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Brazilian Consensus on the management of inflammatory bowel diseases in pediatric patients: a Consensus of the Brazilian Organization for Crohn's disease and colitis (GEDIIB)

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ABSTRACT – Background – Approximately 25% of patients with inflammatory bowel disease (IBD) develop the disease during childhood or adolescence and treatment aims to control active symptoms and prevent long-term complications. The management of Crohn's disease (CD) and ulcerative colitis (UC) can be especially challenging in children and adolescents, related to particularities that may affect growth, development, and puberty. **Objective –** This consensus aims to provide guidance on the most effective medical and surgical management of pediatric patients with CD or UC. **Methods –** Experts in Pediatric IBD representing Brazilian gastroenterologists (Brazilian Organization for Crohn's Disease and Colitis [GEDIIB]) developed this consensus. A rapid review was performed to support the recommendations/statements. Medical and surgical recommendations were structured and mapped according to the disease type, disease activity, and indications and contraindications for medical and surgical treatment. After structuring the statements, the modified Delphi Panel methodology was used to conduct the voting. The process took place in three rounds: two using a personalized and anonymous online voting platform and one face-to-face. Whenever participants did not agree with a specific recommendation, an option to explain why was offered to enable free-text responses and provide the opportunity for the experts to elaborate or explain disagreement. The consensus of recommendations in each round was accepted when reached ≥80% agreement. **Results and conclusion –** The recommendations are presented according to the stage of treatment and severity of the disease in three domains: management and treatment (drug and surgical interventions), criteria for evaluating the effectiveness of medical treatment, and follow-up/ patient monitoring after initial treatment, follow-up/ patient monitoring after initial treatment. Surgical recommendations were grouped according to disease type and recommended surgery. The target audience for this consensus was general practitioners, gastroenterologists, and surgeons interested in the treatment and management of pediatric CD and UC. Additionally, the consensus aimed to support the decision-making of health insurance companies, regulatory agencies, and health institutional leaders and/or administrators.

Keywords – Crohn disease; colitis ulcerative; surgery; children; adolescents, inflammatory bowel diseases; disease management.

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated group of diseases characterized by chronic activation of the intestinal immune system, with relapsing and remitting episodes of gastrointestinal inflammation. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) which share many clinical and histologic findings[1]. IBD develops during childhood or adolescence in up to 25% of the patients. Optimal treatment targets are clinical remission, endoscopic healing, absence of disability, normalized health-related quality of life and restoration of normal growth[104]. This is especially challenging in the pediatric population because both the disease and and some treatments can impair growth, development and puberty[2].

In 2010, the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB) published the first Brazilian consensus on IBD aiming to provide comprehensive, evidence-based recommendations on the management of CD and UC[3]. This Consensus

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however did not have a section for pediatric IBD. Considering the major scientific developments throughout the past decade, a rapid literature review was conducted to supplement the 2010 publication by providing GEDIIB with an overview of the most up-to-date consensus statements for this population. This article provides recommendations to guide clinical practice in pediatric IBD patients' assessment, treatment, and follow-up. It is important to state that these recommendations only are not to be used instead of clinical judgement. In the present consensus, while we are broadly referring to the two major phenotypic forms of IBD (namely CD and uC), it must be recognized that IBD comprises a spectrum of chronic intestinal inflammation, with significant interindividual variation.

Disease classification

Patients are classified according to a variety of measures of disease activity that were developed to allow uniformity among observers when stratifying IBD by severity, extension and/or behavior. Below, we summarize most used commonly methods for classification of each disease.

Crohn's Disease

Crohn's disease is a transmural inflammatory disease of the mucosa. It can affect any part of the gastrointestinal (GI) tract from the mouth to the anus. The hallmark of CD are patchy areas of inflammation, characterized by erythema, mucosal edema, superficial or deep ulceration, luminal narrowing and/or fistulizing disease. The most used clinical scoring tool is the Pediatric Crohn Disease Activity Index (PCDAI) (TABLE 1), developed at a consensus meeting of experts in pediatric IBD and subsequently validated[4]. The tool is comprised of 11 items (symptoms, physical examination, growth, and selected serum inflammatory markers) completed by a physician with scores ranging from 0 to 100, with higher scores indicating worse disease activity. A score of 10 demonstrated the best balance between sensitivity and specificity to distinguish between inactive and mild disease. A score of >30 showed relatively good sensitivity (0.71) with acceptable specificity (0.83) in discriminating moderate/severe from mild disease[5]. Despite its use in CD, it correlates less with endoscopic findings when compared to the PUCAI in UC.

The Paris classification is frequently used to classify pediatric CD according to age at diagnosis, disease location, disease behavior and the presence of growth impairment (TABLE 2)[6].

Ulcerative colitis

In children, UC presents with an extensive disease phenotype in more than 85% of all cases[7], which is associated with greater risk of acute severe exacerbations leading to hospital admissions and requiring colectomy more frequently due to medically refractory disease[8-11].

The most widely employed clinical scoring tool in UC is the Pediatric Ulcerative Colitis Activity Index (PUCAI), a simple, non-invasive clinical index, developed and validated in 2007[12]. The PUCAI highly scores correlate with colonoscopic disease activity (Mayo endoscopic score). The instrument consists of six items: abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal stools, and assessment of patients' daily activity. The sum of these items leads to a final score ranging from 0 to 85, with higher scores indicating worse disease activity. The corresponding PUCAI cut-off scores are: remission - <10 points, mild activity – 10–34

TABLE 1. Pediatric Crohn Disease Activity Index (PCDAI).

Category	Parameter	Detailed Description	Point
History (recall, 1 wk.)	Abdominal Pain	None	0
		Mild (brief, does not interfere with activities)	5
		Mod/Severe (daily, longer-lasting, affects activities, nocturnal)	10
	Stools (per day)	0–1 liquid stools, no blood	0
		Up to 2 semi-formed with small blood, or 2-5 liquid	5
		Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	10
Patient functioning, general well-being (recall, 1 wk.)	No limitation of activities		0
	Occasional difficulty in maintaining age-appropriate activities		5
	Frequent limitation of activity, very poor		10
Laboratory	Hematocrit (%) (use age-specific reference)	Normal	0
		Mild decrease	2.5
		Mod/severe decrease	5
	Erythrocyte sedimentation rate (mm/h)	<20	0
		20–50	2.5
		>50	5
	Albumin (g/dL)	≥3.5	0
		3.1–3.4	5
		≤3.0	10
Examination	Weight	Weight gain or voluntary weight stable/loss	0
		Involuntary weight stable, weight loss 1–9%	5
		Weight loss ≥10%	10
	Height at diagnosis	<1 channel decrease	0
		≥1, <2 channel decrease	5
		≥2 channel decrease	10
	Height follow-up	Height velocity ≥-1 SD	0
		Height velocity ≥-1 SD, >-2 SD	5
		Height velocity ≥-2 SD	10
	Abdomen	No tenderness, no mass	0
		Tenderness, or mass without tenderness	5
		Tenderness, involuntary guarding, definite mass	10
	Perirectal disease	None, asymptomatic tags	0
		1-2 indolent fistula, scant drainage, no tenderness	5
		Active fistula, drainage, tenderness, or abscess	10
	Extraintestinal manifestations (n)	0	0
		1	5
		≥2	10

TABLE 2. Paris Classifications for Crohn's Disease.

	Paris
Age at diagnosis	A1a: 0–<10 y
	A1b: 10– <17 y
	A2: 17–40 y
	A3: >40 y
Location	L1: distal 1/3 ileum ± limited cecal disease
	L2: colonic
	L3: ileocolic
	L4a: upper disease proximal to Ligament of Treitz*
	L4a: upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum*
Behavior	B1: non-structuring non-penetrating
	B2: stricturing
	B3: penetrating
	P: perianal disease modifier
	B2B3: both penetrating and and stricturing disease, either at the same or different times
Growth	G0: No evidence of growth delay
	G1: Growth delay

points), moderate activity (35–64 points), and severe acute colitis (≥65 points). These cut-off points have been extensively validated and found to have sensitivity, specificity and accuracy (as measured by the area under the ROC curve) of >95%. Detailed characteristics of the PUCAI are presented in TABLE 3.

There are some considerations for the adequate application of the PUCAI score. First, the period considered for evaluation: (a) answers should reflect a daily average of the last 2 days; however, if clinical conditions are changing rapidly (e.g., in acute severe colitis), the last 24 hours should be considered; (b) for patients undergoing colonoscopy, answers should reflect the 2 days before starting bowel cleaning. In rectal bleeding, a 'large amount' refers to the amount of blood (>50% of the stool content) present in most stools. Under the number of stools per 24 hours, an episode of clustered several small stools over a short period of time (a phenomenon that could be related to tenesmus or incomplete evacuation) should be considered as 1 stool. Finally, regarding patients' activity level: an occasional limitation of activity would translate to attending school or similar activity, but with some form of reduced activity (e.g., does not play at breaks); and severely restricted activity would mean not to attend school or an equivalent activity[12].

UC extension and severity is also classified using the Paris classification[6] (TABLE 4).

TABLE 3. Pediatric Ulcerative Colitis Activity Index (PUCAI).

Item	Points
Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
Rectal bleeding	
None	0
Small amount only, in < 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of the stool content)	30
Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
Number of stools per 24 h	
0-2	0
3-5	5
6-8	10
>8	15
Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI	0-85

TABLE 4. Paris classifications for UC.

	Paris
Extent	E1: ulcerative proctitis
	E2: left-sided UC (distal to splenic flexure)
	E3: extensive (hepatic flexure distally)
	E4: pancolitis (proximal to the hepatic flexure)
Severity	S0: never severe (PUCAI ≥65)
	S1: ever severe (PUCAI ≥65)

Risk stratification in Crohn's disease

The literature on outcome prediction in pediatric IBD patients has been reviewed by Ricciuto et al. (2021)[15]. The recommendations of the current consensus will be presented based on this risk stratification (as per ECCO-ESPGHAN guidelines) on TABLE 5. This risk stratification of pediatric CD is based on predictors of poor outcomes (low, medium and high-risk) according to the Paris classification and additional risk factors, also providing a therapy suggestion for each case.

Prognostic factors for surgery: factors reported as predictors for surgery include: diagnosis at age over 13 years (compared to younger age, growth impairment at diagnosis, stricturing and/or internal penetrating (B2/B3) phenotype, positivity for NOD2/CARD15 variants, and positive anti–Saccharomyces cerevisiae

TABLE 5. The ECCO-ESPGHAN guideline for predictors of poor outcome in pediatric Crohn's disease and suggested induction therapy, according to Rheenen et al., 2020[16].

Paris classification [at diagnosis]	Additional risk factors	Risk stratification	Suggested induction therapy
B1	None	Low	Exclusive enteral nutrition; corticosteroids
B1	No clinical and biochemical remission 12 weeks after start induction therapy	Medium	Consider accelerated step-up to anti-TNF therapy
B1+G1	Growth delay	Medium	Exclusive enteral nutrition; consider up-front anti-TNF therapy
B1 [L3+L4]	Extensive disease[a] or deep colonic ulcers	High	Up-front anti-TNF therapy
B1+p	Perineal disease	High	Up-front anti-TNF therapy in combination with antibiotic therapy, surgery, or both
B2	None Prestenotic dilatation, obstructive signs, or symptoms, or both	High	Up-front anti-TNF therapy Bowel resection in combination with postoperative anti-TNF therapy
B3	Prestenotic dilatation, obstructive signs, or symptoms, or both	High	Surgery in combination with postoperative anti-TNF therapy

TNF: tumour necrosis factor. [a]Defined as pan-enteric inflammation [i.e., involvement of proximal small bowel, terminal ileum, and colon].

antibodies (ASCA)[17]. Isolated colonic disease is associated with lower risk of surgery. Meanwhile, there is inconclusive evidence if gender is as a predictor for surgery; additionally, ethnicity and presence of granulomas at diagnosis do not seem to predict surgical treatment[16].

Prognostic factors for penetrating and stricturing behavior*:* children who develop CD at older ages, afro-descendants, children with positive ASCA, and with perianal disease may be at increased risk for internal penetrating complications. The presence of small bowel disease, ASCA positivity, polymorphisms of NOD2/ CARD15 gene and the presence of perianal disease are reported as risk factors for stricturing disease. Finally, older age CD onset, afro-descendants and south Asian ethnicity, bacterial serology, and male sex predict perianal disease.

Risk stratification in ulcerative colitis

The literature on outcome prediction in pediatric UC patients has been reviewed by Orlanski-Meyer et al. (2021):

Prognostic factors for acute severe colitis and related outcomes: Disease severity at onset (PUCAI or endoscopic assessment) and hypoalbuminemia at diagnosis are predictors of poor prognosis and increased risk of acute severe colitis (ASC). In ASC, higher PUCAI scores on days 3 and 5 of hospital admission predicts the need for treatment escalation. Shorter time from disease onset to ASC may predict unresponsiveness to intravenous steroids (IVCS).

Prognostic factors for colectomy: Extensive disease, PUCAI score >65 points, low hemoglobin/hematocrit, and high white blood cells (WBCs) at the time of diagnosis may predict colectomy. Additional factors associated with an increased risk of colectomy include PUCAI score >65 during the subsequent 3 months, a family history of UC and the presence extraintestinal manifestations. Children who developed an episode of ASC at any time and especially those who fail intravenous corticosteroid (IVCS) treatment are at an increased risk for a more refractory disease course and colectomy. Toxic megacolon defined as dilatation on plain abdominal x-ray is suggested by colonic width of >56 mm in children older than 10 years of age and >40 mm in younger children and with a significant deterioration are at risk of colectomy. Finally, *Clostridioides difficile* infection, increase of disease extension over time, and presence of neutrophilic infiltration in the gastric mucosa or duodenum, at diagnosis, are also reported as predictors of the need for colectomy[22].

Prognostic risk factors for chronically active pediatric UC: Ethnicity, as well as genetic polymorphisms (particularly in genes associated with the treatment pathways) may predict response to medications. Disease extent at diagnosis may predict medication use and response to treatment; however, it does not predict relapse.

Prognostic risk factors for cancer and/or mortality in children with IBD: Having a first-degree relative with any kind cancer before the age of 50 may be a risk factor for cancer in UC[18]. Malignancy and infection (sepsis and opportunistic infections) are reported as risk factors for mortality. Concomitant diagnosis of ASC, long-standing colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer in IBD.

Outcomes and endpoints

There are several outcome domains of interest for IBD patients such as clinical response, endoscopic remission, histological remission, and quality of life (QoL). In addition, there is significant heterogeneity across studies defining each outcome of interest. Below, we summarized the main outcomes reported and how they are usually defined in the literature.

Clinical response and clinical remission

Clinical response (typically defined as moderate to severe disease improving to mild/inactive disease) can be assessed with a PCDAI decrease by 12.5 points - representing the optimal threshold for detecting a clinically significant response to therapy over a period of time of 4 weeks[20-21]. In CD, clinical remission is usually evaluated with changes in PCDAI and Physician Global Assessment over time[4,21]. Clinical remission is usually defined by a PCDAI ≤10 points[16]. Meanwhile, in UC, clinical remission typically assessed using the PUCAI score with a cut-off point <10 points[22]. Despite these definitions of clinical response and clinical remission, guidelines recognize the importance of mucosal healing. Prior to the de-escalation of treatment. Biochemical evaluation with fecal calprotectin is currently recommended for patients in remission[22].

Endoscopic response

Several endoscopic scoring systems have been developed and used to define endoscopic activity and response to therapy in IBD. For CD, the most used tools to assess complete mucosal healing as an endpoint in clinical trials are the Crohn's Disease Endoscopic Index of Severity (CDEIS)[23] and the Simplified Endoscopic activity Score for Crohn's disease (SES-CD) (TABLE 6). The SES-CD is a reliable endoscopic score that does systematize the recording of features in each segment of the colon[24,25]. It is scored from 0 to 60, and a 50% (or higher) reduction in SES-CD is considered endoscopic response, while a score of <2 indicates endoscopic remission.

The most common visual score to describe UC activity endoscopically is the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (TABLE 7)[27]. Another endoscopic evaluation used is the Mayo endoscopic score, which is simpler and more applicable in practice.

Steroid-free clinical remission

Corticosteroids are frequently used for acute management of

TABLE 6. Simple Endoscopic Score for Crohn's Disease (SES-CD). Recording of features in each segment of the colon.

		Score	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Size of ulcers (diameter)	Absent	0						
	Aphthous ulcers, 0.1–0.5 cm	1						
	Large ulcers, 0.5–2 cm	2						
	Very large ulcers, >2 cm	3						
Ulcerated surface	None	0						
	<10% of the segment	1						
	10–30% of the segment	2						
	>30% of the segment	3						
Affected surface	None	0						
	<50% of the segment	1						
	50–75% of the segment	2						
	>75% of the segment	3						
Presence of narrowing	None	0						
	Single, passable by the scope	1						
	Multiple, passable by the scope	2						
	Not passable, frank stenosis	3						
		Total SES-CD = scored from 0 to 60						

TABLE 7. Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[26].

