Saudi consensus guidance for the diagnosis and management of inflammatory bowel disease in children and adolescents

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Abstract

The management of inflammatory bowel disease (IBD) in children and adolescents is challenging. Clear evidence-based guidelines are required for this population. This article provides recommendations for managing IBD in Saudi children and adolescents aged 6–19 years, developed by the Saudi Ministry of Health in collaboration with the Saudi Society of Clinical Pharmacy and the Saudi Gastroenterology Association. All 57 guideline statements are based on the most up-to-date information for the diagnosis and management of pediatric IBD.

Keywords: Children, Crohn's disease, inflammatory bowel disease, pediatric, ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by gastrointestinal immune-mediated inflammation with heterogeneous manifestation. The management of IBD varies from patient to patient and is dependent on the disease profile, treating physician, and available therapies.[1,2] We previously published 78 evidence-based recommendations for the diagnosis and treatment of ulcerative colitis (UC) and Crohn's disease (CD) in Saudi adults.[3] This article provides new guidelines for the customized management of IBD among Saudi children and adolescents aged 6–19 years. These recommendations are designed to facilitate decision-making in clinical practice and should not be imposed as rigid diagnostic or therapeutic protocols.

METHODOLOGY

Guideline statements for the diagnosis and management of PIBD in Saudi Arabia were developed by the Saudi Ministry of Health (MOH) in collaboration with the Saudi Society of Clinical Pharmacology (SCCP) and the Saudi Gastroenterology Association (SGA). To develop these statements, an extensive literature review of international guidelines for IBD management in children was performed. The developed guidelines were mainly based on recommendations from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN),[4–6] the Canadian Association of Gastroenterology,[7] the European Crohn's and Colitis Organization (ECCO),[8–10] and the North American Society for Paediatric Gastroenterology Hepatology and Nutrition (NASPGHAN).[11]

Following the literature review, 57 guideline statements were generated based on expert opinions and recommendations from reviewed publications and international guidelines. The generated statements were reviewed and revised by a committee of experts, including 13 gastroenterologists and four clinical pharmacists, via a voting process. Members of the committee were allowed to comment on the statements and give their inputs for suggested changes. Accordingly, the statements were edited, revised, and refined. The percentage of agreement with the final editions was depicted below each statement.

RESULTS

Fifty-eight evidence-based recommendations for diagnosing and treating UC and CD in children and adolescents were proposed and refined. The level of evidence and grading structure for each recommendation are provided. These were formulated based on the Oxford Centre for Evidence-based Medicine, for which our levels of agreement are provided.[12–15]

The guidelines include statements focused on diagnosing and treating pediatric IBD (PIBD). The diagnostic approaches described include laboratory, endoscopic, and imaging modalities designed to assess the extent of disease, disease activity, and severity.

Pediatric inflammatory bowel disease

CD, UC, and IBD-unspecified (IBD-U) are the most common chronic inflammatory gastrointestinal (GI) disorders. The prevalence of PIBD ranges from 0.4 to 23.1 cases per 100,000 individuals per year and varies according to the region.[16–20] Up to 4% of patients with PIBD are diagnosed before the age of 5 years.[21–26] The symptoms of PIBD are more severe than those of adult-onset IBD.[27,28] Left-sided UC is common among adults, but pediatric UC can present as pancolitis, though this is not the case for all patients.[29–32] CD is more severe and aggressive, with more upper GI tract involvement.[17] Most PIBD cases present with abdominal pain, weight loss, and bloody diarrhea. Other symptoms include extraintestinal manifestations, such as anemia and poor growth.[33–35] Phase 3 clinical trials assessing the safety and efficacy of advanced PIBD agents typically exclude subjects under 18 years; nonetheless, most patients are treated with agents approved for adults.[36–38] A more detailed understanding of the pathogenesis of PIBD is required to design more effective therapeutics.

A complex interplay between genetic susceptibility, microbiome dysbiosis, environmental factors, and innate immunity dictates the pathology of PIBD.[39,40] Genomewide association studies (GWAS) have identified several nonoverlapping genetic risk loci, including many shared between CD and UC.[39,41–48] The genes implicated in PIBD and adult IBD overlap, suggesting converging predisposition and pathology.[49] Specific susceptibility alleles also require genetic and nongenetic cues to manifest the disease. Risk-associated loci include the alternative splicing of nucleotide-binding oligomerization domain 2 (NOD2), ATG16L1, and IL23R polymorphisms.[49–53] Genetic variants associated with PIBD and adult IBD are also ethnicity-dependent, raising the possibility that they emerged through historical selective pressure.[49] Smoking and vitamin D deficiency are disease-specific modifiers that exacerbate the condition.[54–56] Other common environmental risk factors include diet, stress, appendectomy, and medications. The Westernized diet of artificial additives, sugar-rich foods, fatty foods, and a low intake of fruits and vegetables can also contribute to disease

development.[41,57–61] Epigenetic mechanisms have also recently been proposed, including methylation, lncRNAs, and miRNAs implicated in disease predisposition.[42,51] Genes within several IBD-associated loci indicate a role for barrier integrity as the disease manifests. Examples include *CDH1, GNA12,* and *PTPN2*.[52] Other genetic loci identified in PIBD are associated with innate mucosal defenses, immune regulation, cell migration, autophagy, adaptive immunity, and metabolism.[52,62–64]

Dysbiosis of the gut microbiome through both diet and excessive antibiotic use is strongly linked to IBD. Compared to healthy subjects, certain types of beneficial bacteria, such as Bifidobacterium longum, are more abundant in patients with UC, whereas other types, such as Eubacterium rectale, Faecalibacterium prausnitzii, and Roseburia intestinalis, are reduced in patients with CD and UC.[65–71] In contrast, the number of harmful bacteria, including *Bacteroides fragilis,* is increased. Differences in the abundance of *Clostridium hathewayi*, *Clostridium bolteae, Ruminococcus gnavus, Eubacterium rectum, Akkermansia muciniphila,* and *E. coli* have also been reported.[72–74] Intestinal barrier damage in IBD patients is also mediated through immune cell infiltration. Variability in glycan composition also disrupts the mucosal layer and its associated immunity, contributing to IBD development.[75] Increased intestinal permeability occurs due to the destruction of tight junction proteins that maintain the integrity of the mechanical barrier.[72,76–78] Penetration of the gut luminal contents through the bowel wall also propagates secondary inflammatory responses from the adaptive immune system.[65,66,72,74,76,79] Dendritic cells, myeloid-derived suppressor cells, natural killer cells, and macrophages are frequently altered in patients with IBD.[52,80,81] The mode of delivery, gestational age at birth, and patterns of infant feeding are also thought to contribute to PIBD development, though firm evidence of these associations is currently lacking.

Epidemiology and potential risk factors of PIBD in Saudi Arabia

The mean incidence rate per 100,000 individuals in the Kingdom of Saudi Arabia (KSA) is 0.2, 0.27, and 0.47 for UC, CD, and IBD, respectively.[82] Compared to Western countries, Saudi children with CD have a lower prevalence of IBD in first-degree relatives, a reduced incidence of early-onset disease, delayed development, and a higher frequency of stricturing and penetrating disease.[17,18,23,61,82,83] Regional studies of children highlight a positive association between low fruit consumption and PIBD.[55,61] Low levels of physical activity, antibiotic exposure, appendectomy, and frequent gastroenteritis admissions represent additional risk factors.[30,54,55,61,82,84–86] The quality of life in PIBD patients in KSA is influenced by disease severity and the effectiveness of prescribed medications.[30,87–90]

Classification of PIBD

Pediatric IBD is classified according to the ESPGHAN Porto Criteria into CD, UC, and IBD-U based on features atypical or uncommon in UC (class II) or of rare occurrence [class III; Tables 1 and 2]. Typical features of UC include chronic continuous mucosal inflammation of the colon extending proximally from the rectum, with more severe inflammation in the distal compared to the proximal region (severity gradient).[91–94] Classical CD is characterized by transmural inflammation that can affect any region of the digestive tract. Other features of CD include internal or external fistulae, strictures, and perianal manifestations.[95,96] Inflammatory bowel disease unclassified (IBD-U) is twice as common in children (≤18 years) than in adults. This high frequency is linked to colitis, particularly in young children.[97] Clinical follow-up of pediatric IBD-U patients suggests that up to 80% are reclassified as CD or UC. A smaller fraction is classified as CD or UC during the early stages.

