
I	• Corticosteroids (budesonide MMX + all traditional) • Salicylates (sulfasalazine, mesalazine, mesalazine MMX, suppository, and enema) • Immunosuppressants (azathioprine, 6-MP, cyclosporine, tacrolimus) • Biological ◆ Anti-TNF (infliximab, golimumab, adalimumab) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab) • JAK inhibitors (tofacitinib, upadacitinib) • S1P receptor modulators (ozanimod)
C	Not applicable
O	Consensus or guideline recommendation
Type of study	Consensus or guidelines limited to 2016–2021

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

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TABLE S5. PICO strategy on criteria for evaluating the efficacy of treatment of UC.

P	Adults (≥18 years) with active UC
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 or guidelines limited to 2016–2021

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

TABLE S6. PICO strategy on patient follow-up after initial treatment of UC.

P	Adults (≥18 years) with active UC
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, screening of cancer, and others)
Type of study	Consensus or guidelines limited to 2016–2021

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

TABLE S7. PICO strategy on the efficacy of clinical treatments for UC in adults.

P	Adults (≥18 years) with active UC
I	• Corticosteroids (budesonide MMX + all traditional) • Salicylates (sulfasalazine, mesalazine, mesalazine MMX, suppository, and enema) • Immunosuppressants (azathioprine, 6MP, cyclosporine, tacrolimus) • Biological ◆ Anti-TNF (infliximab, golimumab, adalimumab) ◆ Anti-integrin (vedolizumab) ◆ Anti-interleukin (ustekinumab) • JAK inhibitors (tofacitinib, upadacitinib) ◆ S1P receptor modulators (ozanimod)
C	• Not applicable
O	All efficacy outcomes considered in the published studies (i.e., clinical response and remission, endoscopic response and remission, and mucosal healing)
Type of study	Systematic reviews with meta-analysis

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

Eligibility criteria

Inclusion criteria
- International guidelines or consensus for adults (≥18 years) with UC
- Guidelines or consensus in English
- Guidelines or consensus published in the last five years (from November 2016 until December 2021)
- Systematic reviews with meta-analysis that evaluate the efficacy of classes of drugs, or medications for the adult population with UC.

Exclusion criteria:
- Guidelines or consensus on drug use or specific drug classes recommended for pediatric patients
- Guidelines or consensus published before November 2016
- Reviews of guidelines 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 S8 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 S8. Search strategy

study design	Search strategy	Results (titles)
Guidelines or consensus	(("inflammatory bowel disease"[Title] OR "IBD"[Title] OR "ulcerative colitis"[Title]) AND ("treatment"[Title/Abstract] OR "management"[Title/Abstract] OR "monitoring"[Title/Abstract]) AND ("consensus"[Title] OR "guidelines"[Title]) AND "English"[Language])) AND ((y_5[Filter]) AND (english[Filter]))	81
Systematic literature reviews with meta-analysis	(("inflammatory bowel disease"[Title] OR "IBD"[Title] OR "ulcerative colitis"[Title]) AND ("treatment"[Title/Abstract] OR "management"[Title/Abstract] OR "monitoring"[Title/Abstract]) AND ("meta-analysis"[Publication Type] AND "English"[Language])) AND ((meta-analysis[Filter]) AND (english[Filter]))	301

Search conducted on November 11, 2021.

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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 accelerate 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. In case of divergence, the decision was made with a third reviewer. The screening flowchart can be found in FIGURES S1 AND S2.

Data recovery and extraction

The guidelines or consensus that met all the inclusion criteria and did not meet any 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
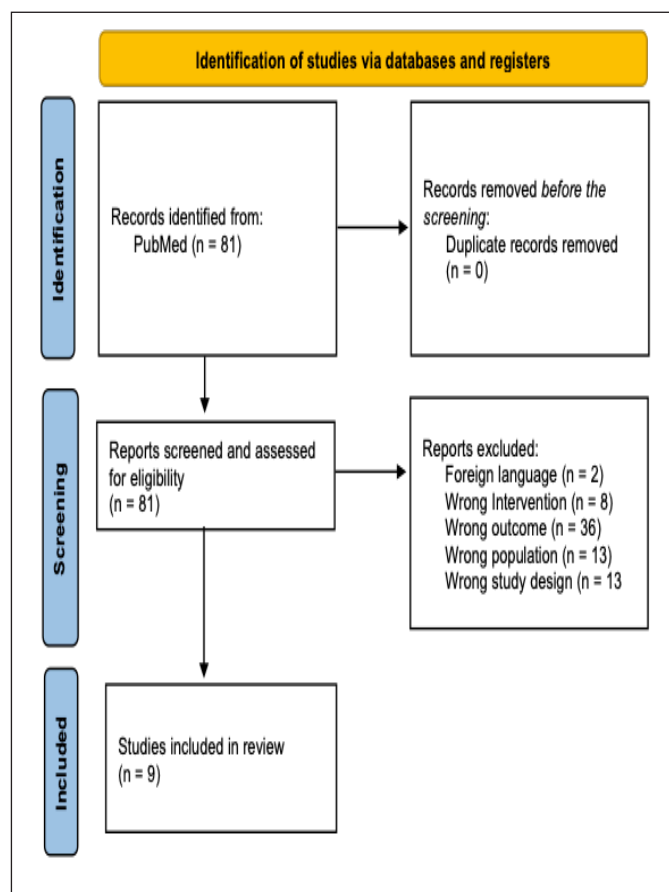- Effect direction.