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 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 an endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers*	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (≤5 mm) defects in the mucosa, of white or yellow color with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa, which 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 the variability in the assessment of severity.

flares in adult and pediatric patients with CD and UC. Although effective for induction, steroids do not lead to mucosal healing and their use is associated with systemic side effects and increased risk of poorer outcomes. Thus, achieving remission without the use of corticosteroids is a treatment goal: Steroid-free clinical remission (SF-CR) has been widely used as a primary endpoint in pediatric clinical trials and is considered a critical endpoint for evaluating new therapies[28-30].

Sustained clinical remission

There is some variation among studies in defining sustained remission. Examples include more broad definitions such as a stable, steroid-free clinical remission during a 1-year follow-up period. In clinical trials, sustained clinical remission has been evaluated using several definitions, in UC for instance, acceptable definitions include: (a) a partial Mayo Score (pMS) of ≤2 with no subscore >1; (b) a rectal bleeding subscore (RBS); (c) PUCAI score <10 points without a flare or without change in medical therapy; and (d) sustained corticosteroid-free remission measured by physician global assessment and patient global assessment[30-32].

Improvement in Quality of Life

With advances in clinical trial designs and the influence of regulatory agencies seeking patient-reported outcomes as primary endpoints, quality of life (QoL) and related psychosocial measures are of increasing significance in IBD research[33]. The first disease-specific quality of life questionnaire developed for pediatric IBD patients was IMPACT-I[34,35]. This questionnaire has subsequently undergone several modifications resulting in IMPACT-III, a self-report measure with 35 closed questions across six domains that uses 5-point Likert scale for all answers, with final scores ranging from 35 to 175 – higher scores suggesting better quality of life. The IMPACT-III is a valid and reliable measure of health-related QoL in pediatric CD[36].

Medical treatment considerations

Salicylic Derivatives

In this group of drugs, we included mesalazine and sulfasalazine (SSZ), also known as 5-aminosalicylate (5-ASA) drugs

Beyond oral formulations, mesalazine is also available for topical use as suppositories, foam, and enema. Furthermore, there are several types of slow release oral mesalazine allowing the drug to be released in specific sites of the gastrointestinal tract. Most patients who are intolerant or allergic to SSZ do tolerate mesalazine (80–90%). A Cochrane review revealed that despite being less tolerated, SSZ is as effective in maintaining remission in UC as mesalazine newest formulations and is also less expensive[37]. For patients with left-sided or extensive mild/moderate, a combination of oral and topical mesalazine may be recommended[37-38].

Side effects of SSZ are more commonly dose-dependent and related to sulphapyridine serum levels. Such effects occur mainly in individuals with low genetic ability of hepatic drug acetylation (slow acetylators) and include abdominal pain, nausea, vomiting, anorexia, headache, hemolysis, and male infertility. Less frequently, SSZ side effects may occur due to hypersensitivity (allergy or idiosyncrasy)[39-40].

Corticosteroids

Corticosteroids are commonly used, preferably for a short period, in the treatment of IBD. It is estimated that up to 80% of children are treated with oral steroids, mainly within 3 months of diagnosis, inducing clinical remission in 50% to 90% of cases following short-term treatment[41]. Their side effects are well-known, especially when used for prolonged periods of time (even at low doses), and include appetite stimulation, increase in body weight, edema, insomnia, emotional lability, psychosis, acne, Cushing syndrome, osteoporosis, growth stunt, myopathies, cataract, skin atrophy, striations, ecchymosis, fatty liver disease, diabetes, hypertension, glaucoma and acute pancreatitis[40]. In addition, long-term steroid usage is also associated with increased risk of permanent growth impairment[42]. Studies have shown that oral Budesonide may be superior to placebo for induction of remission in CD, and it incurs in smaller risks for adverse events compared to prednisone[43-44]. Multi Matrix (MMX) Budesonide formulation is an once-daily oral formulation reported to be effective for induction of clinical and endoscopic remission in adults with UC[45-46].

Immunosuppressors

Thiopurines (Azathioprine, AZA, and 6-mercaptopurine, 6-MP) are considered effective for relapsing prevention in pediatric patients, but not for remission induction. It has been reported that thiopurines are associated with an increased risk of infection, myelosuppression, liver toxicity, pancreatitis, and malignancy[40].

Methotrexate (MTX) can also be used to maintain clinical remission, in case of thiopurine failure or intolerance, or as an alternative first-choice. Nausea and vomiting are significant issues, specially at the beginning of treatment of MTX. In addition, as a recognized teratogen, it is strictly contraindicated in pregnancy, and it should not be used in adolescents of reproductive age. Other MTX reported side effects include an increased risk of myelosuppression, pulmonary toxicity, and hepatotoxicity[40].

Cyclosporine inhibits the production of interleukin-2 activated by T-lymphocytes through a calcineurin-dependent pathway and the synthesis of other inflammatory cytokines[47]. It may be considered a valid option to treat acute severe UC in selected adult patients. Tacrolimus, a calcineurin inhibitor like cyclosporine, has a similar mechanism of action and appears superior to placebo for promoting clinical remission and clinical improvement in corticosteroid-refractory colitis or steroid-refractory proctitis[48-50].

Biologic agents

Seven biologic agents are currently approved for the treatment of IBD refractory to non-biologic medications: four Anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab pegol), two anti-integrin agents (natalizumab and vedolizumab - although the use of natalizumab has been discouraged due to the risk of multifocal leukoencephalopathy from JC virus reactivation and it is not approved for the treatment of IBD in Brazil), and one anti-interleukin (ustekinumab) agent. However, most of these drugs are currently off-label for pediatric patients[49-51]. Anti-TNF alfa agents have been associated with an increased risk of reactivating latent infections, mainly tuberculosis, autoimmunity, demyelinating disease, chronic heart failure, and malignancy[40].

More recently, the anti-integrin agent vedolizumab, a humanized monoclonal antibody designed to specifically antagonize the alpha4beta7 integrin, inhibiting the binding of alpha4beta7 integrin to intestinal mucosal addressing cell adhesion molecule 1 (MAdCAM-1), preferentially expressed on blood vessels and lymph nodes of the gastrointestinal tract and ustekinumab, an antibody that targets the p40 subunit of interleukin (IL)-12 and

IL-23, have been clinically evaluated for IBD patients, especially in UC patients. Ongoing trials are evaluating a next-generation anti-integrin with dual action that targets two pathways of inflammation in the gut, etrolizumab, in CD and UC patients[52].

Janus Kinase Inhibitors (JAK)

JAK inhibitors have already been incorporated into the management of immune-mediated diseases in adults, and they have been approved to use in the UC treatment (in Brazil, since late 2014)[40]. Tofacitinib (TOFA; CP-690,550) is an oral small-molecule drug (SMD) with a molecular weight of 312.3 Da. It inhibits JAK1, JAK3, and, to a lesser extent, JAK2.2-5. This inhibition ends up blocking signals for several inflammatory cytokines such as interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21, and interferon-gamma, among others[53-55]. The drug was approved by ANVISA for the treatment of moderate to severe UC in adults in March 2019[56]. These medications are mostly used in adults and the pediatric population the studies are still preliminary.

Probiotics

The use of probiotics has been suggested to modulate the existing microbiota, with some role in IBD, as the pathogenesis of IBD has been associated with intestinal microbiota antigens and dysbiosis[57]. However, high-quality studies on the effect of probiotics in pediatric IBD are scarce, with only 3 RCTs (two in UC and one in CD). Due to the paucity of clinical trials in CD and UC, there is currently no evidence to support the use of probiotics. The most recent guidelines in CD recommending against it , even though it has been reported that in patients with UC, probiotics (*Escherichia coli Nissle 1917 or VSL#3*) may be effective in inducing remission in patients with mild to moderate disease. It is important to notice that *VSL3#* is not available in Brazil. Probiotics may be used for primary and secondary prevention of pouchitis in patients with UC who have undergone colectomy and pouch-anal anastomosis, and for colectomized patients with a pouch and pouchitis if antibiotic treatment has failed[58,59].

Objective of the consensus

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

METHODS

This consensus addresses the most relevant information to guide the decision-making process for clinical and surgical management of IBD. It synthesizes recommendations developed from evidence-based statements and state-of-art knowledge, although primary research was also reviewed. It does not intend to provide the full range of options for treatment available, neither does it cover all aspects of the condition. The GEDIIB represents the Brazilian key experts in Pediatric IBD, who participated and were involved in this consensus. The consensus targeted general practitioners, gastroenterologists, surgeons, and nutritionists interested in the treatment and management of pediatric patients with UC or CD. Additionally, this consensus aimed to support the decision-making of health insurance companies, institutional leaders, and/or administrators. The Rapid Review approach[33] was considered the most appropriate method suited to the context. The concern for a timely decision on health care and policies was the driving force for this consensus.

According to its definition, the literature review was systematic, but with some limitations such as database number, study design, and search period. Existing high-quality guidelines and/or consensus and level 1 evidence studies (systematic literature review) were eligible, identified, and synthesized to support the recommendations/statements in this document. In order to obtain the most recent evidence, the MEDLINE database search was limited to the past 5 years (from October 2016 to October 2021). The 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 conducted using its respective tools (Additional methodologies data can be found in supplementary material: PICOS [Medical - CD: TABLE S1 to S12; UC: TABLE S23 to S31; Surgical - CD: TABLE S14 to S31; UC: TABLE S33 to S38], search strategy [Medical - CD: TABLE S13; UC: TABLE S32; Surgical - CD: TABLE S22; UC: TABLE S39], screening flowchart [Medical - CD: FIGURE S1 and S2; UC: FIGURE S4 and S5; Surgical - CD: FIGURE S3; UC: FIGURE S6], and quality appraisal [TABLE S40, S41 and S42]). The studies that endorsed the recommendation were captured by "snowballing search" starting from the reference list of the guidelines included in the rapid systematic review.

The quality appraisal of the included studies was conducted by 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 and/or consensus included in the rapid literature review[60]. 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[61]. Originally, the assessment of multiple systematic reviews (AMSTAR) tool was widely 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.

The nonsurgical recommendations were structured and mapped according to the severity of disease for UC and risk-stratification for CD; and, according to the treatment phase of both diseases in three domains: management and treatment (drug and surgical interventions), criteria to evaluate medical treatment efficacy, patient follow-up/monitoring after initial treatment. Surgical recommendations were grouped according to disease type and recommended surgery.

After structuring the recommendations, the modified Delphi Panel methodology was used to conduct the voting. This panel took place in three rounds: two using a personalized and anonymous online voting platform and one face-to-face. Whenever participants disagree with specific statements-recommendations, an option to explain why will be offered to enable free-text responses, allowing experts to elaborate or explain disagreement. The face-to-face consensus was held in São Paulo, Brazil in May 2022. It was composed by six pediatric gastroenterologists, three adult gastroenterologists, two gastroenterologists' surgeons, and one registered dietician, all of them members of GEDIIB. The

consensus of recommendations in each round was considered to have been reached if there was ≥80% agreement[62]. As we have classified activity or severity of disease for recommendations, some of these recommendations have similar discussions that endorse them, because they discuss the same treatment modality for different disease severities. With the purpose of favoring reading, we have not repeated the context or justification for recommendations on the same treatment modalities.

MEDICAL MANAGEMENT FOR PEDIATRIC PATIENTS WITH CROHN'S DISEASE

LOW-RISK ACTIVE CROHN'S DISEASE
Induction of remission

Nutrition

Recommendations

1. We suggest Exclusive enteral nutrition (EEN) to induce clinical remission in low-risk active CD[18-63]. **Agreement:** 91.7%.
2. In patients with low-risk active CD, it is suggested that EEN may be as effective as corticosteroids for induction of remission. Additionally, EEN is more likely to lead to mucosal healing, and positively impacts in body weight[64-65]. **Agreement:** 100%.
3. For children with low-risk active CD, it has been suggested that dietary therapies (CD exclusion diet, EEN, partial enteral nutrition) may induce a rapid clinical response within three weeks. Response to dietary treatment at an early stage may increase the likelihood of achieving remission within 6 weeks[66]. **Agreement:** 100%.

Corticosteroids

Recommendations

1. In low-risk active ileocecal CD, if EEN is insufficiently effective or is not an option, prednisone may be prescribed at doses of 1 mg/kg/day to a maximum of 40 mg/day, and should be tapered once clinical remission is reached, but no later than 4 weeks after initiation[16]. **Agreement:** 91,7%.
2. When EEN has been unsuccessful, not accepted, or cannot be completed it is recommended to use oral prednisone to induce clinical remission in low-risk active CD[63]. **Agreement:** 91.7%.

Nutritional deficiencies and critical nutritional status predict worse clinical outcomes in pediatric patients, including higher infection rates, longer hospital stays, and postoperative complications[67]. Narula et al. reported that 83% of the children using EN achieved remission compared to 61% of steroid patients (risk ratio [RR] = 1.35 [95% CI 0.92 to 1.97])[64]. When a per-protocol analysis was performed, accounting for withdrawals due to inability to tolerate the nasogastric tube or poor palatability of the formulation, 89% of pediatric patients in the EN group achieved remission compared with 61% in the steroid group (RR=1.43 [95%CI 1.03 to 1.97])[64]. There was no difference between the type of formula used for EEN (elemental; semi-elemental e polymeric) and remission rates. Yu et al. (2019) endorsed this evidence demonstrating that EEN was as effective as corticosteroids (odds ratio [OR] = 1.35 [95%CI 0.90 to 2.10; *P*=0.14) for induction of clinical remission, and more effective in achieving endoscopic healing (OR=5.24 [95%CI 2.06 to 13.37], *P*=0.0005), histological mucosal healing (OR=4.78 [95%CI 1.89 to 12.08], *P*=0.0009), and weight gain (mean difference [MD] = 1.92 [95%CI 0.02 to 3.83], *P*=0.05)[65]. These results make EEN especially interesting in the pediatric population, as frequent use of corticosteroids in children has been associated with numerous adverse effects, mainly on growth, bone mineral density, and body image[66,68-69].

Salicylic derivatives

Recommendation

- We do not recommend using 5-ASA or sulfasalazine to induce clinical remission in children or adolescents with low-risk active CD[63]. **Agreement:** 100%.

Immunosuppressants

Recommendation

- We do not recommend the use of thiopurine or methotrexate (MTX) monotherapy to induce clinical remission in children or adolescents with low-risk active CD[16,63]. **Agreement:** 100%.

In children with active CD, it has been established that thiopurine monotherapy is not effective to induce remission[16]. The evidence for the effectiveness of MTX for induction is limited to observational studies: based on this evidence, only half of the children who used MTX achieved clinical remission within 3 to 6 months of treatment, and only one-third remained in clinical remission at 12-months[70]. Therefore, we do not recommend MTX or thiopurine for induction of remission in pediatric CD.

Biological agents

Recommendation

- Anti-TNF therapy (i.e., infliximab or adalimumab) is not recommended as first-line therapy for induction in low-risk pediatric CD[16-63]. **Agreement:** 100%.

Several biological agents have been studied in pediatric patients. However, only two biologics, infliximab, and adalimumab are currently approved for children and adolescents[71]. There is paucity of data for routine recommendation of Anti-TNF therapy as induction agents in low-risk pediatric CD.

Maintenance of remission

Nutrition

Recommendations

1. For pediatric patients already in remission, partial EN (PEN) may be recommended combined with other medications in order to maintain clinical remission[63]. **Agreement:** 100%.
2. In children with low-risk CD who achieved clinical remission, maintenance enteral nutrition (MEN) [50% of daily energy requirements; ≥900 Kcal/day given as formula] may prolong remission[16]. **Agreement:** 87%.

Long-term PEN has been shown to be an effective approach to decrease clinical relapse rates and suppressing endoscopic disease activity. A retrospective study of 58 pediatric patients demonstrated that EN therapy with aminosalicylates is effective in maintaining remission and decreasing the rate of bowel surgery in pediatric CD[72]. Another study, evaluating 42 pediatric CD patients who have achieved clinical remission within 4-12 weeks of EEN and were maintained on PEN reported that more than 50% of patients required concomitant medications within 2 weeks of treatment initiation of PEN to maintain remission. Most patients required concomitant medication at some point after starting PEN[73]. Finally, a meta-analysis of studies conducted with children and adults with CD concluded that consumption of more than 35% of caloric needs from EN is recommended to achieve clinical benefits in maintaining remission[74]. Levine et al. (2020) proposed the Crohn's disease exclusion diet (CDED) as monotherapy, as combined therapy (with pharmacological treatment), as a rescue therapy in refractory patients, and as possible de-escalation from medical therapy[68].

Salicylic derivatives

Recommendation
- We recommended against the use of salicylic derivates to maintain remission in children and adolescents with low-risk active CD[63]. **Agreement:** 100%.

Corticosteroids

Recommendation
- We recommended against the use of corticosteroids to maintain remission in children and adolescents with low-risk active CD[63]. **Agreement:** 100%.

Immunosuppressants

Recommendation
- We recommend the use of thiopurines (azathioprine [AZA] or 6-mercaptopurine [6-MP]) or MTX to maintain remission in children and adolescents with low-risk active CD[63]. **Agreement:** 100%.

In pediatric patients, clinical remission with MTX at one year was reported to be between 25% to 69% in children with CD who did not tolerate or did respond to thiopurine[75]. MTX is often recommended as a second-line immunomodulatory therapy. Thiopurines are typically recommended as the first line and have proven steroid-sparing effects and modest efficacy as maintenance therapy and for prevention of postoperative recurrence[76].