Diagnosis of PIBD

Clinical history is critical in patients with suspected PIBD. Abdominal pain, diarrhea, weight loss, and anemia-related symptoms are common.[98] Physical examination can identify underlying pathologic features. Growth patterns are also critical as weight loss and faltering growth are frequently observed.[57,99,100] Pediatric IBD should also be considered in symptomatic overweight children. The prevalence of obesity is 23.6% in PIBD and 30.1% in

Table 1: ESPGHAN Porto Criteria for the classification of PIBD

No.	Suspected	Phenotypic Features	Diagnostic technique(s)	Imaging suggested Diagnosis	Final Diagnosis
1.	Typical UC	Contiguous disease from the rectum	Consider MRE	UC	UC
2.	Atypical UC	Rectal sparing, short duration, cecal patch, acute severe colitis	MRE/WCE	UC	UC
3.	CD	Noncontiguous aphthous or linear ulcers primarily in the ileum or colon, although CD may involve any area of GI tract.	MRE/WCE	CD	CD
4.	IBD-U	Inflammation limited to the colon. Features that make the differentiation between UC and CD challenging.	MRE/WCE	CD or Negative	CD, UC, or IBD-U

CD: Crohn's disease, GI: Gastrointestinal, IBD-U: Inflammatory bowel disease-unspecified, MRE: Magnetic resonance enterography, UC: Ulcerative colitis, WCE: Wireless Capsule Endoscopy

Table 2: Paris classification of UC

		Paris
Extent*	E1	Ulcerative proctitis
	E2	Left-sided UC (distal to splenic flexure)
	E3	Extensive (hepatic flexure distally)
	E4	Pancolitis (proximal to hepatic flexure)
Severity	S0	Never severe†
	S1	Ever severe†

*Extent defined as maximal macroscopic inflammation

UC.[30,101–104] Clinical symptoms include clubbing, pallor, oral aphthous ulcers, delayed puberty, and skin lesions, including pyoderma gangrenosum and erythema nodosum.[105–108]

Initial laboratory investigations in suspected PIBD cases should include complete blood counts (CBCs), C-reactive protein (CRP), erythrocyte sedimentation rates (ESRs), liver enzymes, serum proteins, and albumin levels.[109,110] Stools should be tested for bacterial pathogens, *clostridium difficile*, ova, and parasites.[111–113] Increased levels of fecal calprotectin (FC) can also serve as a biomarker for intestinal inflammation in suspected cases.[74,114–118]

Statement 1

Initial laboratory investigations for suspected PIBD should include complete blood counts, CRP, albumin, liver enzymes, and fecal calprotectin.
Agreement: 100%

Esophagogastroduodenoscopy (EGD) is a diagnostic procedure for PIBD, which visualizes the esophagus, stomach, and proximal duodenum.[119–123] Similarly, ileocolonoscopy can identify inflammation in the colon and terminal ileum but cannot evaluate inaccessible regions of the small intestine.[1,38,120,124] Bowel imaging can visualize areas of the small bowel inaccessible to optical endoscopic visualization.[6,26,120,125] Capsule endoscopy has replaced fluoroscopic small-bowel imaging to evaluate patients with suspected PIBD.[123,126]

Statement 2

Children with suspected IBD should undergo ileocolonoscopy and esophagogastroduodenoscopy (EGD) at initial evaluation.
Agreement: 93.75%

Pediatric IBD shows both gastrointestinal (GI) and extraintestinal symptoms. Children with CD can present with abdominal pain, bloody diarrhea with colitis, weight loss, growth failure, malaise, fatigue, fever, and anemia. C-reactive protein (CRP), FC, and serum albumin levels can identify children at low risk (negative calprotectin) or high risk (low albumin or positive CRP).[127]

The first line of investigation for suspected PIBD should include an EGD and ileocolonoscopy. The PIBD data registry states that EGD can aid the final diagnosis in approximately 10% of cases.[122,121] Small bowel imaging can identify active inflammation, including mesenteric hypervascularity, bowel wall thickening, fibrofatty proliferation, and extraluminal complications, including intra-abdominal abscesses, enteric fistulae, and free intraperitoneal air.[6,26,125] The noninvasive nature of imaging makes it a favorable tool for diagnosis, disease activity, disease extent, and response to therapy. Magnetic resonance enterography (MRE) is considered the gold standard for the staging and monitoring of fistulae and perianal disease.[125,128–133] Excluding emergency cases, computed tomography enterography (CTE) is not routinely used in PIBD due to radiation risk. Small bowel ultrasound (SBUS) is used to assess disease activity and the response to therapy.[134] This is particularly important in the pediatric population to reduce the frequency of endoscopy and MRE, both of which require deep sedation. Magnetic resonance enterography has a higher specificity for IBD in children than adults.[119]

Statement 3

At diagnosis, we recommend MRE as the imaging technique of choice due to its excellent diagnostic accuracy and low radiation exposure.
Agreement: 93.75%

No gold-standard test is available for the definitive diagnosis of PIBD. Ulcerative colitis is identified based on colonoscopy and histology as it is limited to the colon.[22,121,135,136] Crohn's disease affects the proximal small bowel and is associated with malabsorption symptoms such as weight loss, micronutrient deficiencies, and steatorrhea. Small bowel involvement is also associated with stricturing behavior and multiple bowel surgeries.[137] Imaging can help determine the extent of bowel involvement, which is essential at initial diagnosis and when considering bowel resection.

Statement 4

Small bowel imaging is recommended for all suspected cases of PIBD at diagnosis, including suspected CD, atypical UC, and IBD-unclassified and in patients for which the terminal ileum cannot be intubated.
Agreement: 100%

Classification according to disease onset

Very early-onset IBD (VEO-IBD) is classified as disease symptoms at ≤6 years of age. Infantile-onset inflammatory bowel disease (IO-IBD) is defined as IBD at ≤2 years.[4,138,139] Both follow a more severe clinical course, with poor responses to conventional therapy. This necessitates further genetic and immunological tests to exclude primary immunodeficiency and monogenic forms of IBD.

Statement 5

All children with very early onset IBD (defined as less than 6 years of age) should undergo genetic and immunological testing to exclude primary immunodeficiency and monogenic forms of IBD.
Agreement: 100%

Classification of UC

The Paris classification categorizes UC into four groups [Table 2; E1-E4].[24,98,140,141] In E1, inflammation is confined to the rectum. In E2, inflammation involves a region of the colon distal to the splenic flexure. In E3, inflammation extends distal to the hepatic flexure. In E4, the inflammation extends proximally to the hepatic flexure. Disease extension is dynamic and may progress or regress over time. Using the Paris classification, severity is either S0 (never-severe) or S1 (ever-severe). Severe disease is considered when the Paediatric Ulcerative Colitis Activity Index (PUCAI) score is ≥65.[142]

Classification of CD

The Montreal classification was updated from the Paris classification.[16,140,141] In the Montreal system, age (A1) is subdivided into A1a and A1b, specifying those diagnosed aged ≤10 years or between 10 and 17 years, respectively [Table 3]. Disease location (L4) was updated to L4a and L4b to determine whether upper GI disease is proximal (L4a) or distal (L4b) to the ligament of Treitz. L4 in the Montreal classification (L4a or L4b) can concurrently occur with L1, L2, or L3 [Table 3]. For pediatric disease, an additional category for behavior (B2B3) is included [Table 3]. This category refers to patients with both B2 and B3 phenotypes (combined penetrating and constricting pathologies). This category distinguishes patients with the combined phenotype from those with a purely fistulizing phenotype. The presence of perianal abscesses or fistulae must be considered when describing disease behavior.[121,143,144] The Paris classification of CD considers the presence or absence of growth delay, assigned as G1 or G0, respectively.

Table 3: Montreal and Paris Classifications of CD

		Montreal and Paris
Age at Diagnosis	A1a	<10 years
	A1b	10-17 years
	A2	17-40 years
	A3	>40 years
Location	L1	Distal 1/3 ileum±limited cecal disease
	L2	Colonic
	L3	Ileocolonic
	L4a	Upper disease proximal to Ligament of Treitz*
	L4b	Upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum*
Behavior	B1	Nonstricturing, nonpenetrating
	B2	Stricturing
	B3	Penetrating
	B2B3	Penetrating and stricturing disease, at the same or different times
	p	Perianal disease modifier
Growth	G_0	No evidence of growth delay
	G_1	Growth delay

DIAGNOSTIC APPROACHES

Laboratory investigation

Initial laboratory tests should include CBC, CRP, liver enzymes including gamma-glutamyl transferase (GGT), and serum albumin. Stool tests should be performed for the assessment of *Salmonella, Shigella, Campylobacte, Yersinia* species, *Escherichia coli O157, Clostridiodes difficile* (C. difficile) toxins A and B, ova, parasites, and FC or fecal lactoferrin.[18,23,67,71,114,145–148] Approximately 10–20% of PIBD patients show normal laboratory indicators for which diagnosis should not be excluded. Faecal calprotectin, CRP, and albumin hold utility as biomarkers for assessing treatment responses.[29,57,127,149–151]

Statement 6

After excluding infectious disease, a diagnosis of PIBD can be achieved through detailed history, physical examination, laboratory assessment, upper endoscopy, ileocolonoscopy with biopsy, histology, and examination of the small bowel.
Agreement: 100%

Clostridiodes difficile infection (CDI) is less frequent in PIBD compared to adults and is predominantly asymptomatic.[111–113] A tenfold higher occurrence of CDI in PIBD is found compared to the general pediatric population. Polymerase chain reaction (PCR) analysis of *C. difficile* toxin B (tcdB) can be used to confirm infection and combined with assays for CDI-specific glutamate dehydrogenase activity. All newly diagnosed PIBD patients, particularly those with diarrhea, are recommended to have at least one stool sample collected for CDI screening.[152]

Statement 7

Enteric infections should be excluded in suspected PIBD prior to endoscopy. Bacterial infections, including *Clostridiodes difficile* (C. diff), should be ruled out by microbiological stool tests and the presence of C. diff toxins A and B.
Agreement: 100%

Asymptomatic carrier states of CDI are observed in PIBD cases compared to healthy controls.[153,154] If antimicrobial agents fail to resolve symptoms, this can reflect the presence of resistant CDI or severe PIBD in CDI carriers.[155–157]

Endoscopy and histopathology

Endoscopy can be used to exclude alternative pathology, differentiate CD from UC, and monitor treatment responses.[84,158,159] For suspected PIBD, ileocolonoscopy and EGD should be performed at the initial evaluation.[160] Ileocolonoscopy visualizes the colon and terminal ileum and permits the collection of biopsies. In cases of suspected PIBD, segmental biopsies should be obtained from the ileum and each colonic segment, including the rectum.[161] Segmental colonic biopsies should be obtained from both the normal and affected mucosa. In cases of suspected upper GI involvement, at least two biopsies should be collected during EGD and stored in individual

collection tubes. In pediatric patients, upper gastrointestinal involvement is more common in PIBD than in adults.[160,162] Regardless of symptoms, EGD is recommended for the initial evaluation of suspected PIBD.