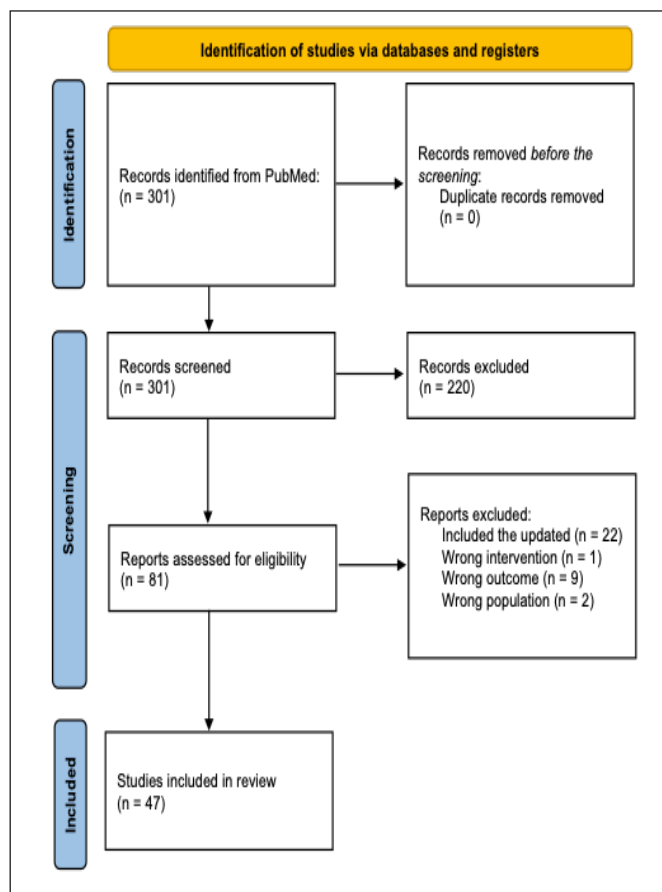FIGURE S1. Screening flowchart of consensus or guidelines for adults with UC.

FIGURE S2. Screening flowchart of the systematic literature reviews with meta-analysis for adults with UC.

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TABLE S9. 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
Abdulrazeg et al., 2019	Management of ulcerative colitis: summary of updated NICE guidance.	66.7	38.9	39.6	66.7	29.2	33.3	45.7
Amiot et al., 2021	Clinical guidelines for managing 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
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
Choi et al., 2017	Second Korean guidelines for the management of ulcerative colitis.	72.2	38.9	68.8	77.8	37.5	58.3	58.9
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
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
Harbord et al., 2017	Third European Evidence-based Consensus on diagnosis and management of ulcerative colitis. Part 2: current management.	77.8	61.1	70.8	88.9	62.5	83.3	74.1
Ko et al., 2019	AGA Clinical Practice Guidelines on the management of mild-to-moderate ulcerative colitis.	88.9	55.6	41.7	61.1	45.8	41.7	55.8
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
Maaser et al., 2019	ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications.	100.0	100.0	75.0	83.3	58.3	83.3	83.3
Magro et al., 2017	Third European Evidence-based Consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders.	77.8	61.1	70.8	88.9	62.5	83.3	74.1
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
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
Raine et al., 2021	ECCO Guidelines on therapeutics in ulcerative colitis: medical treatment.	100.0	100.0	75.0	83.3	58.3	83.3	83.3
Rubin et al., 2019	ACG Clinical Guideline: ulcerative colitis in adults.	72.2	61.1	45.8	72.2	41.7	66.7	60.0
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
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
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

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TABLE S10. AMSTAR 2.

Author	Bonovas	Bonovas	Chande	Chen	Cholapranee	Cohen	Davies	De Cassan	Dignass	Feagan	Feagan	Ford	Gisbert
Year	2018	2019	2014	2016	2017	2000	2020	2012	2019	2012	2012b	2011	2002
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
*2. Did the review report contain an explicit statement that the review methods were established before the conduct of the review, and did the report justify any significant deviations from the protocol?	No	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
*4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
*7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
8. Did the review authors describe the included studies in adequate detail?	Partial	Yes	Yes	Yes	Yes	Partial	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 included in the review?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No
*11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No meta-analysis	Yes	Yes	Yes	Yes	No meta-analysis
12. If a 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?	No	Yes	Yes	No	Yes	No	Yes	No meta-analysis	No	Yes	Yes	No	No meta-analysis
*13. Did the review authors account for RoB in individual studies when interpreting/ discussing the review results?	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	No
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
*15. If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small study bias) and discuss its likely impact on the review results?	No	Yes	Yes	N/A	Yes	No	Yes	No meta-analysis	No	Yes	Yes	Yes	No meta-analysis
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Rating overall	Low	Low	High	Low	Critically Low	Critically Low	High	Critically Low	Critically Low	High	High	Critically Low	Critically Low

TABLE S11. AMSTAR 2 (continuation).