Biological agents

Recommendation
Expert opinion
- We do not recommend biological agents to maintain remission in children and adolescents with low-risk active CD. **Agreement:** 91.7%.

MEDIUM-RISK ACTIVE CD
Induction of remission

Salicylic derivatives

Recommendation
- We do not recommend the use of 5-ASA or sulfasalazine to induce clinical remission in children or adolescents with medium-risk active CD[63]. **Agreement:** 91.7%.

Corticosteroids

Recommendation
- We recommend considering the use of corticosteroids for induction of remission when children with medium-risk active CD are not eligible for EEN. The starting dose of prednisolone is weight-dependent (1 mg/kg/day to a maximum of 40 mg/day) and should be tapered once clinical remission is reached, but no later than 4 weeks after initiation[16,77]. **Agreement:** 100%.

It is reported that patients on EEN are more likely to drop out of treatment than those on corticosteroid therapy due to unpalatable formulations and poor acceptance of a nasogastric tube. When children with medium-risk luminal CD are not compliant or do not tolerate EEN or if EEN therapy is ineffective after 2 to 4 weeks, systemic corticosteroids may be considered to induce remission[64].

Immunosuppressants

Recommendation
- Immunosuppressants are not recommended for induction clinical remission in children with medium-risk active CD[63]. **Agreement:** 100%.

BIOLOGICAL AGENTS

Anti-TNF

Recommendation
- The use of Anti-TNF therapy (adalimumab, infliximab) is recommended to induce clinical remission in children with medium-risk active CD[16]. **Agreement:** 100%.

Expert opinion
- We recommend the use of Anti-TNF to induce remission in children with luminal medium-risk active CD, even if immunomodulatory therapy is previously tolerated. We recommend this same therapeutic approach combined with appropriate surgical intervention for children with perianal disease. **Agreement:** 100%.

The meta-analysis of Ford et al. (2011) including 10 studies with 2,756 patients (adults and pediatrics) demonstrated that Anti-TNF therapy alone or with concomitant therapies was significantly more effective than placebo for patients who failed to achieve symptomatic remission (RR of no remission = 0.87 [95%CI 0.80 to 0,94; *P*=0.0004], 1,598 patients). Results were significant for infliximab and adalimumab, but not for certolizumab pegol. Anti-TNF therapies were also superior to placebo in preventing relapse of luminal CD (RR of relapse = 0.71 [95%CI 0.65 to 0.76])[78].

Maintenance of remission

Corticosteroids

Recommendation

- We recommended against the use of corticosteroids to maintain remission in children and adolescents with medium-risk active CD[63,77]. **Agreement:** 100%.

Biological agents

Recommendations

1. We consider accelerated step-up Anti-TNF therapy for patients with medium-risk CD who had no clinical and biochemical remission 12 weeks after they had started induction therapy[16]. We recommend Anti-TNF therapy to maintain mucosal healing in patients with medium-risk CD who. have achieved clinical response and remission[63]. **Agreement:** 91.7%
2. For patients with medium-risk CD who could not sustain remission with thiopurine or methotrexate, we recommend the use of Anti-TNF[63]. **Agreement:** 83.3%.
3. It is suggested that early use of biologics (adalimumab, infliximab, certolizumab pegol, vedolizumab and ustekinumab) initiated within 2 years of disease diagnosis or "top-down" therapy improves clinical remission, and mucosal healing and avoids relapse rates than late/conventional management[79]. **Agreement:** 100%.
4. We recommend the use of ustekinumab to maintain clinical remission in cases of patients with medium-risk CD who have failed to achieve or maintain clinical remission with Anti-TNF[63]. **Agreement:** 91.7%.
5. Vedolizumab may be considered to maintain clinical remission in patients with medium-risk CD who fail to achieve or maintain clinical remission with Anti-TNF[63]. **Agreement:** 91.7%.

Anti-TNF

The meta-analysis of Li et al. (2019), specifically on pediatric patients, included three eligible randomized controlled trials comparing different dose regimens, 16 prospective cohort studies comparing infliximab with other therapies (adalimumab, exclusive enteral nutrition, or standard of care), and three prospective cohort studies comparing different infliximab regimens. The comparison between infliximab and adalimumab found no significant differences in the outcome of maintenance of endoscopic remission (RR=1.07 [95%CI 0.60 to 1.92]), concluding that both therapies are equally effective and can be recommended to this population[80]. The meta-analysis of real-world data endorsed infliximab efficacy: after 1 year, 83–97% of pediatric patients were still receiving infliximab therapy, and after 2 and 3 years 67–91% and 61–85%, respectively. The likelihood of continuing with infliximab was higher in patients using combination therapy with immunomodulators.

In a clinical trial by Matar et al. (2020), 66 children aged 6 to 17 years who responded to induction with adalimumab (every 2 weeks, either 40 mg in children weighing ≥40 kg or 25 mg/m^2 body surface area in children weighing <40 kg) had their anthropometric parameters evaluated. Patients completed 72 weeks of follow-up, and during this treatment period, the median height z-score improved. A similar effect was observed in children with growth potential (boys under 16 years old, girls under 14 years old). The median weight z score increased as did the body mass index. Sustained clinical and biological remission (weeks 4–72) were positively associated with changes in height z scores[81].

Finally, Ungaro et al. (2020) demonstrated that early use of biologics (adalimumab, infliximab, certolizumab pegol, natalizumab, vedolizumab, ustekinumab, or any combinations of these treatments initiated within 2 years of disease diagnosis or "top-down" therapy) improves clinical remission, and mucosal healing and avoids relapse rates than late/conventional management (treatment initiated after 2 years of disease duration or conventional step-up management, i.e., use after oral immunosuppressants) (clinical remission: OR=3.07 [95%CI 1.59 to 5.94, n=217, *P*=0.00009]; relapse rates: OR=0.18 [95%CI 0.07 to 0.43], n=105, *P*=0.0001])[79].

Anti-integrins

Vedolizumab treatment has been approved in adults, but experience in pediatric patients with CD is still relatively limited. However, vedolizumab is already being used off-label in children with TNF failure. Retrospective observational data in children with IBD previously exposed to Anti-TNF (with primary or secondary loss of response or intolerance to Anti-TNF) have demonstrated the clinical efficacy of vedolizumab in inducing and maintaining remission in pediatric CD[82-84].

Anti-interleukins

Even though the evidence of the efficacy of ustekinumab is not yet consolidated through randomized controlled trials, observational studies have reported its use in the pediatric population. In children with medium-risk active CD, it has been suggested that intravenous ustekinumab induction treatment (3–9 mg/kg for patients with 10 kg to <40 kg body weight or 130–390 mg for patients with ≥40 kg body weight – 16 weeks) may be effective in achieving clinical response and clinical remission[85]. A real-world experience with 52 children and young adults reported that ustekinumab is effective and safe for pediatric patients with IBD[49,86,87].

HIGH-RISK ACTIVE CD
Induction of remission

Corticosteroids

Recommendation

- We recommend considering the use of corticosteroids to induce clinical remission in children with high-risk active CD[63]. **Agreement:** 91.7%.

A very low quality of evidence suggests that pediatric patients with high-risk CD may not achieve clinical response and remission with EEN, and therefore corticosteroids would be the major therapeutic option to induce remission.

Immunosuppressants

Recommendation

- We recommend against the use of thiopurines monotherapy to induce clinical remission in children with high-risk CD[63]. **Agreement:** 100%.

Biological agents

Recommendations

1. In newly diagnosed and therapy naïve pediatric patients with high-risk CD, first-line infliximab combined with azathioprine may be more effective than conventional treatment [exclusive enteral nutrition or prednisolone] associated with azathioprine in achieving short-term clinical and endoscopic remission[88]. **Agreement:** 100%.
2. For children who failed to achieve clinical remission with conventional therapy, we recommend Anti-TNF (infliximab or adalimumab) therapy to induce remission[63]. **Agreement:** 83.4%.

Up-front Anti-TNF therapy should be considered in patients with extensive inflammatory (non-stricturing/ non-penetrating disease involving the proximal small bowel, terminal ileum, and colon) or deep colonic ulcers[16]; as well as for patients who present with stricturing disease[16].

Maintenance of remission

Corticosteroids

Recommendation

- We recommend against the use of corticosteroids to maintain clinical remission in patients with high-risk active CD[63]. **Agreement:** 100%.

Biological agents

Recommendation

1. It is suggested the use of Anti-TNF therapy as first-line therapy to maintain clinical remission in patients with severe inflammatory CD at risk for progressive and disabling disease, and in patients with severe stricturing disease without prestenotic dilation and/or obstructive signs/symptoms[16]. **Agreement:** 91.7%.
2. We recommend the use of ustekinumab to attempt to induce and maintain clinical remission in children with high-risk CD who have failed to achieve or maintain clinical remission with Anti-TNF[63]. **Agreement:** 91.7%.
3. Vedolizumab may be considered to maintain clinical remission in children with high-risk CD who fail to achieve or maintain clinical remission with Anti-TNF[63]. **Agreement:** 91.7%.

Anti-TNF

The first recommendation is based on clinical trials performed in children with high-risk CD, in which the first-line treatment was the combination of Anti-TNF and immunosuppressive therapy in newly diagnosed and treatment-naïve patients[88,89]. "Top-down" therapy is associated with significantly higher rates of symptomatic remission at earlier time points compared to not using early Anti-TNF therapy. A recently published RCT of Jongsma et al. (2022) found that first-line infliximab [five infusions of 5 mg/kg biweekly] combined with azathioprine [2–3 mg/kg] in newly diagnosed and therapy naïve pediatric patients with moderate-to-severe CD had a greater likelihood of maintaining clinical remission in 52 weeks, without the need for treatment escalation 1 year after the start of therapy[88]. Additionally, Ungaro et al. (2020) demonstrated that early use of biologics (adalimumab, infliximab, certolizumab pegol, natalizumab, vedolizumab, ustekinumab, or any combinations of these treatments initiated within 2 years of disease diagnosis or "top-down" therapy) improves clinical remission, and mucosal healing and avoids relapse rates than late/conventional management (treatment initiated after 2 years of disease duration or conventional step-up management, i.e., use after oral immunosuppressants) (clinical remission: OR=3.07 [95%CI 1.59 to 5.94, n=217, *P*=0.00009]; relapse rates: OR=0.18 [95%CI 0.07 to 0.43], n=105, *P*=0.0001])[79]. The *post hoc* analysis of the SONIC trial has suggested that rates of deep remission (clinical remission plus mucosal healing) may be highest in patients with early CD (<18–24 months duration) and treated with Anti-TNF-containing regimens[90]. Real-world data endorsed this evidence demonstrating that, in children newly diagnosed with comparably severe CD, early monotherapy with Anti-TNF enhanced overall clinical and growth outcomes at 1 year compared to early monotherapy with an immunomodulator[91].

Anti-integrin

Retrospective studies assessing the efficacy of vedolizumab demonstrated that severe IBD pediatric patients who were unresponsive, intolerant, or experienced a loss of efficacy with other therapies achieved clinical response and remission when treated with vedolizumab[84,92,93].

Anti-interleukin

A retrospective study found that seven out of ten patients with Anti-TNF refractory pediatric-onset CD required augmented maintenance doses of ustekinumab to achieve clinical response or remission[94]. Aligned with these previous findings, MacDonald et al. (2016) suggested that ustekinumab is effective for induction of clinical remission and clinical improvement in patients with moderate to severe CD with an optimal dosage of 6 mg/kg[84,92,93,95].

TREATMENT OF PERIANAL CD

Biological agents

Recommendation

- We recommend using Anti-TNF as first-line therapy combined with antibiotic therapy or surgical management (or both) to induce and maintain remission in fistulizing perianal CD patients[16]. **Agreement:** 100%.

The literature on the management of perianal CD has focused mainly on adults, with findings that cannot always be extrapolated to the pediatric population. A systematic review included 538 patients with a median age in the intervention of 13.9 years (range 1–18)[96]. Two hundred eighty-nine patients had combined clinical and surgical management. Infliximab therapy had high remission rates, but also a greater number of adverse events. Infliximab therapy resulted in the complete resolution of perianal symptoms in 55% of children when used alone or in concomitant therapies[96]. Similar findings were observed in children with perianal CD, where nearly three-fifths achieved remission with Anti-TNF treatment and approximately 40% of patients maintained remission after 12 months, with a low rate of discontinuation due to serious adverse events. Additionally, more than half of the patients achieved complete fistula closure[97].

Combining seton drainage with infliximab therapy improves the perianal fistula response rates in pediatric patients. A retrospective study with pediatric patients of 14 years old (median age) at diagnosis of fistula who had been managed at induction and maintenance treatment with infliximab after seton placement. Results showed a response rate greater than 90%. After 8 weeks, 77% of patients had a complete response and 15% had a partial response. At the last follow-up, 85% were still responding and 70% were free of perianal symptoms. Most were still on Anti-TNF alfa therapy, but a third had switched to adalimumab. Patients' anorectal function was well preserved and overall satisfaction with treatment was high[98].

CRITERIA TO EVALUATE TREATMENT EFFICACY FOR CD

Imaging remission

Recommendation

- To evaluate treatment response in children and adolescents with luminal small-bowel CD, consider assessing transmural involvement by intestinal ultrasound or magnetic resonance enterography[16]. **Agreement:** 100%.

Magnetic resonance enterography (MRE) is a non-invasive, radiation-free modality with high diagnostic accuracy in the diagnosis of active inflammation in pediatric patients with IBD. MRE is preferred over computed tomography (CT) and fluoroscopy with barium X-rays, because of high diagnostic accuracy and the lack of radiation involved. In a recently published diagnostic meta-analysis, 687 children were evaluated and the sensitivity and specificity of MRE to identify active CD were 83% (95%CI 75–89%) and 93% [95%CI 90–95%], respectively. Based on the per-patient analysis, the summary sensitivity was 86% (95%CI 78–91%) and specificity was 91% (95%CI 82–96%)[99]. Capsule endoscopy, MRE, and small bowel intestinal contrast ultrasound also demonstrated similar diagnostic yields for the detection of small bowel CD in both suspected and established CD[100]. Church et al. (2015) published a meta-analysis on the MRE parameters that more accurately detect inflammation and intestinal damage in children and adults with CD. Sixty-two studies demonstrated the diagnostic accuracy of 22 signs of MRE in identifying inflammation and/or intestinal damage. High sensitivity was observed for wall enhancement, wall thickness, T2 wall hyperintensity, and motility, in addition to a high specificity for T2 wall hyperintensity and mucosal lesions. These results underscore the usefulness of MRE in the assessment of inflammation and damage in CD[101]. MRE has a high specificity to detect colon disease in CD, while the sensitivity is low. Therefore, the test has a high value to rule in CD and considering the higher sensitivity rate of the test in pediatrics, it has the potential to be used as a first-line investigation[102].

The assessment of the diagnostic performance of the MRE and ultrasound was compared to reference standards. The reference standards for active inflammation include clinical indices such as the Crohn's Disease Activity Index (CDAI) or Harvey–Bradshaw Index (HBI), serum inflammatory markers such as C-reactive protein (CRP), and endoscopic scores such as the CDEIS or the SES-CD. Compared with the reference standard, the MRE showed a sensitivity of 93.0% and specificity of 94.6%, while ultrasound showed a sensitivity of 84.1% and specificity of 82.9% compared to the reference standard[103]. Whilst the evidence is stronger to support MRE, only two studies used this exam, and, therefore, additional studies are needed to confirm the diagnostic performance of US for IBD in children[103].

CLINICAL RESPONSE AND REMISSION

Recommendations
Expert opinions

1. Clinical response of children with CD is best reflected by a decrease in PCDAI by at least 12.5 points[104]. ***Agreement:*** 91.7%.
2. We recommend the PCDAI assessment for clinical remission in children with CD (<10 points or <7.5 excluding the height item). **Agreement*:*** 100%.

The pediatric Crohn's disease activity index (PCDAI) has been the standard tool to assess clinical disease activity and response to treatment in clinical trials of pediatric Crohn's disease since this index can incorporate symptoms, signs, laboratory tests, and endoscopic measures (105) . The STRIDE-II consensus recommends considering a 12.5-point decrease in PCDAI as a clinical response. A similar recommendation was made for the clinical remission parameters, which indicate a PDCAI <10 points or a PCDAI <7.5 points if the patient's height is excluded. Corroborating with this recommendation, Turner et al. (2017) showed that the 4 versions of the PCDAI - PCDAI, weighted PCDAI [wPCDAI], abbreviated PCDAI [abbrPCDAI], and the short PCDAI [shPCDAI]- have a reasonable correlation with the Simple Endoscopic Score for Crohn's Disease (SES-CD) and C-reactive protein (CRP). The wPCDAI and PCDAI were superior to the shorter versions when compared to blood tests. In addition to correlation with the reference parameters, the best cut-off points to identify endoscopic mucosal healing was <12.5 points for wPCDAI (sensitivity 58% and specificity 84%) and <10 for PCDAI (sensitivity 63% and specificity 77%)[106]. Studies conducted by the same group of authors also demonstrated that remission by wPCDAI was best defined as <12.5 points (sensitivity 94% and specificity 93%) and response as a drop of at least 17.5 points (sensitivity 86% and specificity 76%). The clinical and endoscopic remission cutoff score for PCDAI was found to be <10 points or <7.5 without the height item[20,107].