Statement 8

Two or more segmental biopsies should be obtained from endoscopically examined segments of the GI tract, including normal mucosa, and placed in different containers.
Agreement: 100%

Small bowel imaging

Video capsule endoscopy (VCE) is a safe, noninvasive technology that can detect early mucosal lesions in CD patients.[163–165] Video capsule endoscopy can visualize the entire small bowel with minimal discomfort. In proximal small bowel segments, VCE permits the more sensitive detection of mucosal lesions than MRE. The limitation of VCE is its inability to control capsule movement, which carries a risk of retention. In children with suspected CD, VCE is a safe and effective diagnostic tool. A systematic review and meta-analysis of pediatric CD reported an overall risk of capsule retention of 1.64% (3.45% in established cases of CD and 1.22% in suspected CD cases).[166,167] A patency capsule is also beneficial in limiting retention rates.

Statement 9

Video capsule endoscopy (VCE) can be used as an alternative for identifying small intestinal mucosal lesions in children with suspected CD for whom ileocolonoscopy and imaging have been nondiagnostic and when MRE cannot be performed.
Agreement: 87.5%

Intestinal ultrasound (IUS) can be used as a first-line screening tool for CD, irrespective of clinical symptoms.[168–170] Intestinal ultrasound is suitable for routine surveillance due to its noninvasive nature and lack of radiation exposure.[169] Color-Doppler imaging and contrast-enhanced US can provide a more accurate assessment of disease activity.[171]

Statement 10

Intestinal ultrasound (IUS) is a valuable screening technique for suspected PIBD. Due to its low sensitivity, it should be supplemented with small bowel imaging techniques.
Agreement: 100%

Immunodeficiency

Primary immune deficiency as a cause for PIBD should be considered. Pediatric IBD causes the immune system to incorrectly respond to environmental triggers, such as viruses or bacteria, leading to inflammation of the GI tract.[172] Patients with suspected PIBD should be investigated for both primary immunodeficiency and immune dysregulation. Table 4 highlights the suite of assays that should be performed.[172]

TREATMENT TARGETS AND MONITORING RESPONSES IN PIBD

Clinical disease activity scores

The Paediatric Ulcerative Colitis Activity Index (PUCAI) can be used to diagnose UC in children [Table 5]. The PUCAI score is based on abdominal pain, rectal bleeding, overall stool consistency, number of stools per 24 h, nocturnal stools (episodes causing wakening), and activity

Table 4: Diagnostic workup of very early onset IBD to be adapted according to the clinical presentation

Basic immune workshop	Genetic Testing
Complete blood counts Neutropenia, Lymphocytopenia, Thrombocytopenia	Candidate gene approach Suspected defect or confirmation of identified defect
Lymphocyte subsets T-/B cell defects, Regulatory T cell defects (FOXP3, CD25)	Gene panel Unclear diagnosis
Ig G-A-M-E SCVID, CVID, B-cell defects, agammaglobulinemia, hyper-IgM/hyper-IgE syndrome	Whole exome or genome sequencing Research protocol for search of new mutations
Oxidative burst CGD	
Functional tests IL 10-axis, XIAP nod-axis Apoptosis assessments	

CGD: Chronic granulomatous disease; CVID: Common variable immunodeficiency; IL: interleukin; SCID: severe immunodeficiency; XIAP: X-linked inhibitor of apoptosis

Table 5: Paediatric ulcerative colitis activity index (PUCAI) score

Item	Category/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 points 3-5=5 points 6-8=10 points >8=15 points
Nocturnal stools (any episode causing wakening)	No=0 points Yes=10 points
Activity Level	No limitation of activity=0 Occasional limitation of activity=5 Severe restricted activity=10
Sum of PUCAI	0-85

PUCAI: Paediatric ulcerative colitis activity index

levels.[173,174] Scores for mild cases: 10–34; moderate cases: 35–64; severe cases >65; and remission <10 (nonactive disease).

Statement 11

We recommend the PUCAI score in children with UC to monitor disease activity at each visit. Therapy should be reviewed when PUCAI are ≥10 points.
Agreement: 100%

For CD in children, the Paediatric Crohn's Disease Activity Index (PCDAI) incorporates symptoms, physical examination, growth, and serum inflammatory markers.[147,175] Higher scores indicate more severe disease. This has been superseded by the weighted PCDAI, which takes clinical symptoms, laboratory markers, anthropometric data, and clinical examination into account [Table 6]. Around 1 in 4 PIBD patients experience acute exacerbations of UC.[91] Direct examination of the colonic mucosa by endoscopy is the gold standard in diagnosing UC, but it is invasive and requires general anesthesia.[135] The PUCAI was developed as a less invasive tool to assess pediatric UC.[174] In a validation cohort, the PUCAI correlated with the Physician's Global Assessment (PGA), Mayo scores, and colonoscopy appearance with R values of 0.91, 0.95, and 0.77, respectively.[176]

Table 6: Paediatric Crohn's Disease Activity Index

Parameter/Detailed Description	Point
Abdominal pain	
None	0
Mild (brief episodes, not interfering with activities)	5
Moderate/severe (frequent or persistent, affecting with activities)	1
Stools	
0-1 liquid stools, no blood	0
2-5 liquid or up to 2 semi-formed with small blood	5
Gross bleeding, >6 liquid stools or nocturnal diarrhea	10
Patient functioning, general well-being (recall, 1 week)	
No limitation of activities, well	0
Occasional difficulties in maintaining age appropriate activities,	5
Frequent limitation of activities, very poor	10
Examination weight	
Weight gain or voluntary weight loss	0
Involuntary weight loss 1-9%	5
Weight loss >10%	10
Height	
< 1 channel decrease (or height velocity >-SD)	0
> 1<2 channel decrease (or height velocity < -1SD> -2SD)	5
>2 channel decrease (or height velocity < -2SD)	15
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness, involuntary guarding, define mass	10
Peri-rectal disease	
None, asymptomatic tags	0
1-2 indolent fistula, scant drainage, tenderness of abscess	5
Active fistula, drainage, tenderness or abscess	10
Extra-intestine manifestations	
Fever >38.5 x 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum	
None	0
One	5
Two	10

Statement 12

The Paediatric Crohn's Disease Activity Index (PCDAI) or Weighted Paediatric Crohn's Disease Activity Index (wPCDAI) can be used with fecal calprotectin assays to assess disease activity and monitor treatment in children with CD.
Agreement: 100%

The response to interventions must be verified using measures of disease activity. Since its introduction, the PCDAI has become the standard index for measuring disease activity in pediatric CD and shows excellent interobserver agreement.[177] It is important to note that PCDAI, including weighted PCDAI (wPCDAI), has limitations, including poor correlation with endoscopic disease activity. Pediatric CDAI should, therefore, be evaluated in the context of objective markers of inflammation, including CRP and FC.[178]

Endoscopic scores

For pediatric CD, the Simple Endoscopic Score for Crohn's Disease (SES-CD) [Table 7] should be used to document the extent of inflammation and response to therapy/healing.[179]

The UC endoscopic index of severity (UCEIS) and Mayo Endoscopic score (MES) can be used to assess mucosal pathology and mucosal healing [Tables 8 and 9]. The UCEIS accurately reflects clinical outcomes and can predict medium- to long-term prognosis in UC patients undergoing therapy.[180–182] The UCEIS and MES findings should be used to support decision-making in clinical practice.[183,184]

Treatment targets

Symptomatic treatment is the historical standard of care for PIBD but fails to prevent disease progression or the need for surgery. Treatment targets must include the remission of disease activity, confirmed through biomarker analysis and mucosal healing to predefined targets.[185] This treat-to-target approach includes meticulous monitoring of inflammation and disease activity/progression, which can reduce the need for surgery.[186–188] Regular monitoring of mucosal inflammation via endoscopy is effective, but its invasive nature makes it impractical.

Short-term targets

Pediatric CDAI and wPCDAI are effective methods for the assessment of CD activity. Both are reliable, reproducible, and accurate. Cutoff values have been established to distinguish specific disease states.[147,175] When a decrease in PCDAI by ≥12.5 and wPCDAI by ≥17.5 points are observed, the clinical response to CD treatment is favorable [Table 10].

Table 7: Simple Endoscopic Score for Crohn's Disease

Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (diameter 0.1 to 0.5 cm)	Large ulcers (0.5 to 2 cm)	Very large ulcers (≥2 cm)
Ulcerated surface	None	≤10%	10-30%	≥30%
Affected surface	Unaffected segment	≤50%	50-75%	≥75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Table 8: Mayo Endoscopic scoring system

	Mayo Endoscopic Scoring System
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)

The PUCAI can guide decision-making pertaining to UC treatment. When PUCAI values are <10, the patient is classified as in remission.[173] A PUCAI score >65 is indicative of active disease.[174] A decrease of the PUCAI ≥20 points from baseline is the recommended cutoff and correlates with an improvement in disease activity.