Author	Guo	Huang	Iheozor-Ejiofor	Jin	Kaur	Khan	Lasa	Lasa	Leung	Liu	Luan	Lv	Ma	Manguso
Year	2019	2011	2020	2015	2020	2011	2017	2021	2008	2015	2016	2014	2019	2007
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	Yes
*2. Did the review report contain an explicit statement that the review methods were established before the conduct of the review, and did the report justify any significant deviations from the protocol?	No	No	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	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	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	yes	Yes
*7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial	No	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	No	Partial	Yes	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
*9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Partial	No	No	Yes	Partial	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No
*11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If a 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?	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
*13. Did the review authors account for RoB in individual studies when interpreting/ discussing the review results?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
*15. If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small study bias) and discuss its likely impact on the review results?	Yes	Yes	Yes	N/A	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	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Rating overall	Low	Low	High	Critically Low	High	Low	Critically Low	Moderate	Low	Critically Low	Critically Low	Low	Low	Critically Low

Baima JP, Imbrizi M, Andrade AR, Chebli JMF, Chebli LA, Argollo MC, Queiroz NSF, Azevedo MFC, Vieira A, Costa MHM, Fróes RSB, Penna FGC, Quaresma AB, Damião AOMC, Moraes ACS, Santos CHM, Flores C, Zaltman C, Vilela EG, Morsoletto E, Gonçalves Filho FC, Santana GO, Zabot GP, Parente JML, Sassaki LY, Zerôncio MA, Machado MB, Ornella Sari Cassol OS, Parra RS, Miszputen SJ, Coy CSR, Ambrogini Junior O, Kotze PG, Saad-Hossne R.
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TABLE S12. AMSTAR 2 (continuation).

Author	Manguso	Mardini	Marshall	Marshall	Marshall	Murray	Narula	Nguyen	Nikfar	Rahimi	Sang	Shen	Sherlock	Singh
Year	2016	2014	1997	2012	2010	2020	2018	2018	2009	2009	2010	2014	2015	2020
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	Yes
*2. Did the review report contain an explicit statement that the review methods were established before the conduct of the review, and did the report justify any significant deviations from the protocol?	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Partial
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	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	Partial
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	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	No	No	No	No	No	Yes	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Partial	Yes	Yes	Yes	Yes	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 included in the review?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
*11. If a meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If a 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	No	No	No	No	Yes	No
*13. Did the review authors account for RoB in individual studies when interpreting/ discussing the review results?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
*15. If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small study bias) and discuss its likely impact on the review results?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	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	No	No	Yes	Yes	Yes
Rating overall	Low	Low	Critically Low	High	High	High	High	High	Critically Low	Critically Low	Critically Low	Critically Low	High	Critically Low

TABLE S13. AMSTAR 2 (continuation).

Author	Sutherland	Wang	Welty	Zeng	Zhao	Zhao
Year	1993	2016	2020	2017	2016	2017
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes
*2. Did the review report contain an explicit statement that the review methods were established before the conduct of the review, and did the report justify any significant deviations from the protocol?	No	Yes	Yes	Partial	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes
*4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	No	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	No	Yes	Yes	Yes	Yes	Yes
*7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Yes	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial	Yes	Yes	Yes	Yes	Yes
*9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies included in the review?	Partial	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	No	Yes	Yes
*11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes
12. If a 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?	No	Yes	No	No	No	Yes
*13. Did the review authors account for RoB in individual studies when interpreting/ discussing the review results?	No	Yes	No	No	Yes	Yes
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results?	No	Yes	Yes	Yes	Yes	Yes
*15. If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small study bias) and discuss its likely impact on the review results?	No	Yes	No	Yes	No	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Yes	Yes	Yes	Yes	Yes
Rating overall	Critically Low	High	Critically Low	Critically Low	Critically Low	Low

Baima JP, Imbrizi M, Andrade AR, Chebli JMF, Chebli LA, Argollo MC, Queiroz NSF, Azevedo MFC, Vieira A, Costa MHM, Fróes RSB, Penna FGC, Quaresma AB, Damião AOMC, Moraes ACS, Santos CHM, Flores C, Zaltman C, Vilela EG, Morsoletto E, Gonçalves Filho FC, Santana GO, Zabot GP, Parente JML, Sassaki LY, Zerôncio MA, Machado MB, Ornella Sari Cassol OS, Parra RS, Miszputen SJ, Coy CSR, Ambrogini Junior O, Kotze PG, Saad-Hossne R.
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