Endoscopic response and remission

Endoscopic scores are the gold standard tool for measuring CD activity and are used in clinical trials to measure pharmacological effectiveness in inducing and maintaining mucosal healing[108]. The CDEIS and the SES-CD are the most used tools in CD patients without bowel resection. Complete mucosal healing in newly diagnosed CD is a predictor of sustained, steroid-free remission for up to 4 years[109]. Additionally, there is evidence to support that endoscopic remission should be an early treatment target, as achieving remission after 3 months of Anti-TNF therapy was predictive of a long-term (1 year) maintenance of remission[110]. Achievement of endoscopic remission is also associated with an increased likelihood of favorable long-term outcomes, which provides further support to the treat-to-target algorithm in addition to its efficacy in inducing endoscopic remission itself[111].

When using biological therapy, the endoscopic mucosal inflammation may be assessed, even if symptom control is maintained, as mucosal healing has been correlated with reduced hospitalization and surgeries. Additionally, endoscopy and/or colonoscopy are performed to confirm the diagnosis of CD and evaluate the severity of the disease, determine the effectiveness of treatment, and conduct surveillance for carcinogenesis[113-114].

PATIENT MANAGEMENT POST INITIAL TREATMENT

Immunosuppressants

Recommendation

- Assessment of mucosal healing in the first year of treatment should be performed in CD patients who are in clinical remission with thiopurine or methotrexate as maintenance therapy to assess the need to modify therapy[63]. **Agreement:** 91.7%.

Mucosal healing (MH) is the goal of the "treat to target" strategy in CD, which seeks to prevent disability[115]. Mucosal healing minimizes the risk of developing disease complications, prolongs steroid-free survival, and reduces hospitalization and the need for surgical intervention. Achieving mucosal healing aimed at resolving subclinical inflammation is associated with the prevention of stenosing and penetrating complications[116]. Based on the potential benefits associated with mucosal healing, the Canadian Association of Gastroenterology consensus suggested that assessing this outcome was a useful management strategy in patients receiving immunosuppressant therapy[63]. The SONIC study was the first to propose mucosal healing as a treatment target, qualified by resolution of ulceration from baseline to week 26. In addition, higher rates of mucosal healing were demonstrated with combined infliximab and azathioprine therapy compared to monotherapy[117]. The meta-analysis by Shah et al. (2016) included 12 prospective cohort studies assessing 673 patients. They found that patients who had achieved mucosal healing had significantly increased rates of long-term clinical remission (OR, 2.80; 95%CI, 1.9–4.10) and maintenance of mucosal healing (OR, 14.30; 95%CI, 5.57–36.74)[118].

Biological agents

Recommendation

- We recommend early proactive therapy drug monitoring (TDM) followed by dose optimization (when necessary) in patients on Anti-TNF therapy. The use of TDM should be considered to guide empirical dose escalation or therapy switching[16]. **Agreement:** 83.4%.

For pediatric patients with CD who have not responded to Anti-TNF induction therapy or have lost response to maintenance therapy, treatment optimization guided by TDM may be effective[63]. Specifically, the first proactive TDM is recommended immediately before the third injection (4 weeks after the first dose) of adalimumab and the fourth infusion of infliximab (6th or 14th week after the first dose)[16]. Patients at risk for accelerated infliximab clearance during induction (i.e., children <30 kg, those with extensive disease, and those with low serum albumin) may have their first proactive TDM at the second or third infusion. The PAILOT trial demonstrated that proactive TDM in children naïve to biological agents but who had responded to adalimumab induction resulted in higher sustained corticosteroid-free clinical remission rates compared with those managed with reactive TDM (82% and 48%, respectively; P=0.002)[119]. Additionally, when compared with the reactive TDM group, the proactive TDM group saved 0.1960 QALYs at a lower cost of USD2021 over a 3-year time frame. Adalimumab drug cost is the most influential factor. Proactive TDM for adalimumab is proven to positively impact the QALYs at a lower cost[120]. Serum adalimumab trough levels at 16 weeks were significantly higher in pediatric patients with CD who achieved mucosal healing and histological remission. TDM may guide in optimizing treatment efficacy and better target mucosal healing[121]. Therapeutic drug monitoring-based treatment enables longer drug retention time, lower hospitalization rate per patient per year, and a higher treatment intensification rate. The retention time is higher in adalimumab compared to infliximab. These findings reflect the utilization of Anti-TNFα agents, with several additional favorable outcomes[122].

SURGICAL MANAGEMENT FOR PEDIATRIC PATIENTS WITH CROHN'S DISEASE

CRITERIA FOR INDICATION OF ELECTIVE AND URGENT SURGERY IN CD

Elective surgery

Recommendation

- Elective surgery for children depends mostly on the nutritional status and severity of the disease. Despite the lack of evidence, surgeons should consider pubertal age and height velocity for bone age to be reduced as well as the previous history of the disease in the patient[123,124]. **Agreement:** 100%.

Surgical procedures performed on pediatric patients are mostly characterized as elective procedures. The decision to proceed with the surgery must be based on a diagnostic evaluation and a close relationship between the surgeon, gastroenterologist, and family[125]. After conducting surgery, the growth and nutrition of pediatric patients improve (by 6 and 12 months after surgery). However, there is a high rate of relapse in these patients. Improving the patient's growth and nutrition before recurrence can be beneficial, particularly during puberty, and may justify surgery in children who do not respond to medications[126]. Elective ileocecal resection is a valid treatment option once it significantly benefits the clinical remission and growth. The Z score height for age postoperatively was improved in children who were at the time of surgery younger than 16 years of age (MD = 0.232 SD; P=0.029) and 55.9% of these children achieved clinical remission[127].

When making the decision to proceed with colectomy in children, the surgeon must assess whether the child's growth is within the parameters of normality, schooling, previous medical treatments, and disease characteristics. Therefore, the most appropriate time is either pre-pubertal or during puberty if height-for-bone

age velocity is reduced over a period of 6 to 12 months despite appropriate medical and nutritional therapy[123]. Elective surgery is not indicated in the following situations: 1) in the absence of refractory disease; 2) for inducing remission in early or mid-puberty in a child with localized CD who is refractory to medical therapies; and 3) due to refusal, intolerance, or increased risks of maintenance medications such as immunomodulators or Anti-TNF agents. In patients with stable health and age-appropriate nutritional status, the surgeon may consider elective resection with primary anastomosis as an effective approach[124].

Urgent surgery

Recommendation

- Emergency surgery is recommended in cases of unsuccessful treatment of intra-abdominal abscess with antibiotics and/or percutaneous drainage; rare cases of complete intestinal obstruction or suspected intestinal ischemia; and patients with colonic CD who present acute severe colitis and clinical deterioration or failure to improve within approximately 1 week[123]. **Agreement:** 83.4%.

Abscess cases are commonly identified during a CT scan and by signs and symptoms of fever, leukocytosis, and pain in the CD set. Drainage, antibiotics, and bowel rest are appropriate in the setting of a stable patient. In emergency situations, abdominal surgery may be complicated by adhesions, fistulas, and severe active inflammation. Other situations of urgent or emergent surgery include: the absence of response to conservative treatment of abscesses, perforation, massive hemorrhage, or suspected intestinal ischemia[123]. A special situation is obstruction with capsule endoscopy: surgical capsule retrieval is recommended if retained after 2 weeks or at any time if the patient presents with pain, vomiting, or other signs of bowel obstruction[125].

MANAGEMENT OF ABDOMINAL CD

Venous thromboembolism prophylaxis

Recommendation

- We recommend caution with patients with CD requiring surgery because they are at a higher risk for venous thromboembolism and prophylaxis measures should be considered unless contraindicated[123]. **Agreement:** 100%.

Venous thrombotic events (VTE) are one of the most common short-term complications in pediatric patients. Therefore, awareness of risk factors for VTE is crucial in pediatric CD. Due to the inflammatory nature of the disease, patients may have risk factors that directly impact VTE, such as steroid use, central venous catheter, parenteral nutrition, prolonged periods of immobilization, active inflammation particularly with colonic involvement, underlying thrombophilia, surgery, hospitalization, or a hypercoagulable state[128].

A meta-analysis with 7,450,272 IBD pediatric patients showed an increased VTE risk (P=0.02) compared to individuals without IBD[129]. The incidence of VTE was related to the portal vein thrombosis (P=0.04), deep vein thrombosis (P=0.03), central venous catheter-related thrombosis (P=0.23) and thromboembolic events (P=0.02). Patients with IBD were more susceptible to VTE risk than those without IBD (OR=2.99 [95%CI 1.45 to 6.18])[129]. There are no published studies on the efficacy and safety of thromboprophylaxis in children with CD undergoing surgery. When indicated, anticoagulation used for the treatment of children VTE are low molecular weight heparins and vitamin K antagonists. The use of direct oral anticoagulants for the treatment or prevention of VTE has not been studied in this pediatric population yet[128]. The use of compression stockings and early mobilization should be standard[123,125].

Nutrition

Recommendation

- Preoperative nutritional support is mandatory in severely undernourished patients and a return to diet/enteral nutrition should be started as soon as the patient can tolerate it in the postoperative period[130,131]. **Agreement:** 83.4%.

Children with refractory medical disease, who develop complications (abscesses) or do not tolerate medical therapy, or both, are candidates for surgery. Nutritional status is a key element for favorable surgical outcomes. Therefore, perioperative nutritional therapy is an important part of care of children and adolescents with CD who have indications for surgical procedures[67,132,133]. It has been demonstrated that malnutrition is a relevant risk factor for postoperative complications, and enteral and parenteral nutritional therapies were efficient in reducing postoperative morbidity[134].

Corticosteroids

Recommendation

- In cases of surgical indication, corticosteroids should not be used to maintain remission due to the risk of complications. Patients should be in the weaning process. For patients with a recent history of chronic steroid use and undergoing major abdominal surgery, perioperative steroid replacement therapy is indicated[124]. **Agreement:** 83.4%.

The perioperative management recommended for patients with CD who will undergo surgery, especially abdominal surgery, indicates the nutritional approach as the primary therapy, especially in children where the adverse consequences of corticosteroid therapy are proportionally greater[135]. Nutritional strategies are part of the preoperative optimization strategy. The study by Li et al. (2015) demonstrated that patients in EEN and weaning from steroids had a lower rate of total and specific infectious complications (wound infection, abscess, and leakage) when compared to the control group (weaned from steroids, but not using EEN) (EEN and weaning from steroids:19%; control group: 29%)[136]. In addition, weaning from steroids, if possible, drainage of percutaneous abscesses if applicable, and intravenous antibiotics if indicated are recommended[137]. A meta-analysis found that risk factors for adverse surgical outcomes were steroid use, low albumin, preoperative surgical history, and preoperative abscess[138]. In adults, "stress doses" of steroid doses are considered the standard of perioperative care for patients on long-term steroid therapy. However, the literature is scarce to support this practice, but the available studies showed no beneficial effect of preoperative steroid stress dose[123].

Biologic agents

Recommendation

- Cessation of Anti-TNF therapy, vedolizumab, or ustekinumab as a preoperative treatment in patients with CD having abdominal surgery is not mandatory[132]. **Agreement:** 83.4%.

Evidence in the pediatric population to support this recommendation is still lacking. Therefore, for adults, the use of Anti-TNF prior to the surgery was not a predictor or has not demonstrated an increased risk for complications in the postoperative. Data on the impact of pre-and postoperative Anti-TNF agents on surgical complications are unclear. There are recommendations to discontinue infliximab 4 to 6 weeks before surgery, but the literature has not demonstrated an increased risk of complications in patients with more recent exposure[124,139,140]. In a recently published meta-analysis, patients who had received Anti-TNF and anti-integrins treatment were not at increased risk of postoperative infectious or overall postoperative complications compared to patients who did not receive biological therapy preoperatively[141-144].

MANAGEMENT OF FISTULIZING AND PERIANAL CD

Clinical management of perianal abscess

Recommendations

Expert opinions

1. We recommend early assessment of the presence of an abscess. If present, drainage should be discussed with a surgeon[124]. **Agreement:** 100%.
2. After effective drainage of the abscess of patients with complex perianal CD, we recommend the use of Anti-TNF as primary induction therapy in combination with surgical intervention[124]. **Agreement:** 91.7%.
3. We recommend the use of antibiotics as adjunctive treatment to cease the abscess or fistula from draining. In patients with a simple perianal fistula, we recommend the use of metronidazole (20–30 mg/kg/day) or ciprofloxacin (10–20 mg/kg/day)[124]. **Agreement:** 91.7%.

The meta-analysis (children and adults) by Zaboli et al. (2017) corroborates previous findings on the efficacy of Anti-TNF as a medical treatment for fistulizing CD. Anti-TNF was notably more effective compared to placebo in maintaining fistula closure (RR=2.36; 95% confidence interval: 1.58–3.55; $P<0.0001$), whereas Anti-TNF was not superior to placebo in improving fistula or fistula closure. Similar findings were observed for adalimumab and certolizumab pegol. Both were effective in maintaining fistula closure in adult patients[145].

The management of perianal CD is essential due to the possible adverse effects on growth, development, and quality of life. The literature on the management of perianal CD has focused mainly on adults, with findings that cannot always be extrapolated to the pediatric population. A systematic review was performed on 538 patients with a median age in the intervention of 13.9 years (range 1–18). Of these, 289 patients had combined clinical and surgical management. Seton placement allowed complete healing in 28.6% of children. Similar results (28.5%) were seen in children undergoing fecal diversion. Infliximab therapy had high remission rates, but also a greater number of adverse events. Infliximab therapy resulted in the complete resolution of perianal symptoms in 55% of children (monotherapy or combination therapy)[96].

MANAGEMENT OF CD WITH ENTEROVAGINAL, ENTEROVESICAL, AND/OR ENTEROENTERIC FISTULA

Enterovaginal

Recommendation
Expert opinion

- When there is a small bowel fistula or a sigmoid-gynecological fistula, we recommend resection of the diseased intestinal segment. A diverting ostomy and an advancement flap may be necessary if conservative treatment fails to correct the rectovaginal fistula. An interposition of the gracilis muscle has successfully been reported in the treatment of recurrent fistulizing diseases[124]. **Agreement:** 91.7%.

Enterovesical

Recommendation
Expert opinion

- The enterovesical fistula should be treated by resection of the diseased segment and primary closure[124]. **Agreement:** 100%.

Enteroenteric

Recommendation
Expert opinion

- CD enteroenteric fistula can be surgically treated by resecting the diseased segment of the intestine and closing the connection with the unaffected segment[124]. **Agreement:** 100% (AMIL-DIAS 2017).

Patients with enterocutaneous fistulas should ideally refrain from surgical resection until clinical optimization by percutaneous drainage of sepsis, correction of electrolyte abnormalities, nutritional support, and wound care in the short term[146]. While high-volume fistulae usually require surgery for symptom control, low volume enterocutaneous fistulae may be controlled with immunomodulator and biological therapy[26]. Enteroenteric and enterovesical fistula often require resective surgery. Enteroenteric fistulae particularly are strongly recommended, especially if associated with abscess and bowel stricture and if they cause excessive diarrhea and malabsorption[112,147,148]. Enterovaginal and enterovesical fistulae should be managed jointly with medical control of inflammation and surgical resection[26]. Symptomatic enterovaginal fistulas generally require surgery, such as diverting ostomy. Fistulas between the small bowel or sigmoid colon and the female genitalia can generally be treated with a resection of the involved bowel[149]. In patients with CD and evidence of fistulizing disease, referral for surgical management is suggested when there has been an inadequate symptomatic response to medical management strategies[148].

MEDICAL MANAGEMENT FOR PEDIATRIC PATIENTS WITH ULCERATIVE COLITIS

MILD UC
Induction of remission

Probiotics

Recommendation
- In pediatric patients with mild active UC, there is little to no effect with the use of probiotics for induction[150]. **Agreement:** 83.3%.

The meta-analysis of Kaur et al. (2020) assessed the efficacy of probiotics compared with placebo or standard medical treatment (5-aminosalicylates, sulphasalazine, or corticosteroids) for the induction of remission of adult and pediatric patients with active UC. The subgroup analysis by age found probiotics to be beneficial in both adults (RR=1.49 [95%CI 1.07 to 2.08]) and children (RR=3.83 [95%1.69 to 8.66]), with a slightly greater effect in the pediatric population (test for subgroup differences: $Chi^2 = 4.42$, P=0.04, I^2=77.4%). However, the evidence included in this analysis had low or very low quality and the data regarding children were based on two studies[150]. Peng et al. (2019) also conducted their meta-meta-analysis including adults and children. The results indicated that the remission rate was significantly higher in the group using probiotics combined with aminosalicylic acid compared to the group using aminosalicylic acid alone (RR=1.40 [95%CI 1.27 to 1.53, P=0.000]). The subgroup analysis of the severity of the disease found that probiotics combined with aminosalicylic acid can significantly improve the remission rate in both mild to moderate (RR=1.33 [95%CI 1.16 to 1.54, P=0.000]) and active stage (RR=1.40 [95%CI 1.27 to 1.64, P=0.000) UC. The results demonstrated by this study pooled adult and pediatric data into a single analysis[151].