Statement 13

We recommend the following clinical response parameters as short-term targets (3 months) for the treatment of children with IBD:
A. Decrease in CD PCDAI scores of at least 12.5 points and 17.5 in wPCDAI.
B. Decrease of UC PUCAI score of at least 20 points.
Agreement: 100%

Intermediate targets

Clinical remission in pediatric CD is defined as PCDAI <10 or <7.5 points when excluding height [Table 10]. Although a score <10 provides a more accurate definition of remission than <12.5, poor growth and active disease can influence the response to treatment. All items in the PCDAI must be normalized. Height, for example, is unlikely to change over a short period, which must be considered in all assessments.[147,175]

A PUCAI cutoff of <10 can distinguish individuals with active illness. This is significant in the clinic to identify those who attain remission. While defining "remission" using the PUCAI is straightforward, the classification of responses requires further insight.[174]

Statement 14

We recommend clinical remission as an intermediate target (6 months) of treatment in children defined as;
Decrease in CD PCDAI score to <10 or <7.5 points (excluding height items) or wPCDAI <12.5 points.
Decrease in UC PUCAI score to <10 points.
Agreement: 93.75%

C-reactive protein and FCP can be used to assess therapeutic responses. In a prospective study of pediatric CD patients, those achieving an FC <250 μg/g within the first 12 weeks of treatment showed a favorable outcome.[189]

Statement 15

Normalization of CRP values and fecal calprotectin (100–250 μg/g) can be used as noninvasive intermediate treatment targets to monitor treatment responses in CD and UC.
Agreement: 100%

Statement 16

We do not recommend histologic remission as a therapy target in patients with UC.
Agreement: 71.43%

Long-term targets

The therapeutic landscape for PIBD has substantially changed in recent years. Historically, the purpose of treatment was to reduce symptoms. Advances in imaging technologies coupled with increased knowledge of disease processes mean that therapy can now be targeted to induce mucosal healing and restore growth.[146] The most appropriate nutritional, pharmacological, and surgical interventions for underlying disease must first be achieved to manage growth deficiency.[100,190–193] Enteral nutrition can improve remission and patient health.[192,194–196]

Statement 17

We recommend growth restoration as a long-term treatment target (>1 year). Should this not be achieved, IBD activity should be evaluated. Other causes impacting growth should also be considered. Adequate nutritional support should be provided.
Agreement: 100%

Recent updates to the ECCO-ESPGHAN suggest that clinical disease indices such as the PCDAI fail to correlate with mucosal inflammation between children and adults.[6] Up to 50% of those in clinical remission have mucosal ulcerations. The superior diagnostic accuracy of wPCDAI compared to other versions has been reported.[197,198] Pediatric CDAI and wPCDAI scores cannot confirm therapeutic success if endoscopic healing is the treatment goal.[199] Further noninvasive tests are now a composite of FC, CRP, and clinical scores.

Statement 18

Transmural healing reflects a deeper level of healing but is not recommended as a therapeutic target in patients with CD.
Agreement: 100%

Table 9: Summary of MES and UCEIS characteristics

Characteristics	Mayo Endoscopic Score (MS)	Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
Type	Discrete (4 classes)	Continuous
Variables	Mucosal lesions, bleeding, and hyperemia	Mucosal lesions, vasculature, bleeding
Range	0-4	0-8
Mucosal healing	Score 0-1	Not specified
Severe disease	Score 3	Score ≥7
Statistical validation	Partial	Partial
Used in trials	Yes	Scant
Diffuse in clinical practice	Yes	No
Strength	Simple, diffuse	Objective, prognostic value
Limitation	Subjective, imperfect agreement	More complex

Table 10: Recommended cutoff values of PCDAI versions

	Remission	Mild	Moderate	Severe	Small improvement	Moderate improvement
PCDAI	≥10-≤7.5 excluding height	≥17.5	≥27.5	≥37.5	≥12.5	≥22.5
wPCDA1	≤12.5	≥27.5	≥40	≥57.5	≥17.5	≥37.5

Endoscopic healing assessed by ileocolonoscopy strongly predicts sustained long-term steroid-free clinical remission.[1,38,197] Recent studies have, however, challenged its effectiveness, given that CD is a transmural illness with active intramural inflammation.[122,170] It has been proposed that "bowel healing" or "deep healing," which describes recovery of the entire intestinal wall, represents a more accurate therapeutic goal.

Cross-sectional imaging (CSI) to measure transmural healing can independently predict improved long-term outcomes.[169] In CD, transmural healing can be considered a therapeutic endpoint.[38,188,200] This is an evolving concept with accurate descriptions still to be established.

Statement 19

We recommend endoscopic healing as a long-term treatment target (6–12 months) measured by CD SES-CD score <3 points or the absence of ulcerations (e.g., SES-CD ulceration subscores=0/1); UC Mayo endoscopic subscore=0–1 points or UCEIS ≤1 points. Agreement: 84.61%

MEDICAL MANAGEMENT OF PEDIATRIC CD

Risk stratification

Criteria to predict disease outcomes in pediatric-onset CD patients at diagnosis are lacking.[201] Table 11 shows the established predictors of poor treatment outcomes, defined as a requirement for early surgical intervention or the probability of rapid progressive bowel disease. Advances in this area are urgently required.

According to observational studies in young patients with CD, failure to achieve clinical and biochemical remission following induction therapy can be predictive of a poor outcome. Patients with PCDAI scores greater than 5 ($P = 0.012$), CR*P* values >20 mg/L ($P = 0.019$), and FC levels >400 μg/g ($P = 0.001$) at week 12 of induction therapy were at a higher risk of relapse at the end of the observational period, according to the GROWTH CD study.[202]

The same patient cohort was followed for 104 weeks to identify risk factors for early surgery. Two years post diagnosis, 26% of children with stricturing disease required early surgery, compared to 8% without stricturing disease ($P = 0.001$).[203] Regarding stricturing, real-world analysis of anti-TNFα treatment showed a limited long-term but significant short-term response.[204]

Induction therapy in luminal CD

Exclusive enteral nutrition

Exclusive enteral nutrition (EEN) includes a nutritionally complete liquid diet to replace regular solids and fluids (other than water) for up to 8 weeks. Close support is required to guide appropriate volumes to meet caloric requirements. Food is gradually reintroduced once the EEN phase is complete. When returning to a regular diet, supplemental enteral nourishment can maintain remission. Children can receive maintenance therapy prior to or after the completion of EEN.[205–208]

Multiple systematic reviews have demonstrated that EEN is as effective as corticosteroids for the induction of clinical remission in pediatric CD.[194,196,203,206,209] Patients were more likely to cease EEN due to unpalatable formulations and the discomfort of nasogastric tubes. Patients receiving EEN also frequently reported diarrhea and vomiting.[129,209,210] Reintroducing calories with EEN or a regular diet in pediatric CD patients deprived of food for an extended time period can also result in refeeding syndrome. Slowly introducing calories and monitoring serum electrolytes are important measures during rapid weight gain.[117,205,211] Current regimens

Table 11: Risk stratification of pediatric CD according to disease behavior at diagnosis

Risk stratification	Paris classification at diagnosis
Low	B1 (Inflammatory)
Medium	B1 and failure of induction therapy at week 12
	B1 with growth delay
High	B2 with extensive disease or deep ulcers
	B2 with perianal disease
	B2 (stricturing disease)
	B3 (penetrating disease)

deliver 80–90% of the calories the patient requires through NGT during the night for 8–12 weeks. Patients are then permitted to intake 10–20% of calories freely during the day.

Statement 20

We recommend exclusive enteral nutrition (EEN) for the induction of remission in children with luminal CD.
Agreement: 100%

Crohn's disease-Treat (CD-TREAT) and Crohn's Disease Exclusion Diet (CDED) are newly introduced food-based diets designed to be more palatable.[117,212,213] In a recent RCT, pediatric CD patients tolerated CDED combined with partial enteral nutrition (PEN) better than EEN.[214] A higher number of patients also achieved prolonged clinical remission at week 12. Further studies are required to confirm the effectiveness of this intervention for endoscopic healing.

Statement 21

We recommend partial enteral nutrition (PEN) with CDED to induce clinical remission in pediatric CD patients.
Agreement: 100%

Corticosteroids

Corticosteroids are potent, fast-acting, oral, or parenteral medications that can be used to treat patients with moderate-to-severe IBD relapses.[215–218] Budesonide has low bioavailability due to its high susceptibility to first-pass metabolism but can be used to treat individuals with ileocecal CD with low systemic toxicity.[219]

Systemic corticosteroids can induce remission when EEN is poorly tolerated or unsuccessful.[196,220] Although their use has been documented in adult CD for decades, evidence of their benefits in children is limited. Corticosteroids have been linked to an increased risk of infection, intra-abdominal or pelvic abscesses, weight gain, sleeplessness, and Cushingoid facies.[221]

Statement 22

Corticosteroids can be used for the induction of remission when EEN is not well tolerated in children with luminal CD.
Agreement: 100%

The starting dose of methylprednisolone is weight-dependent (1.6 mg/kg/day) and should be tapered until clinical remission is achieved.[222–225] This should not, however, exceed 4 weeks of therapy (maximum 1000 mg). Weaning off steroids over several weeks following 1 to 2 weeks of induction can lower the risk of relapse. In a single study, patients treated with methylprednisolone (dosing scheme of 1.6 mg/kg/day; maximum dose: 60 mg/day) for 4 weeks, followed by 6 weeks of tapering until a dose of 5 and 10 mg/day was achieved, showed lower relapse rates. When EEN is ineffective for treating mild ileocecal CD (L3), ileal-release budesonide is superior to prednisolone. Budesonide should be dosed at 9 mg once daily for 6 weeks for those weighing ≥40 kg. This should be decreased to 6 mg daily for 6 weeks and then 3 mg once per day for 4 weeks.[226–231]

Anti-TNFα therapy

Statement 23

In high-risk newly diagnosed CD patients, anti-TNFα therapy is recommended for induction and maintenance of remission.
Agreement: 78.57%

Infliximab and adalimumab are among the most effective therapies for clinical and endoscopic CD remission.[232,233] Both have had a considerable impact on pediatric patient care. In a single propensity-score-matched analysis of the RISK study, anti-TNFα monotherapy within 3 months of diagnosis showed improved remission at 1 year compared to induction with EEN or corticosteroids, followed by immunosuppressant therapy.[177,234,235]

In children with a high risk of poor outcomes, anti-TNFα therapy is recommended as a primary induction and maintenance therapy. In patients with developmental delays or those who fail to achieve clinical PCDAI <10 and biochemical remission (FC <250 μg/g) after induction with EEN or corticosteroids, anti-TNFα medications should be considered as an early treatment strategy.