Salicylic derivatives

Recommendation
- Oral 5-ASA compounds are recommended for mild to moderate UC, and rectal monotherapy is recommended for mild ulcerative proctitis[19]. **Agreement:** 100%.

The various forms of administration of mesalazine remain the standard first-line treatments for uncomplicated ulcerative colitis[152]. Meta-analyses of randomized, controlled trials have shown its superiority over both placebo and rectal steroids in the induction treatment of UC[153]. For the treatment of proctitis, topical mesalazine is more effective than topical steroids and is thus the agent of choice for inducing remission[154]. Despite the consolidated efficacy of 5-ASA, it can cause exacerbation of colitic symptoms due to intolerance to 5-ASA, mainly in pediatric patients, in a median time of 10 days[155]. The different regimens of mesalazine have similar efficacy but it is hypothesized that patients would be more compliant with to once-daily treatment than twice-daily – this hypothesis could not be demonstrated in the randomized controlled trial conducted with children[156].

Corticosteroids

Recommendation
- If 5-ASA failed to improve the symptoms of mild UC (oral or rectal), oral steroids are recommended[19]. **Agreement:** 100%.

Studies have reported that children with UC treated with oral steroids, once started on maintenance therapy, will remain in remission on short-term (1-3 months) in more than 50% of cases[157-159]. Less than a third will require surgery[8,157,158]. Higher rates of steroid dependence are reported in children when compared to adults (45% vs 8%, respectively)[160]. Children are more vulnerable to steroid-related complications, including osteopenia, acne, glaucoma, and cataract; these major side-effects can decrease a patient's long-term quality of life[161].

Immunosuppressants

Recommendation
- Immunosuppressive medications should not be used for induction of remission in children with mild UC[19]. **Agreement:** 100%.

Biological agents

Recommendation
- Mild pediatric UC patients should not be treated with biological agents for induction of remission[19]. **Agreement:** 100%.

Maintenance of remission

Salicylic derivatives

Recommendations
1. 5-ASA compounds are recommended for mild UC as a first-line maintenance treatment[19]. **Agreement:** 100%.
2. Pediatric mild ulcerative proctitis is a rare phenotype – rectal monotherapy with 5-ASA should be reserved for those cases[19]. **Agreement:** 100%.

The European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology, and Nutrition recommend using mesalazine regimes as first-line therapy for maintaining remission of mild-to-moderate UC. In cases of non-response, oral mesalazine may be combined with mesalazine enemas and/or switched to locally active steroids[19]. In cases of proctitis, if mesalazine alone does not induce remission, it should be combined with topically or systemically administered steroids. Left-sided ulcerative colitis with mild to moderate inflammatory activity that is unresponsive to mesalazine can be treated with oral budesonide-MMX .

Corticosteroids

Recommendation
- We recommend against the use of Corticosteroids to maintain remission in mild pediatric UC patients[19]. **Agreement:** 100%.

Immunosuppressants

Recommendation
- Immunosuppressive drugs are not recommended for the maintenance of remission in mild pediatric UC[19]. **Agreement:** 92.3%.

MODERATE UC

Induction of remission

Salicylic derivatives

Recommendation
- Induction therapy with oral 5-ASA compounds is recommended for children with moderate UC. Combined oral and rectal 5-ASA therapy has more benefits than oral 5-ASA monotherapy[19]. **Agreement:** 100%.

A Cochrane meta-analysis of studies conducted in adults demonstrated a significant relative risk of successful induction of clinical and endoscopic remission with 5-ASA[153]. Several studies have reported that more than one-third of pediatric patients with UC were successfully treated with 5-ASA at approximately 1 year of follow-up[8,162,163]. A clinical trial in mild to moderate pediatric ulcerative proctitis demonstrated that mesalazine suppositories were associated with improved disease activity in 3 and 6 weeks[164]. By combining oral and rectal therapy with 5-ASA, clinical outcomes improved (i.e., bleeding cessation), in addition to a better quality of life[37,165,166].

Corticosteroids

Recommendation
- For moderate pediatric UC that does not respond to 5-ASA (oral + rectal), oral steroids should be considered second line treatment. When a disease is at the high end of the moderate range, these drugs can be considered as first-line treatment[19]. **Agreement:** 100%.

Biological agents

Recommendation
1. If the patient has steroid-dependency or chronically active UC that has not responded to 5-ASA and thiopurines, we recommend infliximab for induction of remission in moderate disease[19]. **Agreement:** 84.6%.
2. In pediatric patients with moderate-to-severe UC, it is suggested that adalimumab as induction therapy is effective in achieving remission rates[71]. **Agreement:** 100%.
3. We recommend vedolizumab for chronically active or steroid-dependent patients as second-line biologic therapy after Anti-TNF failure[19]. **Agreement:** 92.3%.

Infliximab is effective in treating moderate/severe UC in adults. However, evidence from pediatric studies is still limited. Based on uncontrolled studies in children with moderate to severe UC, the short-term (mean 2.2 weeks) response and remission rate of infliximab were 75% (95%CI 64–83%) and 63% (95%CI 47–76%), respectively. Over the long term (mean 7.9 months), these rates declined, with response and remission achieved in 43% (95%CI 33–55%) and 57% of cases, respectively[167]. In the ENVISION I phase 3 randomized controlled trial with pediatric patients with moderate-to-severe UC, adalimumab administered concomitantly with oral corticosteroids or immunosuppressants showed remission rates significantly higher when compared with placebo (partial Mayo score remission at week 8: 41 [53%] of 77 patients; $P<0.0001$). At week 8, 80% of children who were responders continued to the maintenance period. 84% patients were randomly assigned to receive high-dose (0.6 mg/kg each week) or standard-dose maintenance adalimumab treatment (0.6 mg/kg each other week) and 16% patients received placebo. Similarly, full Mayo score remission at week 52 in children who were week-8 responders was reported in a significantly higher proportion of patients who received high-dose maintenance adalimumab (14 [45%] of 31 patients) versus external placebo at week 52 (18·4%; $P=0·0001$). The most common adverse events were headache, anemia, and ulcerative colitis flare during the induction period and ulcerative colitis flare, headache, and nasopharyngitis during the maintenance period. Therefore, adalimumab is an efficacious and safe treatment option for children with moderate-to-severe ulcerative colitis, although the study evaluated a low number of patients of an uneven regional distribution of patients and compared with adult placebo controls[71]

Evidence from adult studies has shown that vedolizumab is effective in inducing and maintaining remission[168]. A retrospective observational study describing the use of vedolizumab in 64 IBD children found that one-third of patients achieved steroid- and EEN–free remission at week 14 and sustained remission at 1 year. Specifically in children with UC, the clinical remission rate was 36.6% and the corticosteroid-free remission rate was 39% at the last follow-up. Importantly, 22% of patients discontinued vedolizumab at a median of 14 weeks, mainly due to poor response. Mucosal healing was observed in 15.8% of patients who had initial and follow-up colonoscopy evaluations[92]. The retrospective case series of Schneider et al. (2018) demonstrated similar results, but in patients who started vedolizumab therapy after Anti-TNF failure or intolerance[84].

Maintenance of remission

Salicylates derivates

Recommendation
- We recommend 5-ASA maintenance for children with moderate UC. Consider using a combination of oral and rectal 5-ASA therapy instead of oral 5-ASA monotherapy[19]. **Agreement:** 100%.

Findings from the meta-analysis by Marshall et al. (2012) with UC adults and children demonstrated that 5-ASA rectal therapy is effective and safe for maintaining remission of mild to moderately active distal UC. However, the effectiveness of combination therapy (oral and rectal) for maintaining remission has not been assessed and may be evaluated in future studies[169]. Finally, several data reported that more than a third of pediatric patients with UC were successfully treated with 5-ASA at approximately 1 year of follow-up[8,162,163].

Biological agents

Expert opinion

- Infliximab is the preferred second-line medical therapy for steroid-refractory patients who have failed thiopurine maintenance therapy, unless vedolizumab bridging is being considered[22]. **Agreement:** 92.3%.

Recommendation

- In pediatric patients with moderate-to-severe UC, it is suggested that adalimumab is effective in maintaining remission rates[71]. **Agreement:** 90%.

In a multicenter cohort study of 332 pediatric patients with UC, 52 (16%) received infliximab (23% <3 months from diagnosis, 38% 3–12 months, 38% >12 months), concomitantly with other therapies, for a median follow-up of 30 months. The inactive corticosteroid-free disease was observed in 38% and 21% of patients at 12 and 24 months, respectively. At 24 months, 61% of patients avoided colectomy[170]. In the ENVISION I phase 3 randomized controlled trial with pediatric patients with moderate-to-severe UC, adalimumab (0.6 mg/kg weekly) administered concomitantly with oral corticosteroids or immunosuppressants showed remission rates significantly higher compared with placebo (full Mayo score remission at week 52: 23 [37%] of 62 patients; *P*=0•0001)[71]. If remission is induced under treatment with infliximab and azathioprine, remission maintenance treatment can be performed with that combination or with either of these two drugs alone (depending on what the patient was previously taking)[152].

ACUTE SEVERE COLITIS (ASC)

Induction of remission

First-line treatment

Recommendation

- ASC should be treated with intravenous steroids[22]. Agreement: 100%.

Intravenous corticosteroids have been the mainstay of treatment for ASC[171,172]. It remains controversial whether children are at higher or lower risk for colectomy when compared to adults[173]. Turner et al. (2008) evaluated the predictors of response to intravenous corticosteroid therapy in ASC: 28% of the children required hospitalization for intravenous corticosteroid therapy, of which 53% responded, predictors associated with failure of corticosteroid therapy were CRP and the number of nocturnal stools on days 3 and 5 after admission; the cumulative colectomy rates at discharge, 1 year, and 6 years were 42%, 58%, and 61%, respectively. From these findings, the authors concluded that the PUCAI determined on day 3 (>45 points) should be used to screen patients with a probability of corticosteroid failure and on day 5 (>70 points) to dictate the introduction of second-line therapy[10].

Salicylates derivates

Recommendations

1. We recommend the discontinuation of mesalazine compounds (oral and rectal) upon hospital admission, aiming to exclude intolerance[22]. **Agreement:** 100%
2. We recommend for the hospital discharge of pediatric patients with ASC exclusive mesalazine maintenance therapy while weaning steroids if the response to steroids was rapid and the patient was mesalazine naïve before admission[22]. **Agreement:** 92.3%.

After discharge from pediatric ASC, 14% of patients became steroid dependent and 51% of initial IVCS responders lost clinical response despite maintenance therapy with mesalazine or thiopurine during the subsequent 1 year[174]. Azathioprine was shown to be superior to mesalazine in maintaining post-intravenous corticosteroid remission[175-177].

Corticosteroids

Recommendation

1. We recommend intravenous steroids for induction of remission in pediatric patients with ASC[19]. **Agreement:** 100%.
2. We recommend intravenous methylprednisolone as the initial treatment at admission. Higher doses of intravenous methylprednisolone are indicated for severe cases and for children who have failed oral steroids before admission[19,22]. **Agreement:** 91.7%.
3. Before discharge, methylprednisolone should be switched to the biologically equivalent dose of oral prednisone[22]. **Agreement:** 91.7%.
4. When children are not responding to intravenous corticosteroids after 3 days of therapy, consider the assessment of cytomegalovirus (CMV) colitis[22]. **Agreement:** 83.3%.

First-line treatment of patients with ASC is intravenous systemic glucocorticoid therapy[172,178]. Approximately 60% to 70% of patients with a moderate to severe UC flare who have not responded to oral prednisone will respond to the intravenous formulation. Intravenous steroids reduced the mortality rate from 24% to 7%[105,178,179]. However, as it has been previously discussed and recommended, steroids should only be given on a short-term basis and not as maintenance therapy[152]. Intravenous corticosteroid uses in high doses and for a short period can be effective[180]. A meta-analysis of pediatric patient data showed a pooled estimate of a 34% failure rate (95%CI: 27–41%), slightly higher than that seen in adults[173]. Also, intravenous methylprednisolone should be used as initial treatment at admission at a dose of 1mg per kg per day. Higher doses of 1,5 mg per kg per day in 1 or 2 doses should be reserved for the more severe and for children who have failed oral steroids before admission[22].

The treatment of ASC is based on early recognition of signs and symptoms, in addition to the rapid and effective administration of intravenous corticosteroids. If no clinical or biochemical improvement is observed on the third day of therapy, rescue treatment with infliximab or cyclosporine should be initiated[181].

Biologics agents

Recommendations

1. For Anti-TNF-naïve children with ASC who have not responded to intravenous corticosteroids, we recommend infliximab as a second-line treatment[22]. **Agreement:** 100%.

2. Infliximab should be continued as a maintenance treatment for pediatric patients after discharge if they have responded to infliximab during ASC[22]. **Agreement:** 92.3%.

The efficacy of infliximab in 10 corticosteroid-refractory pediatric ASC patients was demonstrated by Aloi et al. (2015). They found that 80% responded to therapy (20% underwent colectomy during the flare); however, during follow-up, 50% of these required elective colectomies[182,183].

Immunosuppressants

Recommendation

1. In selected cases of ASC when a third-line therapy is used still during the management of ASC flare, we suggest the use of calcineurin inhibitors (tacrolimus or cyclosporine)[22]. **Agreement:** 83.3%.
2. We recommend weaning off cyclosporine or tacrolimus (if initiated during ASC treatment) as a bridge to thiopurine or other maintenance medication (such as vedolizumab) to reduce adverse events[22]. **Agreement:** 83.3%.

The use of cyclosporine as salvage therapy in steroid-refractory children with UC had a short-term success rate (i.e., the patient had no indication for colectomy) of 81% and a long-term success rate of only 39%. When immunomodulatory therapy is introduced at hospital discharge, the long-term success rate increases to 71%[184,185]. It is important to emphasize the long-term toxic profile of cyclosporine. In adults, about 15% of patients treated with cyclosporine experienced significant adverse events, including nephrotoxicity, serious infections, seizures, anaphylaxis, and, very rarely, death. Therefore, it should only be given as a transition to thiopurine therapy. Cyclosporine should be discontinued as soon as thiopurine proves to be effective: usually after 3 to 4 months. In cases of patients who at hospital admission were already on thiopurine, infliximab should be the therapy of choice[186,187].

Compared with oral cyclosporine, tacrolimus has better bioavailability and less toxicity[188]. In adults, tacrolimus, at levels of 10–15 ng/mL, may be as effective as cyclosporine[189]. In children, data are very scarce and demonstrate short-term success rates of 79% and long-term success rates of only 9%[190-192]. In addition, tacrolimus is a potential therapy when used concomitantly with vedolizumab. Hamel et al. (2018) demonstrated by real-world pediatric data that tacrolimus combined with vedolizumab when initiated for acute illness severity during hospitalization or ongoing flare-up during outpatient care is effective in preventing colectomy or surgery related to inflammatory bowel disease[193].

Nutritional management

Recommendations

1. We do not recommend a specific nutritional therapy for ASC cases[22]. **Agreement:** 83.3%.
2. If possible, a regular diet should be continued in most ASC cases. Enteral (or parenteral in those not tolerating enteral) nutrition may be used if oral feeding is not tolerated[22]. **Agreement:** 83.3%.
3. Oral or enteral feeding is contraindicated in cases of megacolon, or when surgery is imminent[22]. **Agreement:** 100%.
4. We recommend iron supplementation after discharge for patients diagnosed with anemia. We recommend the use of intravenous iron for specific cases such as severe anemia, active disease, or if the child cannot tolerate oral iron supplementation[22]. **Agreement:** 83.3%.

Studies in adults indicate that bowel rest does not increase the response and remission rate in ASC[194-196]. Therefore, there is no rationale for keeping the patient fasting, in addition to not being well tolerated by children. Nil per os is recommended only in cases of abdominal surgery or any other case where toxic megacolon or perforation is suspected[105]. Parenteral nutrition may be considered during the acute inflammatory phase in selected malnourished patients[197].

Antibiotics

Recommendations

1. We do not recommend the use of antibiotics as standard treatment when managing children with ASC. We consider the use of this therapy in cases of suspected *Clostridioides difficile* or other bacterial infection[22]. **Agreement:** 91.7%.
2. In the absence of oral vancomycin, consider using oral metronidazole at a dose of 7,5 to 10 mg per kg per dose 3 times daily (to a maximum of 2 g per 24 h) for 10 to 14 days[22]. **Agreement:** 83.3%.

Patients with UC have a higher risk of -CD-associated disease. *C. difficile* infections in IBD are predominantly confirmed within 48 hours of admission, suggesting that most were acquired before hospitalization[198].

A retrospective study by Turner et al. (2014) found that the use of an oral wide-spectrum antibiotic (metronidazole, amoxicillin, doxycycline, and vancomycin) cocktail in pediatric UC seems promising in half of the patients, refractory to other salvage therapy[199]. However, this "cocktail" of antibiotics has not become routine care in the management of ASC.