Infliximab can be administered intravenously in three doses of 5 mg/kg (weeks 0, 2, and 6), followed by maintenance therapy at 5 mg/kg every 8 weeks.[236,237] Children under 30 kg with extensive illness and low blood albumin levels require induction doses of up to 10 mg/kg and shorter dosing intervals to achieve appropriate trough levels. Adalimumab can be used for induction and maintenance in CD.[238] The initial adalimumab induction dose is 160 mg, followed by 80 mg (week 2) and a maintenance dose of 40 mg every other week in children weighing 40 kg or more. Adalimumab doses of 80 mg at week 0, 40 mg at week 2, and 20 mg every 2 weeks from week 4 onward are recommended for patients weighing less than 40 kg. Given

the frequency of underdosing in young children, larger and more frequent doses are required for those who respond poorly. A maximum single follow-on dose of 20 mg adalimumab for patients aged 2–4 years and up to 40 mg adalimumab for patients aged 4–12 can be administered every other week.[239]

A Top-Down Infliximab Study in Kids with Crohn's Disease (TISKIDS) was the first in children with moderate to severe CD.[236] The study compared top-down infliximab to conventional first-line EEN or corticosteroids. Treatment consisted of 5 infliximab infusions combined with azathioprine versus step-up therapy consisting of standard induction treatment with oral prednisolone or EEN combined with an immunosuppressant. The primary endpoint of clinical remission at 52 weeks (wPCDAI <12.5 points in the absence of therapy escalation) was achieved in 41% of top-down infliximab patients compared to 12% of patients receiving conservative treatment ($P = 0.002$). This supports using infliximab as a first-line therapy in newly diagnosed CD cases.

Statement 24

We recommend anti-TNFα treatment (infliximab or adalimumab) in children with active CD who do not achieve clinical remission with corticosteroids.
Agreement: 78.57%

5-ASA, sulfasalazine, and thiopurines

Amino salicylic acids (5-ASAs) are used to treat adult UC for which a series of derivatives have been developed. Five amino-salicylic acids, however, fail to induce remission or prevent relapse in pediatric CD patients.[240–243] Evidence supporting the use of sulfasalazine for use in mild colonic CD is also weak.[244] Sulfasalazine has two components: 5-aminosalicylate and sulfapyridine. The sulfapyridine is responsible for its documented side effects, while the 5-ASA component mediates its beneficial effects for IBD.[245] A GRADE analysis of the quality of evidence gathered in systematic reviews reported no differences in adverse outcomes between sulfasalazine and placebo groups.[246] Sulfasalazine was, however, less efficacious than corticosteroids and inferior to corticosteroid combination therapy. At weeks 17–18, 43% (55 / 128) of sulfasalazine patients achieved remission, compared to 60% (79 / 132) of corticosteroid patients.[246] Sulfasalazine was more effective than the placebo for the induction and maintenance of remission in UC.

Statement 25

We recommend against the use of 5-ASA to induce clinical remission in children with CD.
Agreement: 100%

Thiopurines are immunosuppressive agents that can reduce inflammation in IBD patients.[247] A recent prospective study on 129 children with mild-moderate IBD showed that thiopurines effectively achieved steroid and EEN-free remission without treatment escalation by 12 months in 21% and 29% of children with CD and UC, respectively.[248] Up to 20% of patients, however, discontinued thiopurine treatment due to adverse effects in a retrospective, single-center study of 391 children with PIBD.[249] In CD, early treatment with thiopurines was associated with an appreciable reduction in the risk of surgery in 1595 incident cases that were respectively analyzed but did not reduce the risk of surgery in UC (1175 patients).[250] The use of thiopurines in adults with CD or UC is also debatable due to contradictory results on efficacy and safety concerns.[251,252]

Statement 26

We recommend against monotherapy with thiopurines to induce remission in children with active CD.
Agreement: 100%

Induction therapy in fistulizing perianal CD

Perianal fistulizing CD is an aggressive and debilitating phenotype that afflicts approximately 1 in 3 patients.[253] For complex perianal fistulizing disease, the treatment of active disease and sepsis are the priority. Definition of the anatomy, the maintenance of nutrition, and co-management with colorectal surgery should form the treatment plan.[253,254] Pelvic MRI and direct examination under anesthesia can also improve diagnosis.[255]

Perianal CD encompasses nonfistulizing (i.e., fissures) and fistulizing lesions. Medical treatment alone can improve fissures and skin tags. Fistulizing lesions (abscesses and fistulas) require aggressive medical treatment for which consensus recommendations have been reported.[256,257] Symptomatic fistulas with abscesses must be drained with loose, noncutting Setons before anti-TNFα therapy. This reduces inflammation around the tract and prevents recurring abscesses. Antibiotics such as ciprofloxacin or metronidazole can be administered concomitantly with anti-TNFα therapy.[258] Complex perianal fistulas can be refractory to a combination of medical therapy and Seton placement and may require a diverting ostomy to control the disease.[259]

Statement 27

We recommend the use of anti-TNFα for the induction and maintenance of remission in CD patients with fistulizing perianal disease. This should be combined with antibiotics, surgical treatment, or both.
Agreement: 92.86%

Maintenance therapy

Methotrexate

Methotrexate (MTX) is a chemotherapeutic and immunosuppressant agent. In patients with steroid-

refractory or steroid-dependent CD, intramuscular or subcutaneous methotrexate can achieve and maintain remission.[260] Recommended doses in children are 15 mg/m^2 once per week, which can be increased to a maximum dose of 25 mg/m^2 administered subcutaneously or intramuscularly.[261] In cases of clinical remission exceeding 3–6 months, the weekly dose of MTX should be reduced to 10 mg/m^2 (maximum of 15 mg/m^2).[262] Bone marrow suppression, infections, teratogenicity, hepatic fibrosis, and pneumonitis are possible side effects. Contradictions for MTX therapy include chronic liver and kidney disease, obesity, diabetes, infections, and malignancy.[263–267]

In a Cochrane review of five RCTs comprising 333 participants, weekly MTX (15 mg) was more efficacious than placebo in maintaining clinical remission [RR: 1.67; 95% CI: 1.05– 2.67].[268] Low-dose oral MTX (12.5 mg) was, however, ineffective. In three retrospective cohort studies (314 patients), pooled remission rates of 37.1% [95% CI: 29.5%–45.5%] at 12 months were observed.[268] Six observational studies (409 patients) showed the maintenance of remission in 37.1% of patients treated with MTX [95% CI: 29.5%–45.5%] at 12 months. A systematic assessment of ten observational studies using less stringent exclusion criteria reported remission in 25%–53% of CD cases at 12 months and a mean remission of 21–24 months.[261] Observational retrospective cohort studies also report the successful use of MTX following the failure of thiopurines.[269] No trials on the use of thiopurines following MTX failure have been reported.

Thiopurines

The thiopurine S-methyltransferase (TPMT) activity test can guide the use and dosing of thiopurines in PIBD patients.[250,270] In a series of prospective, double-blind, placebo-controlled trials, the efficacy of thiopurines in both CD and UC was documented, with benefits in maintaining disease remission.[268] Thiopurines have also been used with anti-TNFα therapy to prevent immunogenicity.

TPMT can be profiled using genotyping or the direct assessment of enzyme activity.[271] This should be initiated for dose determination. Alternatively, azathioprine can be administered at low doses and gradually increased. A Cochrane review of six RCTs with 489 participants summarized the effectiveness of thiopurines (azathioprine or 6-mercaptopurine) in the maintenance of remission in adult CD.[272] Azathioprine was more successful than placebo for maintaining steroid-free remission [RR: 1.19; 95% CI 1.05–1.34] but caused a higher incidence of pancreatitis, leukopenia, nausea, infection, and other serious adverse events. Observational trials reported 12-month corticosteroid-free remission rates for 6-mercaptopurine ranging from 23% to 60%.

Statement 28

Thiopurine (azathioprine or 6-mercaptopurine) can be used to maintain remission in pediatric CD cases.
Agreement: 80%

If typical doses of thiopurines are administered to patients with low TPMT activity, a higher risk of severe and life-threatening myelotoxicity occurs. Single up-front thiopurine dose reduction in those with heterozygosity can reduce the incidence of adverse reactions by approximately 89%.[273] Pretreatment genotyping is, however, unsuitable for hematological safety monitoring. Complete blood counts and liver enzyme activity must be assessed before thiopurine therapy in CD patients.[251] Close monitoring of CBC and liver enzymes should be performed monthly for the first 3 months and once every 3 months thereafter.[274] Lower doses of thiopurine are recommended in patients heterozygous for TPMT or with intermediate enzymatic activity. TMPT activity tests are preferred over genotyping.[247,275]

Statement 29

We recommend testing for thiopurine methyltransferase (TPMT) through genotyping or enzymatic activity in pediatric CD patients. This should be initiated when available and affordable before thiopurine treatment for dose determination. Alternatively, azathioprine can be initiated at low doses and gradually increased. This must be accompanied by monitoring for potential side effects, including bone marrow suppression, pancreatitis, and hepatitis, both clinically and biochemically.
Agreement: 100%

A study of genetic variants associated with thiopurine-induced myelosuppression (TIM) highlighted mutations in Nudix hydrolase 15 (*NUDT15*) linked to a higher incidence in IBD patients of European ancestry.[276] Therefore, genotyping for NUDT15 and the assessment of NUDT15 activity are recommended prior to thiopurine treatment.