Thromboprophylaxis

Recommendation

- The use of anticoagulation for the prevention of venous thromboembolic events (VTE) is recommended when ≥1 of its risk factors is present (depending on age)[22]. **Agreement:** 100%.

Children with ASC are at increased risk of VTE, especially during active disease. The VTE incidence was 3.72 per 10,000 person-years, 14-fold higher than in the general pediatric population[209]. Treatment of VTE in children with IBD and intestinal failure traditionally consists of heparin (unfractionated heparin), followed by low molecular weight heparin (LMWH) or vitamin K antagonists (VKAs)[128,201]. In adolescents, subcutaneous LMWH should be considered in the presence of ≥1 risk factors: smoking, oral contraceptives, complete immobilization, central venous catheters (including PICC line), obesity, concurrent significant infection, known prothrombotic disorder, previous and/or family history of VTE while in prepubertal children, is required the presence of ≥2 risk factors[202-205].

Toxic megacolon

Recommendation

- In toxic megacolon, we recommend urgent management with NPO, intravenous steroids, intravenous antibiotics, and surgical evaluation[22]. **Agreement:** 100%.

Toxic megacolon is a rare complication of ASC, affecting up to 1% to 2% of pediatric patients, in addition to having high mortality rates if left untreated[206]. Risk factors for toxic megacolon include CMV or *C. difficile* infection, hypokalemia, hypomagnesemia, and the use of drugs that decrease colonic motility, such as anticholinergics, narcotics, and antidepressants with anticholinergic properties[207]. Additionally, early discontinuation or rapid reduction of steroids or aminosalicylates and diagnostic procedures that can cause colonic distention (colonoscopy and barium enema) are also risk factors for the development of toxic megacolon[208]. Children with toxic megacolon should be treated by surgeons and conservative management should only be considered in stable clinical conditions and in highly specialized centers under close monitoring; urgent colectomy is recommended if no improvement is apparent within 24 to 72 hours[22].

Clinical monitoring of ASC

Recommendation

- We suggest monitoring disease activity daily using the PUCAI score to reevaluate treatment in ASC[19]. **Agreement:** 92.3% (TURNER 2018a).

It is recommended the following clinical monitoring for ASC pediatric patients: 1) PUCAI >45 points on the third day of intravenous corticosteroids treatment should dictate planning for second-line therapy between days 3–5; 2) PUCAI >65 points: second-line therapy should be initiated on the fifth day of IVCS treatment, and 3) PUCAI of 35–65 on day 5: intravenous corticosteroids should be continued for an additional 2-5 days; recommended: daily monitoring for confirming gradual response before a decision on second-line therapy is made in most cases within a total of 7–10 days of treatment[22].

The PUCAI cut-offs for remission, mild, moderate, and severe disease have been validated and have been successfully used to assess disease activity in pediatric patients with UC and, therefore, guide the choice of initial treatment at the onset of disease[12-14]. Monitoring PUCAI scores can predict steroid resistance and guide the implementation of second-line therapy in hospitalized children. Using PUCAI's suggested cut-off values, approximately half of patients who would fail on steroids can have their treatment escalated as early as the fifth day of admission. Those with a PUCAI score of lower than 65 points on day 5 may be slow responders and should be treated for an additional 3 to 5 days until the response is clear[174].

Discharge recommendations for children who presented acute severe colitis

Recommendations

1. If disease activity is not mild at most (PUCAI <35 points) or close to remission (PUCAI <10 points), we recommend against hospital discharge[22]. **Agreement:** 91.7%.
2. As a pre-discharge checklist, patients should have stable vital signs, adequate oral nutrition, stable hemoglobin, improving inflammatory markers, tolerating oral medication, and discontinuing pain medications 24 hours prior to discharge[22]. **Agreement:** 91.7%.
3. *Pneumocystis jiroveci* pneumonia (PJP) should be treated with trimethoprim-sulfamethoxazole prophylaxis, along with Anti-TNF or a calcineurin inhibitor as well as two other immunosuppressants, primarily steroids[22]. **Agreement:** 91.7%.

Maintenance of remission after ASC

Immunosuppressants

Recommendation

- If chronically active disease, if the patient has 2–3 flares per year, or if the patient presents with ASC while using 5-ASA, we recommend adding thiopurines (azathioprine 2–2.5 mg/kg once daily or 6- mercaptopurine 1.5 mg/kg once daily) after the flare has been treated (if there is a good response to steroids), as maintenance therapy[19]. **Agreement:** 100%.

It is established that the efficacy of thiopurines (azathioprine) is not superior to placebo in inducing remission, but it is effective for preventing relapses[183,209,210]. Prospective studies found steroid-free remission rates of 49% at 1 year[211] and 72% at 2 years[212] among children with UC. No benefit was found for the early use of thiopurines on the outcome of preventing or reducing the risk of colectomy[184,186,213].

Biological agents

Recommendations

1. If the disease is still chronically active or the patient has frequent flares despite optimal thiopurine treatment, consider using Anti-TNF therapy[19]. **Agreement:** 100%.
2. In cases where disease is active even with optimal levels of Anti-TNF or if more than one therapy with an Anti-TNF has failed, we recommend the use of vedolizumab[19]. **Agreement:** 100%.
3. After a failed biological therapy (including dose optimization) and all other diagnoses have been excluded, consider a colectomy[19]. **Agreement:** 100%.

Identifying children at risk of progression to severe disease may lead to more aggressive and precise treatment. In UC, the "top-down" strategy is practiced less frequently, but severely ill patients may benefit from early aggressive and/or combination therapy. If medical treatment fails, in refractory cases, or if there is neoplasia associated with colitis, colectomy is the indicated surgical treatment. Reported rates of colectomy range from 8% to 24% over ten years. However, short-term, and long-term complications associated with colectomy must be individually balanced considering existing and future quality of life[152,199,214].

Infliximab is an effective and safe therapy for pediatric patients with moderate to severe UC and an inadequate response to existing treatment. The open-label, uncontrolled, multicenter, Phase 3 study by Tajiri et al. (2019) found that infliximab therapy (IFX 5 mg/kg by intravenous infusion over a period of ≥2 hours at weeks 0, 2, and 6) rapidly improved clinical symptoms, and this effect was maintained for up to 30 weeks. The remission rate based on the Clinical Activity Index was 42.9% and the overall remission rate based on the PUCAI was 19.0%. Patients on steroids at baseline (57.1%) had a maximum dose reduction of 79.31% after IFX treatment at Week 30. Although derived from a small number of patients, these results show that administration of IFX in pediatric patients with UC holds promise for treatment remission, reduction, and withdrawal of corticosteroids[215].

In adults, vedolizumab is considered effective in inducing and maintaining remission[168]. Overall, vedolizumab appears to be a moderately effective and safe option for pediatric patients with IBD refractory to standard-of-care therapy. While the medication adds a promising therapeutic option for pediatric patients with IBD, larger, prospective studies are warranted to define the drug's place more clearly in therapy as well as optimal dosing and long-term safety[216]. There have been retrospective studies assessing the efficacy of vedolizumab demonstrated that pediatric IBD patients with severe IBD who are unresponsive, intolerant, or experience a loss of efficacy with other therapies, showing that treatment with vedolizumab is also effective in children[84,92,93]. Several real-world experience studies with vedolizumab have been published to date. The systematic review by Engel et al. (2018) with pediatric and adult patients summarized the real-life experience with vedolizumab. It has been demonstrated that maintenance therapy with vedolizumab leads to clinical response and remission at week 52 in 48% and 39% of patients, respectively. Adverse effects were mostly minor and occurred in 30.6% of patients; infections were reported in 3.4% of patients[217].

CRITERIA TO EVALUATE TREATMENT EFFICACY IN UC

Clinical response and remission

Recommendations

1. We recommend that a clinically significant response should be considered as a PUCAI change of at least 20 points or entering remission[19,104]. **Agreement:** 92.3%.
2. We recommend that the clinical remission should be considered as PUCAI <10 points, mild disease as 10 to 34 points, moderate disease as 35 to 64 points, and severe disease as equal or greater than 65 points[19,104]. **Agreement:** 92.3%.

Colonoscopy

Recommendation

- Colonoscopy is recommended at diagnosis, prior to making major therapeutic modifications, when determining whether symptoms are caused by disease, and when the level of fecal calprotectin is high. It is not routinely recommended in cases of non-severe relapse[19]. **Agreement:** 100%.

Surveillance colonoscopy should be performed as chromoendoscopy or as high-resolution white light endoscopy, with targeted biopsies in both cases. It should be performed regularly, starting 6 to 8 years after the diagnosis of ulcerative colitis, at intervals that depend on risk stratification. Whenever possible, it should be performed in remission or in a phase of lower inflammatory activity, as there is a possibility of a false positive due to the inflammatory process that accompanies low-grade intraepithelial neoplasia[218].

The meta-analysis by Aardoom et al. (2018) demonstrated an increased risk of cancer in pediatric patients with IBD (pooled standardized incidence ratio 2.23 [95%CI 1.98 to 2.52]) with the most frequent non-fatal cancer type being lymphoma. Colorectal carcinomas were the most frequently reported fatal cancer in pediatric patients with IBD, and these were particularly associated with primary sclerosing cholangitis[200]. Specifically for pediatric patients with UC, the pooled incidence rate for cancer was 0.031 (95%CI 0.018 to 0.052). The pooled incidence rate of colorectal cancer and hematologic cancers was 0.020 (95%CI 0.012 to 0.034) and 0.0045 (95%CI 0.0026 to 0.0079), respectively. The cumulative meta-analyses showed a decreasing trend in the incidence of these cancers in pediatric IBD patients[219]. Similar findings were demonstrated by El-Matary et al. (2021) and they add that the longer duration of inflammation may explain that 50% of the cases, because who developed colorectal cancer/dysplasia were diagnosed with IBD before the age of 6 years although the very early onset of IBD could be an independent risk factor for developing colorectal cancer/dysplasia[220].

Fecal calprotectin

Recommendation

- If possible, we recommend testing for fecal calprotectin during sustained clinical remission. In cases where high levels of calprotectin are observed, we recommend an endoscopic evaluation[19]. **Agreement:** 92.3%.

The reliability of fecal calprotectin assessing endoscopic activity in UC adult patients is well established (pooled sensitivity of 87.3%, specificity of 77.1%)[221]. Examining the optimum fecal calprotectin cut-off levels, the best sensitivity (90.6%) was achieved at 50 µg/g, whereas the best specificity (78.2%) was found at levels >100 µg/g[221]. Additionally, serial fecal calprotectin measurements may be useful in monitoring IBD patients in remission, as it appears to be a reliable predictor of short-term relapse and endoscopic activity[222]. Iwańczak et al. (2020) compared the clinical activity and inflammatory markers with the endoscopic activity of UC and mucosal healing in pediatric patients[223]. A strong positive correlation between PUCAI, fecal calprotectin, and serum mucoprotein, with the endoscopic activity, was demonstrated, concluding that these biomarkers may be helpful in the assessment of large intestine mucosal healing[223]. Finally, fecal calprotectin was a reliable biomarker to diagnose neutrophilic inflammation of the distal ileum. The sensitivity, specificity, positive predictive value, and negative predictive value for fecal calprotectin concentrations over 300 µg/g to detect recurrent pouchitis were 57%, 92%, 67%, and 89%, respectively, in pediatric patients who had undergone proctocolectomy with ileoanal anastomosis[224].

SURGICAL MANAGEMENT FOR PEDIATRIC PATIENTS WITH ULCERATIVE COLITIS

CRITERIA FOR INDICATION OF ELECTIVE SURGERY IN UC

Elective surgery

Recommendation

- For pediatric UC, we recommend a restorative proctocolectomy combined with ileal pouch-anal anastomosis and a covering loop ileostomy. It is also recommended for children with active or steroid-dependent UC, as well as those with dysplasia of the colon, to consider elective colectomy, despite appropriate medical therapy[19]. **Agreement:** 100%.

Restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) is the recommended elective surgery for children with UC. In ambulatory children, colectomy as an elective procedure is typically indicated in cases of chronic ongoing disease, often in steroid-dependent patients. Elective colectomy in pediatric UC is less common and generally guided by quality-of-life issues; in rare instances in pediatric age, elective colectomy is performed for dysplasia or carcinoma identified by routine surveillance biopsy[225]. A retrospective study with hospital records of 30 pediatric patients who had undergone restorative proctocolectomy and laparoscopic IPAA. The measure of health-related quality of life after the surgery improved significantly (P<0.05), impacting symptoms, school attendance, social activities, and emotional aspects. Data confirmed that surgical treatment improves the overall quality of life of pediatric patients with UC[226].

CRITERIA FOR INDICATION OF URGENT SURGERY OF ACUTE SEVERE COLITIS

Urgent surgery

Recommendation

- If pediatric patients with ASC are treated with high-dose steroids or received Anti-TNF therapy recently, are severely malnourished, or with IBDU (inflammatory bowel disease unclassified), we recommend a three-stage procedure (subtotal colectomy with ileostomy first). However, the final decision should be based on patient-specific considerations. Also, prompt referral for urgent colectomy is recommended following the failure of one second-line medical therapy. Finally, a minimally invasive laparoscopic approach is recommended in children as there are equivalent outcomes to open surgery both for urgent and elective cases and possibly superior outcomes regarding fertility in girls[19,22]. **Agreement:** 92.3%.

At least 25% of children and adolescents hospitalized with UC require urgent or emergent operation for persistent or escalating, symptomatic colitis despite optimal medical management[105,208]. UC-related morbidity and complications in children include gastrointestinal hemorrhage, sepsis, intestinal perforation, toxic megacolon, and, with long-term illness, dysplasia. Life-threatening bleeding, sepsis, perforation, or colon dilatation requires emergent surgical evaluation and may require urgent colectomy. The diagnosis of toxic megacolon is based on the presence of transverse colonic dilatation greater than 56 mm with systemic sepsis[105,208]. In this case, an urgent colectomy is warranted if symptoms worsen or do not improve within 48 hours. In the absence of colonic dilation, hospitalized children with acute fulminant colitis who do not respond to medical therapy have indications for urgent colectomy[105,208]. Immunosuppression with high doses of steroids and/or the use of biological agents that attenuate the inflammatory response to injury and infection associated with generalized disease, the surgical approach becomes mandatory in most pediatric patients. In the urgent or emergency setting, laparoscopic or open subtotal colectomy with final ileostomy bypass is indicated[208].

PERIOPERATIVE MANAGEMENT OF REFRACTORY UC

Laparoscopic resection

Recommendation

- For both urgent and elective cases, we recommend a minimally invasive laparoscopic approach given its equivalence in outcomes compared to open surgery and possible superiority regarding fertility in girls[19]. **Agreement:** 100%.

With experienced surgeons, laparoscopic colectomy/ileostomy is safe and feasible for both ASC and ambulatory patients[227]. In female patients, laparoscopic IPAA may decrease the risk of subfertility compared to open IPAA[228]. Laparoscopy-assisted ileostomy (LAI) represents a cornerstone for the stepwise approach to UC. Seventy-two LAIs were performed in 37 pediatric patients with UC with a median age at surgery of 12 years. Surgical complications occurred after eight procedures (median of 31 postoperative days). Complications related to the procedure were significantly more frequent in the case of BMI-z score >-0.51 and in the case of preoperative administration of azathioprine[229].

ELECTIVE SURGERY TECHNIQUES FOR REFRACTORY MODERATE TO SEVERE UC

Total colectomy with ileorrectal anastomosis

Recommendations

1. In the absence of response to medical therapy, the need for a colectomy should be discussed whenever second-line medical therapy is introduced[22]. **Agreement:** 92.3%.
2. If pediatric patients with ASC are treated with high-dose steroids or received Anti-TNF therapy recently, are severely malnourished, or have the diagnostic label of inflammatory bowel disease unclassified (IBDU), we recommend a three-stage procedure (subtotal colectomy with ileostomy first). However, the final decision should be based on patient-specific considerations[19]. **Agreement:** 100%.

Expert opinion

3. Within 1 year, children with ASC who are steroid-refractory are at high risk for colectomy. When second-line therapy is initiated or a colectomy is decided, ineffective corticosteroids should be weaned off to reduce unnecessary immunosuppression and to avoid other undesired side effects. Based on the previous exposure to steroids and the clinical situation, tapering strategies should be modified accordingly[22]. **Agreement:** 92.3%.

Total proctocolectomy with ileoanal pouch (reconstructive)

Recommendation

- Restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA) and a covering loop ileostomy is the procedure of choice in children, as it is an adults, given the favorable long-term outcomes. **Agreement:** 100%.

The long-term post-surgical functional outcomes of IPAA in children are promising, in which most children with UC can wean off corticosteroids and immunomodulatory drugs, as well as experience significant improvements in quality of life, growth, and nutritional status[230]. Restorative proctocolectomy with IPAA also has been associated with favorable long-term results with respect to gastrointestinal function, quality of life, and patient satisfaction, benefits that are judged to outweigh the risks[231] in elective, but not emergency patients[232]. Patients with UC undergoing IPAA may present pouchitis more commonly than in patients with familial polyposis. Higher rates of pouchitis are seen in children and adults with extraintestinal manifestations of UC, especially primary sclerosing cholangitis. Biochemical signs of anemia and elevated erythrocyte sedimentation rate are identified in patients with symptoms of pouchitis[208]. To confirm the hypothesis of pouchitis histology through flexible sigmoidoscopy of the pouch with biopsies is required[208].

Authors' contribution

Lomazi EA, Oba J, Rodrigues M, Marmo MCR, Sandy NS, Sdepanian VL, mbrizi M, Baima JP and Saad-Hossne R: methodology, literature review, recommendations decision making, writing and review, and final review of the manuscript. Magro DO, Albuquerque IC, Zabot GP, Cassol OS, Saad-Hossne R: recommendations decision making.

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RESUMO – Contexto – Aproximadamente 25% dos pacientes desenvolvem doença inflamatória intestinal (DII) durante a infância ou adolescência, e o tratamento visa controlar os sintomas ativos e prevenir complicações a longo prazo. O tratamento da doença de Crohn (DC) e retocolite ulcerativa (RCU) pode ser especialmente desafiador em crianças e adolescentes, relacionado a particularidades que podem afetar o crescimento, o desenvolvimento e a puberdade. **Objetivo –** Este consenso visa fornecer orientações sobre o tratamento clínico e cirúrgico mais eficaz de pacientes pediátricos com DC ou RCU. **Métodos –** Gastroenterologistas brasileiros especialistas em DII Pediátrico membro da Organização Brasileira para Doença de Crohn e Colite (GEDIIB) desenvolveram este consenso. Uma revisão rápida foi realizada para apoiar as recomendações/declarações. As recomendações médicas e cirúrgicas foram estruturadas e mapeadas de acordo com o tipo de doença, atividade da doença e indicações e contraindicações para tratamento médico e cirúrgico. Após a estruturação das declarações, foi utilizada a metodologia modificada do Painel Delphi para conduzir a votação. O processo ocorreu em três rodadas: duas por meio de uma plataforma de votação online personalizada e anônima e uma presencial. Sempre que os participantes não concordavam com a recomendação específica, uma opção para explicar o motivo era oferecida para permitir respostas em texto livre e dar a oportunidade para os especialistas elaborarem ou explicarem a discordância. O consenso das recomendações em cada rodada foi aceito quando houve concordância ≥80%. **Resultados e conclusão –** As recomendações são apresentadas 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, acompanhamento/monitoramento do paciente após tratamento. As recomendações cirúrgicas foram agrupadas de acordo com o tipo de doença e cirurgia recomendada. O público-alvo deste consenso foram clínicos gerais, gastroenterologistas e cirurgiões interessados no tratamento e manejo da RCU e DC pediátrica. Além disso, o consenso visava apoiar a tomada de decisão das operadoras de planos de saúde, agências reguladoras e líderes e/ou administradores de instituições de saúde.

Palavras-chave – Doença de Crohn; colite ulcerativa; cirurgia; crianças; adolescentes; doenças inflamatórias intestinais; gerenciamento de doenças.

Supplementary Material of the Brazilian Consensus on the management of inflammatory bowel diseases in pediatric patients: a Consensus of the Brazilian Organization for Crohn's Disease and Colitis (GEDIIB)

CROHN'S DISEASE
Medical Treatment

Defining the question to be answered

The acronym PICO-S (patient, intervention, comparator, outcome, and study design) in TABLES S1-S12 describe the questions to be answered regarding the medical treatment of pediatric patients with Crohn's Disease (CD).

TABLE S1. PICO strategy on induction treatment of low-risk active CD.

P	Children and adolescents (≤18 years) with low-risk active CD
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for low-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S2. PICO strategy on induction treatment of intermediate-risk active CD.

P	Children and adolescents (≤18 years) with intermediate-risk active CD.
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for intermediate-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S3. PICO strategy on induction treatment of high-risk active CD.

P	Children and adolescents (≤18 years) with high-risk active CD.
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for intermediate-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S4. PICO strategy on maintenance treatment of low-risk active CD.

P	Children and adolescents (≤18 years) with low-risk active CD.
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years

Question: What are the recommended maintenance treatments for low-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S5. PICO strategy on maintenance treatment of intermediate-risk active CD.

P	Children and adolescents (≤18 years) with intermediate-risk active CD.
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended maintenance treatments for intermediate-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S6. PICO strategy on maintenance treatment of high-risk active CD.

P	Children and adolescents (≤18 years) with high-risk active CD.
I	• Corticosteroids (budesonide of ileal release, budesonide mmx + all traditional) • Probiotics • Salicylates (sulfasalazine, mesalazine, mesalazine mmx, suppository and enema) • Immunosuppressants (azathioprine, 6MP, MTX) • Biological ◆ Anti-TNF (infliximab, adalimumab, certolizumab pegol) ◆ Anti-Integrin (vedolizumab) ◆ Anti-Interleukin (ustekinumab, risankizumab)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended maintenance treatments for high-risk active CD in children and adolescents, according to the international guidelines and/or consensus?

TABLE S7. PICO strategy on the clinical treatment of perianal fistulizing CD.

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

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

TABLE S8. PICO strategy on the criteria for evaluating the efficacy of clinical treatment of pediatric CD.

P	Children and adolescents (≤18 years) with active CD
I	Not applicable
C	Not applicable
O	Criteria used to assess the efficacy of treatment: • Clinical response • Clinical remission • Endoscopic response • Endoscopic remission • Imaging remission (including US, entero-CT, and entero-RNM) • Histological remission • Corticosteroid-free clinical remission • Improvement in quality of life • Adverse events • Others found in the literature
Type of study	Consensus and/or guidelines limited to the last five years.

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

TABLE S9. PICO strategy on patient follow-up after initial treatment.

P	Children and adolescents (≤18 years) with active CD
I	Not applicable
C	Not applicable
O	Follow-up of the patient after initial treatment (e.g., clinical value, including pubertal growth and development, PCR, calprotectin, colonoscopy, imaging [periodicity of tests and consultation], therapeutic failure, treatment drug monitoring (TDM), screening for infections – tuberculosis, CMV, *C. difficile*, cancer and others)
Type of study	Consensus and/or guidelines limited to the last five years.

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

TABLE S10. PICO strategy on the efficacy of nutritional treatments for CD in children and adolescents.

P	Children and adolescents (≤18 years) with low-risk and intermediate-risk CD
I	Nutritional diets: • EXCLUSIVE ENTERAL DIET • PARTIAL EXCLUSION DIET
C	• Not applicable
O	Efficacy: • Clinical response and remission • Endoscopic response and remission • Mucosal healing
Type of study	Systematic reviews with meta-analysis

Question: What is the efficacy of nutritional approaches in low-risk and intermediate-risk pediatric CD, according to the systematic reviews with meta-analysis?

TABLE S11. PICO strategy on the efficacy of clinical treatments for CD in children and adolescents.

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

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

TABLE S12. PICO strategy on the efficacy of clinical treatments for CD in children and adolescents.

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

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

Eligibility criteria

Inclusion criteria

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

Exclusion criteria:

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

Search Strategy

The search strategy was conducted on MEDLINE (National Library of Medicine of the United States and Medical Database of the National Institutes of Health, using the PubMed interface). TABLE S13 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 S13. Search strategy.

Study design	Search strategy	Results (titles)
Guidelines and/or Consensus	("inflammatory bowel disease" [Title] OR "IBD" [Title] OR "crohn" [Title]) AND ("treatment" [Title/Abstract] OR "management"[Title/Abstract] OR "monitoring" [Title/Abstract]) AND ("consensus" [Title] OR "guidelines" [Title]) AND (y_5 [Filter]) AND (english [Filter]) AND (pediatric OR child OR children OR adolescent OR paediatric))	24
Systematic Literature Reviews with meta-analysis	(("inflammatory bowel disease" [Title] OR "IBD" [Title] OR "crohn" [Title]) AND ("treatment" [Title/Abstract] OR "management" [Title/Abstract] OR "monitoring" [Title/Abstract])) AND ((meta-analysis [Filter]) AND (english [Filter]) AND (pediatric OR child OR children OR adolescent OR paediatric))	56

Search conducted on December 7, 2021.

Screening of studies

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

Data recovery and extraction

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

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

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

- Author, year;

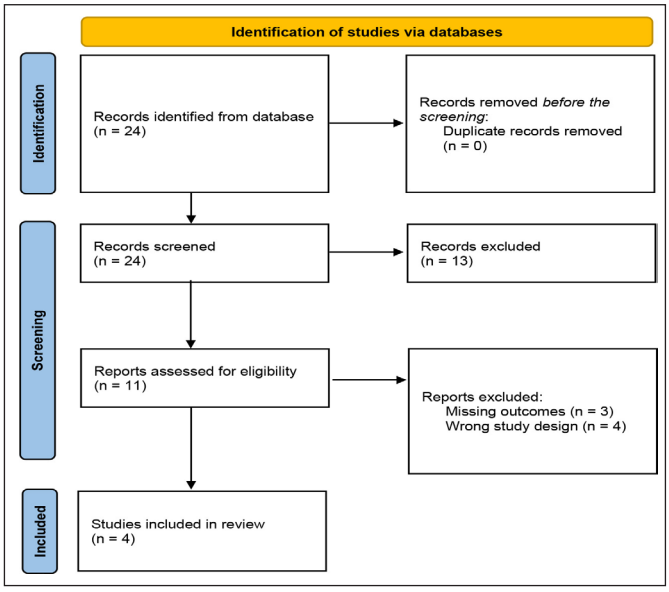

FIGURE S1. Screening flowchart of Consensus and/or Guidelines.

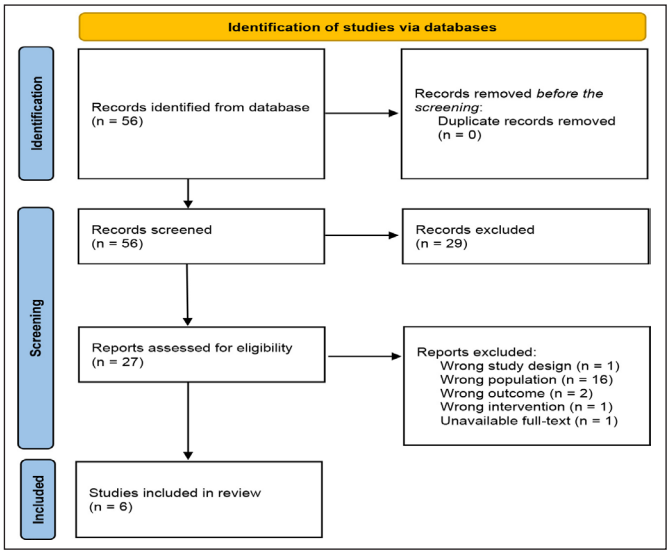

FIGURE S2. Screening flowchart of Systematic Literature Reviews with meta-analysis.

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

Surgical treatment

Defining the question to be answered

The following acronym PICO-S indicated in TABLES S14-S21 describes the question to be answered, regarding the surgical treatment of pediatric patients with CD.

TABLE S14. PICO strategy on criteria for indication of elective or urgent surgery of abdominal CD in children and adolescents.

P	Children and adolescents (≤18 years) with abdominal CD
I	Elective surgery
C	Not applicable
O	Criteria to indicate elective or urgent surgery
Type of study	International guidelines and/or consensus published after 2016

Question: What are the criteria to indicate elective or urgent surgery of abdominal CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S15. PICO strategy on perioperative management of abdominal CD in children and adolescents.

P	Children and adolescents (≤18 years) with abdominal CD
I	Perioperative management
C	Not applicable
O	• Nutrition • Prophylaxis of venous thromboembolism • Sepsis control • Corticosteroids • Immunosuppressants • Anti-TNF • Anti-integrin • Anti-interleukin
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommendations for perioperative management of abdominal CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S16. PICO strategy on the management of small bowel and perianal fistulizing CD in children and adolescents.

P	Children and adolescents (≤18 years) with small bowel and perianal fistulizing CD
I	Management of Crohn's disease – Small bowel and perianal fistulizing disease
C	Not applicable
O	• Management of intra-abdominal and perianal abscess • Percutaneous drainage guided by imaging • Clinical treatment of intra-abdominal and perianal abscess • Surgical treatment of intra-abdominal and perianal abscess
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommendations for the management of small bowel and perianal fistulizing CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S17. PICO strategy on the management of abdominal CD in children and adolescents - Enterovaginal, enterocutaneous, enterovesical, and/or enteroenteric fistula.

P	Children and adolescents (≤18 years) with enterovaginal, enterocutaneous, enterovesical, and/or enteroenteric fistula CD
I	Management of Crohn's disease - Entero-vaginal, entero-bladder, enterocutaneous, enteroenteric fistula
C	Not applicable
O	• enterovaginal fistula management • enterovesical fistula management • enteroenteric fistula management • enterocutaneous fistula management
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommendations for the management of enterovaginal, enterocutaneous, enterovesical, and/or enteroenteric fistula CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S18. PICO strategy on the management of abdominal CD in children and adolescents - enteroenteric fistula.

P	Children and adolescents (≤18 years) with CD and enteroenteric fistula
I	Management of CD - Enteroenteric fistula
C	Not applicable
O	• Management of intra-abdominal abscess • Percutaneous drainage guided by imaging • Clinical treatment of intra-abdominal abscess • Surgical treatment of intra-abdominal abscess
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommendations for the management of enteroenteric fistula CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S19. PICO strategy on the management of abdominal CD in children and adolescents - Enterocutaneous fistula.

P	Children and adolescents (≤18 years) with CD with enterocutaneous fistula
I	Management of CD - enterocutaneous fistula
C	Not applicable
O	• Management of intra-abdominal abscess • Percutaneous drainage guided by imaging • Clinical treatment of intra-abdominal abscess • Surgical treatment of intra-abdominal abscess
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommendations for the management of enterocutaneous fistula CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S20. PICO strategy on the management of CD in children and adolescents - Stenosing disease.

P	Children and adolescents (≤18 years) with CD
I	Management of stenosing CD
C	Not applicable
O	• Endoscopic treatment • Surgical Treatment (Stenoplasty and Resection)
Type of study	International guidelines and/or consensus published after 2016

Question: How to manage stenosing CD in children and adolescents, according to international guidelines and/or consensus?

TABLE S21. PICO strategy on elective surgery techniques in CD of children and adolescents.

P	Children and adolescents (≤18 years) with CD
I	Elective surgery
C	Not applicable
O	Surgical techniques for CD: • Surgical access • Temporary ostomy (for the preservation of anastomosis) • Primary anastomosis • Laparoscopic resection • Type of anastomoses • Segmental colectomy • Derivation (no resection) • Total proctocolectomy with definitive ileostomy • Total proctocolectomy with ileoanal pouch
Type of study	International guidelines and/or consensus published after 2016

Question: What are the recommended elective surgery techniques for CD in children and adolescents, according to international guidelines and/or consensus?

Eligibility criteria

Inclusion criteria

- Guidelines and/or international consensus with recommendations for the surgical treatment of children and adolescents (≤18 years) with active CD;
- Guidelines and/or consensus in English;
- Guidelines and/or consensus published in the last 5 years (from November 2016 until December 2021).

Exclusion criteria:

- Guidelines and/or consensus published before November 2016;
- Reviews of guidelines and/or consensus.

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 S22 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 S22. Search strategy.

Databases	Search strategy	Results (titles)
Guideline and/or Consensus	("inflammatory bowel disease" [Title] OR "IBD" [Title/Abstract] OR "Crohn" [Title] OR "DC" [Title/Abstract]) AND ("treatment" OR "management" OR "surgery" OR "surgical") AND ("consensus" [Title] OR "guidelines" [Title]) AND ((y_5 [Filter]) AND (english [Filter]) AND (pediatric OR child OR children OR adolescent OR paediatric))	31

Search conducted on December 7, 2021.

Screening of studies

The selection of title and abstract according to eligibility criteria was carried out through the f Rayyan® Platform. It is a tool specifically developed to speed up the initial screening of abstracts and titles using a semi-automatic process. The selected publications were evaluated in full text based on the inclusion and exclusion criteria. Two independent researchers screened the studies in a blinded fashion way, and in case of divergence, the decision was made with a third reviewer. The screening flowchart can be found in FIGURE S3.

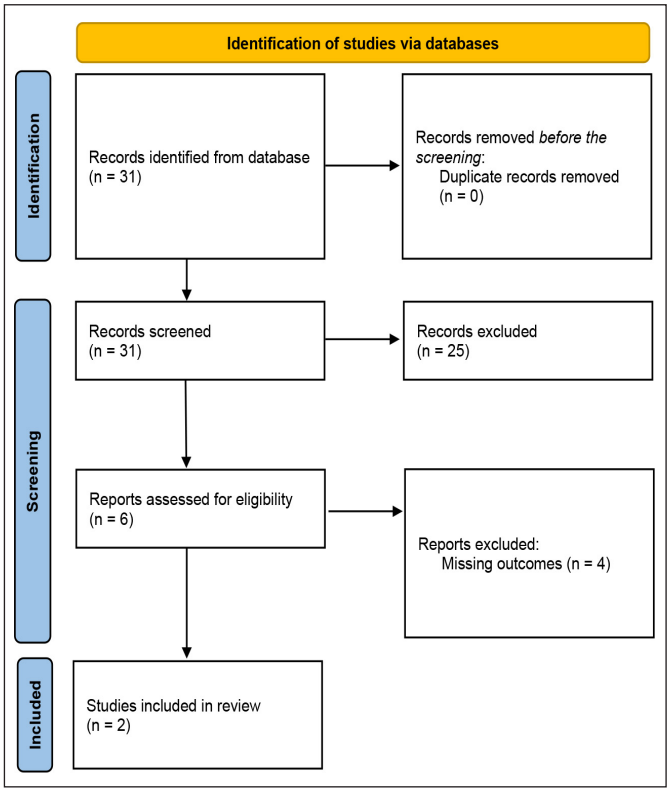

FIGURE S3. Screening flowchart of Consensus and/or Guidelines for surgical treatment.