An observational cohort study (CESAME) identified a hazard ratio of 5.28 for lymphoproliferative disorders in patients receiving thiopurines.[277] Ebstein Barr virus (EBV) infection also resulted in fatal mononucleosis-associated disorders in two male patients. A prospective study of PIBD showed thiopurine exposure was a significant cause of malignancy and hemophagocytic lymphohistiocytosis.[278] EBV status should be checked before the initiation of thiopurines in pediatric patients and should be avoided in EBV-negative individuals.[279]

Biologics

Treatment with biological agents, particularly TNF-α inhibitors, is associated with an increased risk of tuberculosis (TB) infection.[280] Latent TB testing is advised for all patients with CD prior to biologic therapy.[281–283] Screening should include assessing risk factors, interferon-gamma release assays, tuberculin skin tests, and chest X-rays.[284,285] In positive cases, TB therapy should be initiated prior to biologics but can be applied concurrently if treatment is urgent.[281] Management involving gastroenterologists, infectious disease specialists, and pharmacists is recommended. Ongoing surveillance is also required during therapy.[286,287]

Statement 30

Testing for latent TB and verification of protective hepatitis B immunization status should be performed prior to the initiation of biological therapy.
Agreement: 100%

Adalimumab has been used in low- and high-dose regimens and can induce and maintain clinical remission in PIBD patients.[288] In 192 patients with PCDAI scores >30, adalimumab effectively induced and maintained remission in children with CD.[289] The therapy was generally safe and well tolerated, with no adverse events or deaths. As for infliximab, adalimumab was approved for the treatment of CD in children who fail to respond to standard therapy and in individuals in which the condition is linked to fistulation.[258,290] Adalimumab can successfully induce remission in children with severe disease.[291]

According to 2020 guidelines for pediatric CD management, ustekinumab or vedolizumab are options for individuals who fail to maintain remission despite the use of immunomodulators and anti-TNF medications.[292–295] Long-term corticosteroid treatment leads to adverse effects and shows limited clinical efficacy for CD remission.[296] Anti-TNFα can improve remission in CD and can be used to avoid repeat corticosteroid prescriptions.[297]

Statement 31

Regardless of severity, we recommend against the use of corticosteroids to maintain clinical remission in children with CD.
Agreement: 100%

Maintenance therapy after surgical resection

Advances in therapy have lowered the rates of surgical resection in CD patients. Surgical intervention is, however, required in the event of bowel obstruction, abscesses, fistulae, or medically refractory disease.[298–300] Crohn's disease has a 10-year risk of surgical resection, and many patients relapse. The incidence and severity of recurrence must be weighed against the risks of medical therapy.

Therapeutic intervention can decrease recurrence in CD patients. In a single proof-of-concept study, 24 patients were randomly administered infliximab within 4 weeks of surgery, which was continued for 1 year.[301] The infliximab-treated group showed a significantly decreased rate of endoscopic recurrence (9% vs 85%; $P = 0.0006$). These findings initiated a 297-patient worldwide, multicenter, placebo-controlled RCT. At 18 months postresection, infliximab-treated patients showed significantly lower rates of endoscopic recurrence compared to the placebo group (30.6% vs 60%; $P < 0.001$).[301,302]

Statement 32

In CD patients with a high risk of endoscopic recurrence following ileocecal resection, we recommend postoperative prophylaxis with anti-TNFα therapy and the assessment of recurrence at 6–12 months post-resection.
Agreement: 100%

A multicenter Postoperative Crohn's Endoscopic Recurrence Study (POCER) found that early colonoscopy at 6 months after surgery, followed by therapy escalation if endoscopic recurrence occurs, was superior to the standard of care (no colonoscopy) in preventing endoscopic recurrence at 18 months.[303] Immediate and continuous postoperative treatment with adalimumab (40 mg every 2 weeks) was superior to thiopurines in preventing endoscopic recurrence at 6 months in a secondary study of high-risk patients (21% vs 45%; $P = 0.028$).

Optimizing anti-TNFα therapy

Combining biologic therapy with immunomodulators

Combination therapy can boost the efficacy of anti-TNFα by slowing drug clearance and preventing immune modulation. Simultaneously, using azathioprine, 6-MP, and MTX with anti-TNFα agents in CD can improve treatment efficacy and reduce immunogenicity.[304] An increased risk of infection and lymphoma (particularly fatal hepatosplenic T-cell lymphoma) has been reported in patients treated with a combination of infliximab and thiopurines.[304] In 2010, a Study of Biologic and Immunomodulator naive patients in Crohn's Disease (SONIC) found that the combination of azathioprine and infliximab in 169 patients led to 96 (56.8%) patients achieving corticosteroid-free clinical remission at week 26, compared to 75 / 169 patients (44.4%).[304] Serious infections developed in 3.9% of patients in the combination group, 4.9% in the infliximab group, and 5.6% in the azathioprine group.

The combination of infliximab and MTX was linked to a decrease in circulating antibodies in the Combination of Maintenance Methotrexate-Infliximab (COMMIT) trial (4% vs 20%; $P = 0.01$).[305] Compared to infliximab

monotherapy, combination therapy was associated with higher median infliximab trough levels (6.35 g/mL vs 3.75 g/mL; $P = 0.08$). A meta-analysis showed that over 50% of pediatric CD patients induced with MTX achieved clinical remission within 2 months.[261] Methotrexate monotherapy for CD showed high initial remission rates among pediatric patients, despite variable responses being reported in other studies. In contrast to thiopurines, hepatosplenic T-cell lymphoma (HSTCL) has not been reported for MTX combination therapy. As such, MTX combination therapy is preferred.

Statement 33

We recommend combining infliximab and immunomodulators in children with moderate-to-severe inflammatory CD. This therapy can be maintained for at least 6 months to maintain clinical remission.
Agreement: 93.3%

Statement 34

We recommend methotrexate over thiopurines in male children with CD who require immunomodulators in conjunction with anti-TNF medication.
Agreement: 100%

Evidence supporting the use of adalimumab concurrently with immunomodulators is limited. An open-label DIAMOND study assessed the efficacy of adalimumab and azathioprine compared to adalimumab monotherapy.[306,307] Adult patients naive to immunomodulators or biologics showed comparable remission rates at week 26, regardless of adalimumab monotherapy or combination therapy (68% vs 72%, respectively, $P = 0.63$). The rate of endoscopic improvement was higher with combination therapy at 6 months but was comparable to monotherapy at 12 months.

Statement 35

We recommend adalimumab monotherapy over a combination with an immunomodulator in anti-TNFα naïve patients. Adalimumab can be combined with an immunomodulator following the failure of infliximab.
Agreement: 100%

Post-hoc analyses of cohort data from RCTs in adults found no significant advantage in combining adalimumab with thiopurines or MTX, compared to adalimumab alone (OR: 0.88; 95% CI: 0.60–1.27) for the maintenance of remission (OR: 0.88; 95% CI: 0.58–1.35). Remission rates between those receiving a concomitant immunosuppressant (36% vs 30%) were comparable in the Inflammation, Microbiome, and Alimentation: Gastro-Intestinal and Neuropsychiatric Effects (IMAGINE-1) trial, in which 60% of patients receiving concomitant thiopurines or MTX along with adalimumab showed no additional benefits.[308]

A single multicenter, randomized, open-label study of 188 children with CD was performed to assess the efficacy of adalimumab therapy.[309] Patients who weighed more than 40 kg at baseline received subcutaneous adalimumab (160 mg at week 0; 80 mg at week 2). Patients who weighed less than 40 kg at baseline received subcutaneous adalimumab (80 mg at week 0; 40 mg at week 2). At week 4, patients were randomly assigned to either high-dose or low-dose adalimumab maintenance therapy groups for 48 weeks. At week 26, 63 patients (33.5%) were in clinical remission, with no significant differences between high- and low-dose groups (36 / 93 [38.7%] vs 27 / 95 [28.4%]; ($P = 0.075$)).

Biologics following anti-TNF failure

Ustekinumab

Ustekinumab is a monoclonal antibody targeting the p40 subunit of IL12 and IL23 that has been investigated for treating pediatric patients with moderate-to-severe CD. Its use is also advocated in cases where disease activity cannot be managed with corticosteroids or immunosuppressants.[310] In a randomized placebo-controlled trial, ustekinumab effectively induced and maintained clinical remission in adult patients with active CD. This included those who previously failed to tolerate anti-TNFα therapy.[311] In the Intolerant to anti-TNFα Therapy (UNITI-1) trial, a single intravenous infusion of ustekinumab at 6 mg/kg resulted in 34% remission compared to 21% at week 8 in patients previously treated with anti-TNFα agents. The mean change in SES-CD at week 8 with ustekinumab (-2.3 points) was higher than placebo (+0.2 points) in a substudy of UNITI-1 that assessed endoscopic outcomes.[312–324]

A trial conducted in Japan monitored 82 patients who were administered 6–9 mg/kg ustekinumab intravenously. The steroid-free clinical remission rates were 59% at week 26, 50% at week 52, and 70% after 1 year.[317] In a further observational cohort study, children who received intravenous or subcutaneous ustekinumab were followed up for 1 year. Ustekinumab was efficacious and safe, with higher rates of remission in bio naïve pediatric IBD patients.[325]

Vedolizumab

Vedolizumab is a gut-selective humanized monoclonal antibody that affects lymphocyte trafficking in the GI tract. It targets the α4β7 integrin and is effective in patients with IBD who do not respond to systemic corticosteroids, immunosuppressants, or anti-TNFα therapy.[326] The short-term effectiveness and safety of vedolizumab were highlighted in a European multicenter pediatric IBD cohort (19 centers). Corticosteroid-free remission was reported in

39% of UC cases and 24% of CD patients. Anti-TNFα-naive patients also showed higher remission rates.[326,327]

Statement 36

Ustekinumab or vedolizumab should be considered in pediatric CD patients who fail anti-TNF agents.
Agreement: 100%

Microbial manipulation in CD

Probiotics

Probiotics can modulate immune function, but a lack of robust evidence exists to support their use for the induction or maintenance of remission in CD.[328] *Lactobacillus rhamnosus* GG, when administered with maintenance therapy, leads to greater relapse rates compared to placebo.[329] Cochrane reviews on probiotics for the induction and maintenance of remission in adult CD patients also reported minimal beneficial effects of these agents.[330]