Data recovery and extraction

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

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

ULCERATIVE COLITIS

Medical treatment

Defining the question to be answered

The acronym PICO-S indicated in TABLES S23-S31 describes the question to be answered regarding the medical treatment of pediatric patients with Ulcerative Colitis (UC).

TABLE S23. PICO strategy on induction treatment of mild UC.

P	Children and adolescents (≤18 years) with mild 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)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for mild active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S24. PICO strategy on induction treatment of moderate UC.

P	Children and adolescents (≤18 years) with moderately 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)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for moderately active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S25. PICO strategy on induction treatment of severe UC.

P	Children and adolescents (≤18 years) with 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)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended induction treatments for severe active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S26. PICO strategy on maintenance treatment of mild UC.

P	Children and adolescents (≤18 years) with mild 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 receiver modulators (ozanimod)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended maintenance treatments for mild active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S27. PICO strategy on maintenance treatment of moderate UC.

P	Children and adolescents (≤18 years) with moderate 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 receiver modulators (ozanimod)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended maintenance treatments for moderately active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S28. PICO strategy on maintenance treatment of severe UC.

P	Children and adolescents (≤18 years) with severe 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 receiver modulators (ozanimod)
C	Not applicable
O	Consensus and/or guideline recommendation
Type of study	Consensus and/or guidelines limited to the last five years.

Question: What are the recommended maintenance treatments for severe active UC in children and adolescents, according to the international guidelines and/or consensus?

TABLE S29. PICO strategy on the criteria for evaluating the efficacy of clinical treatment in UC.

P	Children and adolescents (≤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 and/or guidelines limited to the last five years.

Question: What are the criteria used to evaluate the efficacy of treatment of active CU in children and adolescents, according to the international guidelines and/or consensus?

TABLE S30. PICO strategy on patient follow-up after initial treatment.

P	Children and adolescents (≤18 years) with UC
I	Not applicable
C	Not applicable
O	Follow-up of the patient after initial treatment (e.g., clinical value, calprotectin, PCR, colonoscopy, periodicity of tests and consultation, therapeutic drug monitoring (TDM), infection screening - TBC, CMV, *C. difficile*, cancer surveillance, and others)
Type of study	Consensus and/or guidelines limited to the last five years.

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

TABLE S31. PICO strategy on the efficacy of clinical treatments for UC in children and adolescents.

P	Children and adolescents (≤18 years) with UC
I	• Corticosteroids (budesonide mmx + all traditional) • Probiotics • 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)
C	Not applicable
O	All efficacy outcomes considered in the published studies (i.e., clinical response and remission, endoscopic response and remission, mucosal healing, etc.)
Type of study	Systematic reviews with meta-analysis

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

Eligibility criteria

Inclusion criteria:

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

Exclusion criteria:

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

Search strategy

The search strategy was conducted on MEDLINE (National Library of Medicine of the United States and Medical Database of the National Institutes of Health, using the PubMed interface). TABLE S32 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 S32. Search strategy.

Study design	Search strategy	Results (titles)
Guidelines and/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]) AND (pediatric OR child OR children OR adolescent OR pediatric))	23
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]) AND (pediatric OR child OR children OR adolescent OR paediatric))	38

Search conducted on December 7, 2021.

Screening of studies

The selection of title and abstract according to eligibility criteria was carried out through the f Rayyan® Platform. It is a tool specifically developed to speed up the initial screening of abstracts and titles using a semi-automatic process. The selected publications were evaluated in full text based on the inclusion and exclusion criteria. Two independent researchers screened the studies in a blinded fashion way, and in case of divergence, the decision was made with a third reviewer. The screening flowchart can be found in FIGURES S4 and S5.

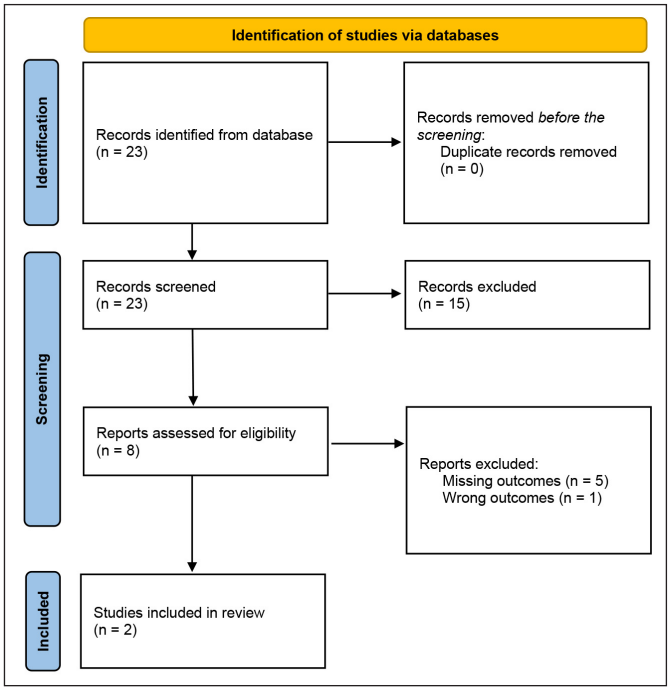

FIGURE S4. Screening flowchart of Consensus and/or Guidelines.

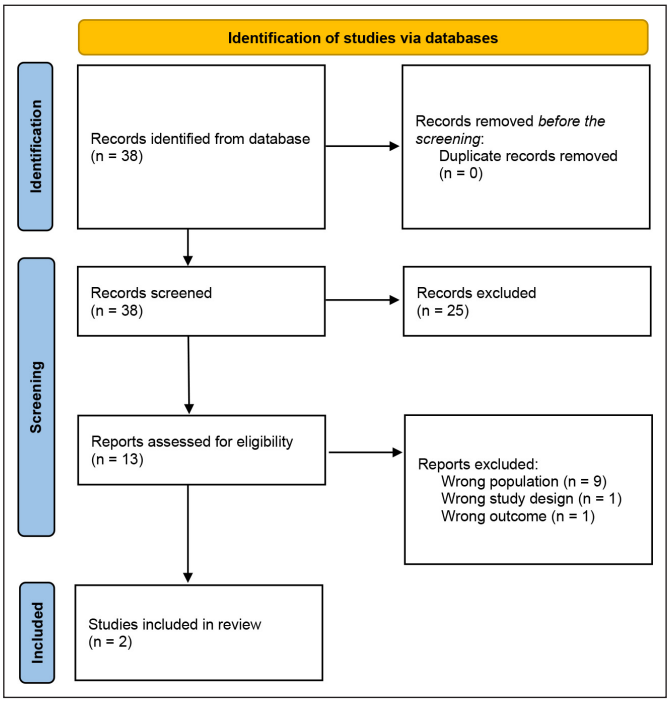

FIGURE S5. Screening flowchart of Systematic Literature Reviews with meta-analysis

Data recovery and extraction

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

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

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

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

Surgical treatment

Defining the question to be answered

The acronym PICO-S indicated in TABLES S33-S38 describes the question to be answered regarding the surgical treatment of pediatric patients with UC.

TABLE S33. PICO strategy for the indication of elective surgery in UC in children and adolescents.

P	Children and adolescents (≤18 years) with UC
I	Elective surgery
C	Not applicable
O	Eligibility criteria for indication of elective surgery
Type of study	International guidelines and/or consensus published after 2016

Question: What are the criteria for the indication of elective surgery in UC in children and adolescents, according to international guidelines and/or consensus?

TABLE S34. PICO strategy on the perioperative management of refractory moderate to severe UC in children and adolescents.

P	Children and adolescents (≤18 years) with refractory moderate to severe UC
I	Perioperative management
C	Not applicable
O	• Nutrition • Prophylaxis of VTE • Corticosteroids • Immunosuppressants • Anti-TNF • Anti-integrin • Anti-interleukin • JAK inhibitors
Type of study	International guidelines and/or consensus published after 2016

Question: How to manage the perioperative procedure of refractory moderate to severe UC in children and adolescents, according to international guidelines and/or consensus?

TABLE S35. PICO strategy on techniques for elective surgery of refractory moderate to severe UC in children and adolescents.

P	Children and adolescents (≤18 years) with refractory moderate to severe UC
I	Elective surgery
C	Not applicable
O	• Total proctocolectomy with ileal (reconstructive) • Total proctocolectomy with ileostomy • Total colectomy with ileorectoanastomosis • Surgical access • Temporary ostomy (for the preservation of anastomosis) • Primary anastomosis • Laparoscopic resection • Type of anastomoses • Fertility and delivery routes
Type of study	International guidelines and/or consensus published after 2016

Question: What are the elective surgery techniques for refractory moderate to severe UC in children and adolescents, according to international guidelines and/or consensus.

TABLE S36. PICO strategy on complications related to the ileal pouch in severe UC in children and adolescents.

P	Children and adolescents (≤18 years) with severe UC
I	Not applicable
C	Not applicable
O	Complications related to the ileal scholarship: • Fistulas and dehiscence of anastomosis • Pouchitis (acute, chronic, and refractory) • Ileoanal pouch failure
Type of study	International guidelines and/or consensus published after 2016

Question: What are the complications related to the ileal pouch in severe UC in children and adolescents, according to international guidelines and/or consensus?

TABLE S37. PICO strategy on criteria for indication of urgent and emergency surgery in ASC in children and adolescents.

P	Children and adolescents (≤18 years) with ASC
I	Urgent and emergency surgery
C	Not applicable
O	Criteria for indication of urgent and emergency surgery
Type of study	International guidelines and/or consensus published after 2016

Question: What are the criteria to indicate urgent and emergency surgery in ASC in children and adolescents, according to international guidelines and/or consensus?

TABLE S38. PICO strategy on the complications related to the total colectomy in urgency and emergence in ASC in children and adolescents.

P	Children and adolescents (≤18 years) with ASC
I	Not applicable
C	Not applicable
O	Complications related to total colectomy in urgency and emergency • Intra-abdominal abscesses • Rectal stump dehiscence • Complications of ostomy
Type of study	International guidelines and/or consensus published after 2016

Question: What are the complications related to the total colectomy in urgency and emergence in ASC in children and adolescents, according to international guidelines and/or consensus?

Eligibility criteria

Inclusion criteria

- Guidelines and/or international consensus with recommendations for the surgical treatment of children and adolescents (≤18 years) with active CU;
- Guidelines and/or consensus published in English;
- Guidelines and/or consensus published in the last 5 years (from November 2016 until December 2021).

Exclusion criteria:

- Guidelines and/or consensus published before November 2016;
- Guidelines and/or consensus published in languages other than English;
- Reviews of guidelines and/or consensus.

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 S39 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 S39. Search strategy.

Databases	Search strategy	Results (titles)
Pubmed	("inflammatory bowel disease" [Title] OR "IBD" [Title/Abstract] OR "ulcerative colitis" [Title] OR "UC" [Title/Abstract]) AND ("treatment" OR "management" OR "surgery" OR "surgical") AND ("consensus" [Title] OR "guidelines" [Title]) AND ((y_5 [Filter]) AND (english [Filter]) AND (pediatric OR child OR children OR adolescent OR paediatric))	26

Search conducted on December 7, 2021.

Screening of studies

The selection of title and abstract according to eligibility criteria was carried out through the f Rayyan® Platform. It is a tool specifically developed to speed up the initial screening of abstracts and titles using a semi-automatic process. The selected publications were evaluated in full text based on the inclusion and exclusion criteria. Two independent researchers screened the studies in a blinded fashion way, and in case of divergence, the decision was made with a third reviewer. The screening flowchart can be found in FIGURE S6.

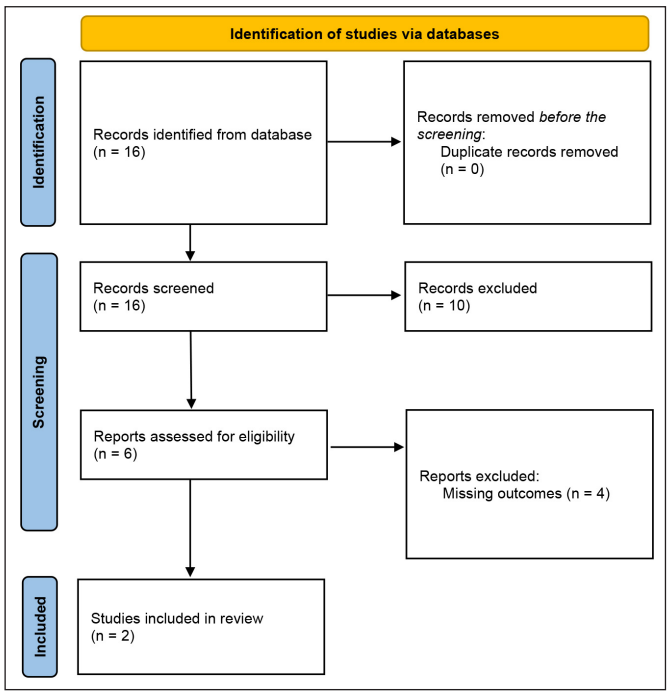

FIGURE S6. Screening flowchart of Consensus and/or Guidelines for surgical treatment.

Data recovery and extraction

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

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

Quality assessment of the included studies

The Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II) was used to evaluate the quality of the guidelines and/or consensus included in the pragmatic literature review. This instrument was developed to address the issue of variability in the quality of practice guidelines. Overall, researchers point out that the results of an AGREE II appraisal should be viewed with caution, as different guideline assessors may interpret the items and scoring system differently[48]. Therefore, AGREE II results were not used as an exclusion criterion in the current review but serve as an indicator of the quality of the reviewed guidelines. The assessment of the quality of included studies using AGREE-II can be found in TABLE S40 and S41. The quality appraisal of the included systematic literature reviews with meta-analysis was conducted by the MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2). Originally, the assessment of multiple systematic reviews (AMSTAR) tool was widely used for investigating the methodological quality of systematic reviews (SR). The AMSTAR 2 was developed for SRs of randomized controlled trials. The rate of overall confidence in the results of the systematic literature reviews is classified as high, moderate, low, or critically low. The assessment of the quality of included studies using AMSTAR 2 can be found in TABLE S42.

TABLE S40. Quality assessment of the Guidelines/Consensus of DC 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
Amil-Dias et al., 2017	Surgical Management of Crohn Disease in Children: Guidelines from the Paediatric IBD Porto Group of ESPGHAN.	66.7	61.1	52.1	83.3	37.5	66.7	61.2
Bemelman et al., 2018	ECCO-ESCP Consensus on Surgery for Crohn's Disease.	83.3	94.4	85.4	83.3	62.5	75.0	80.7
Mack et al., 2019	Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease.	66.7	72.2	95.8	100.0	54.2	100.0	81.5
Turner et al., 2018a	Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition	83.3	94.4	85.4	83.3	62.5	75.0	80.7
Turner et al., 2018b	Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis-An Evidence-based Consensus Guideline from the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.	83.3	94.4	85.4	83.3	62.5	75.0	80.7
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
van Rheenen et al., 2020	The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update	83.3	94.4	85.4	83.3	62.5	75.0	80.7
Wei et al., 2017	Management of Crohn's disease in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease.	55.6	38.9	25.0	61.1	37.5	8.3	37.7

TABLE S41. Quality assessment of the Guidelines/Consensus of UC 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
Turner et al., 2018b	Management of paediatric ulcerative colitis, Part 2: acute severe colitis-an evidence-based Consensus Guideline from the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.	18	20	49	18	19	11	80.7
Turner et al., 2018a	Management of paediatric ulcerative colitis, Part 1: ambulatory care-an evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition	18	20	49	18	19	11	80.7

TABLE S42. Quality Assessment of the Systematic Literature Review by the AMSTAR 2 tool.

Author	Colman	Dziechciarz	Gisbert	Kaur	Narula	Rolfe	Ungaro	Yu
Year	2018	2007	2007	2020	2018	2006	2020	2019
1. Did the research questions and inclusion criteria for the review include the components of PICO?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	Yes	Yes	Yes	Partial	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	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
5. Did the review authors perform study selection in duplicate?	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
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Partial	Yes	Partial	Yes	Yes	Yes	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	Yes	Yes	Yes	Yes	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No	Yes	Yes	Yes	Yes	No	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	No	No	Yes	Yes	Yes	No	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	N/A	Yes	Yes	Yes	Yes	No	No
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
Rating overall	Critically low	Critically low	Critically low	High	High	High	Critically low	Critically low

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