Statement 37

Probiotics should not be used to induce or maintain remission in patients with CD.
Agreement: 100%

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) involves the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient to directly change the recipient's gut microbial composition.[331] The effective use of FMT to treat recurrent CDI prompted an assessment of its benefits for various GI and extraintestinal illnesses linked with gut microbiota dysbiosis. The benefits of FMT for patients with IBD have shown promise for UC, but further studies in this area are required.[332–335]

Statement 38

We do not recommend fecal microbiota transplantation to induce or maintain remission in children with CD.
Agreement: 100%

A Cochrane review failed to identify RCTs assessing FMT in CD. Fecal microbiota transplantation was linked to short-term remission rates in adults and children with CD, but these results should be interpreted with caution.[336]

MEDICAL MANAGEMENT OF PEDIATRIC UC

Risk stratification

A multicenter inception cohort (PROTECT trial) was designed to investigate the natural history of children newly diagnosed with UC.[337] A total of 428 children were treated with 5-ASA and corticosteroids and monitored for further therapeutic intervention using the PUCAI system. Corticosteroid-free remission at weeks 12 and 52 was achieved in 34% and 38% of patients receiving 5-ASA, respectively. Clinical remission at week 4 was considered a predictor for corticosteroid-free remission at weeks 12 and 52. Over 12 months, 50% of the patients required escalation to an immunosuppressant or anti-TNF therapy. Colectomy was required in 6% of the subjects.[337]

Induction of remission

First-line therapy

Ulcerative colitis medical management depends on disease activity, location, and extraintestinal manifestations. First-line therapeutic interventions include 5-ASA, budesonide, systemic steroids (prednisone and derivatives), azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, and certolizumab. Efforts to improve current IBD therapies have identified 5-ASA as the treatment of choice for mild-to-moderate UC.[338]

Statement 39

The induction of remission using thiopurines is not recommended in children with UC.
Agreement: 100%

In a single prospective, multicenter inception cohort of 213 children aged 16 years or younger administered oral 5-ASA within 30 days of UC diagnosis, 40% achieved corticosteroid-free remission after 1 year.[339] In a randomized, multicenter, double-blind study of patients aged 5–17 years who received body weight-dependent doses of oral, delayed-release mesalamine for 6 weeks, treatment success was reported in 56% and 55% of low- (27–71 mg/g/day) and high-dose groups (53–118 mg/g/day), respectively.[340]

Statement 40

For mild-to-moderate UC, oral 5-ASA is recommended as a first-line therapy for the induction of clinical remission. Oral and rectal 5-ASA combination treatment is more effective than oral 5-ASA alone.
Agreement: 100%

Statement 41

Rectal monotherapy is recommended for mild-to-moderate ulcerative proctitis. 5-ASA is preferable over corticosteroids.
Agreement: 100%

Budesonide MMX is a once-daily oral formulation that uses Multi Matrix colonic delivery technology to permit drug release at a controlled rate throughout the colon.[341] A pooled analysis of CORE I and II studies showed that budesonide MMX (9 mg for 8 weeks) was more effective than placebo for achieving combination clinical and endoscopic remission in mild-to-moderate UC patients (17.7% improvement over placebo; $P = 0.0002$). Budesonide MMX also significantly improved clinical symptoms and mucosal healing.[342,343]

Statement 42

In patients with moderately active UC, Budesonide MMX should be favored over conventional corticosteroids for remission, given their side effects.
Agreement: 100%

Second-line therapy

Corticosteroids are efficacious for remission in UC patients. Biological therapies such as infliximab and adalimumab can be used to induce and maintain remission.[344] Over 50% of children with moderate-severe UC treated with prednisolone 2 mg/kg/day (maximum 60 mg/day) orally or intravenously achieve complete remission after 30 days of treatment.[344]

Statement 43

Oral corticosteroids should be administered as a second-line treatment to induce remission in mild-moderate UC patients who do not respond to 5-ASA therapy.
Agreement: 100%

Budesonide MMX is effective for remission induction in children with UC, with rates of 55% for clinical remission and 40% for endoscopic remission reported.[341] When used as a short-term therapy, adverse events are rare compared to long-term treatment.[345]

Statement 44

In children with mild disease that fail to respond to 5-ASA, second-generation oral corticosteroids including beclomethasone propionate (BDP) and budesonide-MMX can be administered before oral prednisolone therapy is initiated.
Agreement 100%

Infliximab has been shown to induce remission in 73% of patients who fail to respond to conventional therapy.[177,346–349] Others have similarly highlighted infliximab's effectiveness in treating pediatric UC.

Adalimumab is offered as either a first- or second-line therapy in UC patients who fail or are intolerant to AZA and/or 6-MP.[350–352] Adalimumab is currently offered as an alternative to infliximab as it can be self-administered via subcutaneous injection. In a double-blind RCT, 93 children aged 4–17 years with moderate-to-severe UC were randomly assigned to either high-dose (2.4 mg/kg; maximum 160 mg at weeks 0 and 1) or standard-dose adalimumab (2.4 mg/kg at week 0 and placebo at week 1). Both groups received 1.2 mg/kg (maximum 80 mg) at week 2 and 0.6 mg/kg (maximum 40 mg) at weeks 4 and 6. Remission rates for adalimumab were significantly higher compared to placebo.[353] A case series further showed that 54% of those administered adalimumab following infliximab achieved clinical remission within a median duration of 25 months. A total of 36% of cases, however, underwent colectomy.

In a pivotal phase III RCT, vedolizumab was superior to placebo for the induction and maintenance of remission in adult patients with moderate to severe UC.[327] Of a total of 142 children with IBD (48% with UC), vedolizumab was administered at baseline and weeks 2, 6, and 14 at a 177 mg/m² body surface area (up to 300 mg maximum). The primary outcome was steroid-free and EEN-free clinical remission at 14 weeks, achieved in 42% (95% CI 30–54) of patients.

A clinical trial reported only modest differences in clinical remission between AZA/6-MP and placebo.[354] When combined with infliximab in the SONIC study, greater rates of remission were reported. Thiopurines are ineffective as a monotherapy for remission due to their slow onset of action.[355] The recommendation is to continue with steroids or 5-ASA induction for the pediatric population.

AZA can cause nausea, myelosuppression, and erythrocyte aplasia.[356] Reactions in the first few weeks tend to be related to allergic hypersensitivity. Symptoms such as fever, joint pain, rash, pancreatitis, and gastrointestinal disturbances have also been reported. In a retrospective analysis of 30 UC patients aged ≤6 years of age receiving 6-MP/AZA therapy (3.1 mg/kg/day), 62% achieved clinical remission. Severe adverse events, including hepatitis and leukopenia, were observed in 4 patients.[354]

Maintenance of remission

Five amino salicylic acid (5-ASA)

Five amino salicylic acid (5-ASA) is effective as a first-line therapy for maintaining clinical remission for mild to moderate UC. It can be administered as a suppository, enema, or orally.[357] Rectal therapy can achieve higher concentrations at the site of inflammation and induce remission more rapidly than the oral route, particularly for left-sided UC.[358] For remission and maintenance therapy, rectal and oral administrations are more effective than oral administration alone.[359]

Statement 45

Thiopurines are recommended as a maintenance therapy and corticosteroid-sparing agent for cases of corticosteroid dependency or in frequently relapsing children with UC (≥two relapses yearly) in addition to 5-ASA therapy.
Agreement: 100%

Thiopurines

Thiopurines are widely used to maintain remission in UC cases of corticosteroid dependence. Thiopurines can serve as a potential steroid-sparing treatment and can enhance

rescue therapy in combination with cyclosporine in patients with steroid-refractory disease.[360] Thiopurines represent the preferred treatment option in pediatric patients with UC who fail to respond to 5-ASA or corticosteroids.

Corticosteroid therapy can induce remission in IBD patients but should not be used for the maintenance of remission. Pediatric patients with IBD do respond to corticosteroids but may experience relapse, leading to the requirement for multiple treatments. Approximately 30–40% of patients partially respond to corticosteroids or become steroid-dependent.[361] For patients who fail to respond to prolonged corticosteroid therapy, monoclonal antibodies and immunosuppressants should be considered.[362] Prolonged or frequent corticosteroid use has adverse effects on physical growth and development.

Statement 46

We recommend against the use of corticosteroids to maintain remission in patients with UC. Corticosteroid-sparing medications should be used in corticosteroid-dependent children or in cases of frequently relapsing disease.
Agreement: 100%

Biologics

Approximately 1 in 3 patients administered corticosteroids for moderate to severe UC require colectomy. The efficacy of infliximab and adalimumab for mucosal healing and clinical remission has been documented in moderate to severe UC patients.[363] An RCT reported that 73% of the pediatric population with moderate to severe UC responded to infliximab, and 38% maintained remission after 1 year.[364] Retrospective studies demonstrated the long-term efficacy of infliximab in UC patients with remission rates of 40% over 2 years. Higher doses of infliximab for induction (10 mg/kg) and an increased dosing frequency were required.[365] A lower occurrence of colectomy and a higher rate of clinical remission were also reported compared to standard dosing.

Statement 47

We recommend using infliximab to induce and maintain remission in chronically active UC patients who fail to respond to 5-ASA or oral corticosteroids or are corticosteroid-dependent.
Agreement: 93.33%

Vedolizumab can be used as a second-line biological following the failure of infliximab. High rates of clinical remission have been reported in pediatric patients.[366] The combination of infliximab with thiopurines can improve clinical and endoscopic remission in pediatric patients with UC. The improved efficacy is likely related to the synergistic effects of the agents or their higher concentrations due to anti-drug antibody suppression and reduced clearance. Combining thiopurine and anti-TNFα agents is associated with a higher risk of HSTL, but the individual absolute risk remains low.[367]

Statement 48

Vedolizumab is recommended for pediatric UC as a second-line biological therapy following the failure of anti-TNFα therapy.
Agreement: 86.87%

Statement 49

In biologic naïve UC patients, we advise against the combination of vedolizumab with thiopurines.
Agreement: 100%

The combination of adalimumab with thiopurines does not improve clinical remission in UC. The advantages of combination therapy should be balanced with potential adverse events such as malignancy and infection. Combination therapy is appropriate in children with severe disease complications or those who fail to respond to anti-TNFα therapy. Due to the higher risk of malignancy and infection, immunosuppressants should be withdrawn after 6–12 months of treatment in those achieving treatment goals.[368,369]

Statement 50

We recommend the combination of infliximab with thiopurines for the initial 6–12 months of therapy in male children with UC.
Agreement: 93.33%

Statement 51

In biologic naïve UC patients, we do not recommend combining adalimumab with thiopurines. Adalimumab can however be combined with an immunomodulator when used following the failure of infliximab.
Agreement: 86.67%

Based on the Saudi immunization schedule,[370,371] several live-attenuated vaccines are mandatory in children such as measles, mumps, rubella (MMR), and varicella zoster vaccines. It has been documented that reactivation of viruses and bacteria can occur in immunocompromised patients.[372] To date, no solid data exist about the actual risk of viral or bacterial reactivation in children receiving biologics.[372,373] Current guidelines, however, state that there is a potential risk for pathogen reactivation with live attenuated vaccines in children receiving biologics, and therefore, the vaccines are strictly contraindicated.[372–377]

Statement 52

Live attenuated vaccines should be avoided in patients with PIBD who receive biologics
Agreement: 100%

Microbial manipulation in UC

Probiotics

Probiotics maintain the diversity of the intestinal microbiota. In a single large cohort study, nonpathogenic

E. coli Nissle 1917 strain was as effective as standard mesalazine for the maintenance of remission in UC patients.[378,379] Several studies have investigated the effectiveness of VSL#3, a probiotic mixture of *Lactobacilli (L.) (L. casei, L. acidophilus, L. delbrueckii subsp., Bulgaricus*), three *Bifidobacteria (B.) (B. longum, B. breve, B. infantis)*, and *Streptococcus* (Streptococcussalivarius subsp. thermophilus). Promising results for mild to moderate UC were reported.[380] Low-dose balsalazide combined with a high-potency probiotic preparation was also more effective than balsalazide or mesalazine for treating mild-to-moderate UC.[381,382] A meta-analysis also confirmed the effectiveness of VSL#3 as an adjunctive therapy for mild to moderately active UC.[383] The most beneficial bacteria for reducing colon damage were *E. faecium, L. reuteri, L. acidophilus,* and *L. coryniformis*. These studies are, however, limited, and further research is required using larger sample sizes and higher-quality experimental designs. Probiotics are, therefore, not currently recommended as a maintenance therapy in UC.

Statement 53

In pediatric UC, we do not recommend the use of probiotics as a maintenance monotherapy.
Agreement: 100%

Antibiotics

Antibiotics can decrease bacterial diversity in the gut, leading to an increased abundance of pathogenic fungi (candida), bacteria (C. difficile), and bacteriophage.[294] Patients with IBD and C difficile are frequently treated with antibiotics and immunosuppressants, but this combination is associated with a poor outcome.[384] Antibiotic combinations and standard therapy can reduce the PUCAI score after 5 days of treatment in children with severe colitis.[294,385]

Statement 54

The routine use of antibiotics for the induction and maintenance of clinical remission is discouraged.
Agreement: 100%

Fecal microbiota transplant

The use of FMT is an emerging area of research, most notably to counter the burden of current IBD medications.[386–388] Fecal enemas have shown efficacy in childhood UC. A recent meta-analysis suggested that FMT is safe, but its efficacy is variable in IBD patients.[386] Further RCTs are required to confirm efficacy, safety, durability, doses, routes of administration, and donor selection.

Statement 55

Fecal microbiota transplantation is not recommended for pediatric UC due to the limited literature precedent of its effectiveness.
Agreement: 100%

THERAPEUTIC DRUG MONITORING IN PIBD[389–394]

Reactive therapeutic drug monitoring (TDM) is widely accepted in IBD patients who fail to respond to anti-TNFα agents.[395–397] Proactive TDM is effective for those with severe UC and fistulizing CD initiated on anti-TNFα therapy, specifically infliximab and, to some degree, adalimumab.[390–392] To date, proactive TDM has not been widely used for ustekinumab and vedolizumab and further studies are required before this is accepted within clinical practice. Therapeutic drug monitoring is similarly beneficial for patients considering de-escalation from combination therapy. However, these drugs' immunogenicity rates are low, and therapeutic doses have not been defined. Proactive TDM is promising in patients initiated on infliximab or adalimumab. Postinduction TDM for infliximab and adalimumab in patients with severe UC and fistulizing CD shows improved outcomes.[392]

Statement 56

Should anti-drug antibodies develop, we recommend switching to a different anti-TNFα therapy.
Agreement: 93.33%

TDM is useful for patients considering de-escalation with thiopurines. Assessment of the effectiveness of anti-TNFα therapy before cessation of the concomitant immunosuppressant represents a potential strategy.[398]

Statement 57

Based on literature precedent, early proactive therapeutic drug monitoring (TDM) is recommended for patients receiving anti-TNFα therapy for dose or frequency optimization.
Agreement: 80%

DISCUSSION

This report highlights a series of consensus statements developed by the MOH in collaboration with the SGA and the SCCP. These were compiled following a detailed evaluation of responses and remission rates of PIBD sufferers using real-world data. Guidelines were adapted from the ECCO, ESPGHAN, NASPGHAN, and Canadian Association of Gastroenterology Guidelines and agreed upon using a voting process. A total of 58 evidence- and expert opinion-based guidelines for diagnosing and treating UC and CD in children and adolescents are provided.

It is suggested that the diagnosis of PIBD is reached through a combination of history, physical examination, laboratory assessments, upper endoscopy, ileocolonoscopy with histology, and small bowel imaging (particularly when the terminal ileum cannot be intubated or with a diagnosis of CD/IBD-U). Enteric infections should be excluded

as a source of symptoms before endoscopy. Complete blood counts, CRP, fecal calprotectin, serum albumin, and liver function tests encompass the recommended laboratory approaches. Suspected IBD cases should have an ileocolonoscopy and EGD at initial evaluation. If PIBD is suspected, multiple biopsies should be obtained from endoscopically examined GI tract segments, including normal mucosa for confirmation. Our analyses strongly advocate MRE and WCE as alternatives for detecting small intestinal mucosal lesions.

The PUCAI should be used for children with UC to monitor disease activity. A score of at least 20 points should act as a short-term treatment target. For children with CD, we advocate the use of the PCDAI or wPCDAI to assess disease severity and monitor treatment responses. Regarding treatment, we recommend normalizing CR*P* values and targeting FC levels of ≤250 μg/g in UC and CD. Restoration of standard growth patterns should represent a long-term target. Endoscopic evaluation can confirm long-term healing. Transmural healing through cross-sectional imaging or bowel US in CD patients can also reflect deep healing.

For the treatment of PIBD, we recommend exclusive EEN for remission and corticosteroids when EEN is not tolerated. Thiopurines are also recommended as a maintenance monotherapy, with dosing optimized following TPMT genotyping and activity. Adalimumab and infliximab are recommended for fistulizing perianal CD to maintain remission with antibiotics and surgical treatment. We advocate MTX as an immunosuppressant to maintain remission or following thiopurine failure or intolerance. If these fail, anti-TNFα therapy is recommended for moderate-to-severe inflammatory CD.

As a general rule, we recommend using red flag systems and increasing medical education to help identify and refer patients to specialists at the earliest possible opportunity. Home or point-of-care calprotectin testing can also aid in assessment and diagnosis. A wider availability and affordability of drugs with a similar biological profile can also lead to more effective therapy.

CONCLUSIONS

We have compiled 57 guidelines covering recommendations for diagnosing and managing PIBD in Saudi Arabia. The statements have been designed using evidence-based arguments. We did not include details on surgical management, healthcare personnel intervention, transition of care, or guidance for health care. In addition, it should also be considered that children with IBD are at risk of adverse psychosocial outcomes. In such cases, treatment interventions can negatively affect patients and their families. Our recommendations are based on the most up-to-date information and provide guidance alone. They should not replace the clinical judgment of practicing physicians or the opinion of the potential impact of treatment on the patient. Regarding clinical practice, families with a child or adolescent with IBD should be assisted with clinical and professional interventions. The therapeutic strategies discussed can aid clinicians in the most effective disease management.

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Conflicts of interest

Dr. Mahmoud Mosli has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Falk, Sandoz, Hikma, Pfizer, BMS, and Orgenon. Dr. Mosli has received research funding from Celgene, Pfizer, and Takeda. Dr. Abdulelah Almutairdi has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Pfizer, BMS. Dr Nahla Azzam has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Falk, Sandoz, Hikma, Pfizer, BMS, and Orgenon. Dr. Azzam has received research funding from Pfizer and Abbvie. Dr. Shakir Bakkari has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Pfizer, BMS and lilly . Dr. Badr Al-Bawardy has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Pfizer, BMS and lilly. Dr. Othman alharbi has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Falk, Sandoz, Hikma, Pfizer, BMS, and Orgenon. Dr.othman alharbi has received research funding from Celgene, Janssen. Dr. Majid Almadi has served on advisory boards, and received speaker fees, and/or consultation fees from Abbvie, Takeda, Janssen, Ferring, Hikma, Pfizer.

All other authors declare that they have no conflicts of interest.

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