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POSITION STATEMENT

Gastroenterology: Inflammatory Bowel Disease

Management of pediatric inflammatory bowel diseases in limited-resource settings: A position paper from the Paediatric IBD Porto Group of ESPGHAN

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Abstract

Objective: Pediatric inflammatory bowel diseases (PIBDs), despite being more prevalent in westernized nations, show an increasing incidence worldwide. Accurate evaluation, diagnosis, therapy, and monitoring are mandatory for the adequate management of patients, as is a sensible use of expensive resources, which may be limited in some parts of the world. This limitation often poses challenges to diagnose and treat patients. As the long-term prognosis very much depends on early diagnosis and remission of active disease, it is important to consider reasonable alternatives that may help clinicians to act accordingly within resource constraints, without downgrading previously published guidelines.

Methods: A group of experts from the "Paediatric IBD Porto Group" of European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) as well as pediatric and adult IBD experts, trained in IBD centers and having working experience in limited-resource settings (LR settings), joined efforts to suggest alternative options in settings where resources are limited, while prioritizing an acceptable cost-effectiveness ratio. Almost all recently published ESPGHAN guidelines and position papers on PIBD were evaluated, and the writing group framed proposals for adaptation in situations with limited access to more expensive resources or tools.

Results: Ninety consensus-based recommendations, derived from the available evidence, were formulated. Diagnostic protocol, biochemical evaluation, imaging and endoscopy, monitoring and options for nutritional, medical and surgical treatment were addressed. Cooperation between professionals and institutions was suggested to improve quality of care and optimize use of available expertise. Patient education, counseling, mental health and transition of care were also addressed.

For affiliations refer to page 26.

Disclaimer: ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of the healthcare provider.

Conclusion: Diagnosis and management of PIBD are complex and costly in medical resources, but some alternative protocols could provide acceptable results and help with accurate diagnosis and management. These recommendations and practice points may offer useful guidance in settings where resources may be limited while still providing good medical practice.

KEYWORDS
child, low-income countries, middle-income countries, pediatric

1 | INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U) are traditionally regarded as diseases of westernized nations. However, the epidemiology of IBD is rapidly changing, and the worldwide increase in IBD incidence now also includes newly industrialized and developing countries in Africa, Asia, and South America, with annual percentage changes of up to 17.8% for CD and 14.9% for UC.[1] A similar trend was shown for pediatric-onset IBD (PIBD) among 144 population-based studies from 38 countries[2]: Currently, incidences are sharply increasing in Southern and Eastern Europe and in Oceania; and annual incidence rates are as high as 11.4/100,000 person-years in Asia and the Middle East compared with 15.2/100,000 in North America. In addition, in time-trend analyses, almost 70% of CD studies reported an increasing incidence.[2] Most countries with limited-resource settings (LR settings) are currently in the "Acceleration Incidence" stage as defined by Kaplan, where there is a dramatic increase of incidence, despite still having a low prevalence[3] (Figure 1).

Even in high-income countries (HICs) the quality of PIBD management may differ, and significant diagnostic delay in remote German regions due to lack of referral centers[4] and widespread variation in PIBD management in Northern America[5] were reported. However, in many low- and middle-income countries (LMICs), these challenges are more widespread and pronounced, as in addition to a general lack of resources, structured health insurance systems and well-equipped centers, there are neither formally trained pediatric gastroenterologists nor training programs.[6] General practitioners, general pediatricians, or adult gastroenterologists without special training in PIBD will manage children with IBD who regardless of this will have limited treatment options. However, current guidelines usually primarily target an audience with a subspecialist level of training, often assisted by contemporary diagnostic and treatment facilities.

We, therefore, aimed to adjust the recommendations made in relevant PIBD guidelines published by the European Crohn's and Colitis Organisation (ECCO)/European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), for countries with LRs, with suitable alternative protocols that may provide acceptable results in diagnosis and treatment. In our recommendations, we tried to balance the need to control the disease fully with available

What is Known

- In high-resource settings, thorough guidelines and position papers guide the diagnosis and control of pediatric inflammatory bowel disease (PIBD).
- Recommendations emphasize the use of advanced tools for early and accurate diagnosis, for example, magnetic resonance enterography, endoscopy with histopathology, and biomarker tests, as well as treatment options with costly nutritional and pharmacological therapies, including therapeutic drug monitoring.
- Overall, these recommendations are mostly dependent on expensive diagnostics, consistent endoscopic surveillance, and availability of biologics, which present challenges in limited-resource settings due to financial and structural constraints.

What is New

- Rather than relying significantly on expensive biologics and frequent high-tech diagnostics, management protocols should prioritize the use of widely accessible tests and medications, affordable immunomodulators as well as nutritional alternatives to costly formulas.
- The disparity in care can be bridged by customizing treatment algorithms to prioritize symptom-based monitoring, using simplified diagnostic protocols, and implementing accessible therapeutic interventions, ensuring that PIBD patients in low-resource settings receive sustainable, effective treatment.
- Present recommendations derive from the joint expertise of Pediatric Gastroenterologists of countries with diverse access to diagnostic and therapeutic resources, providing balanced recommendations for the management of PIBD.

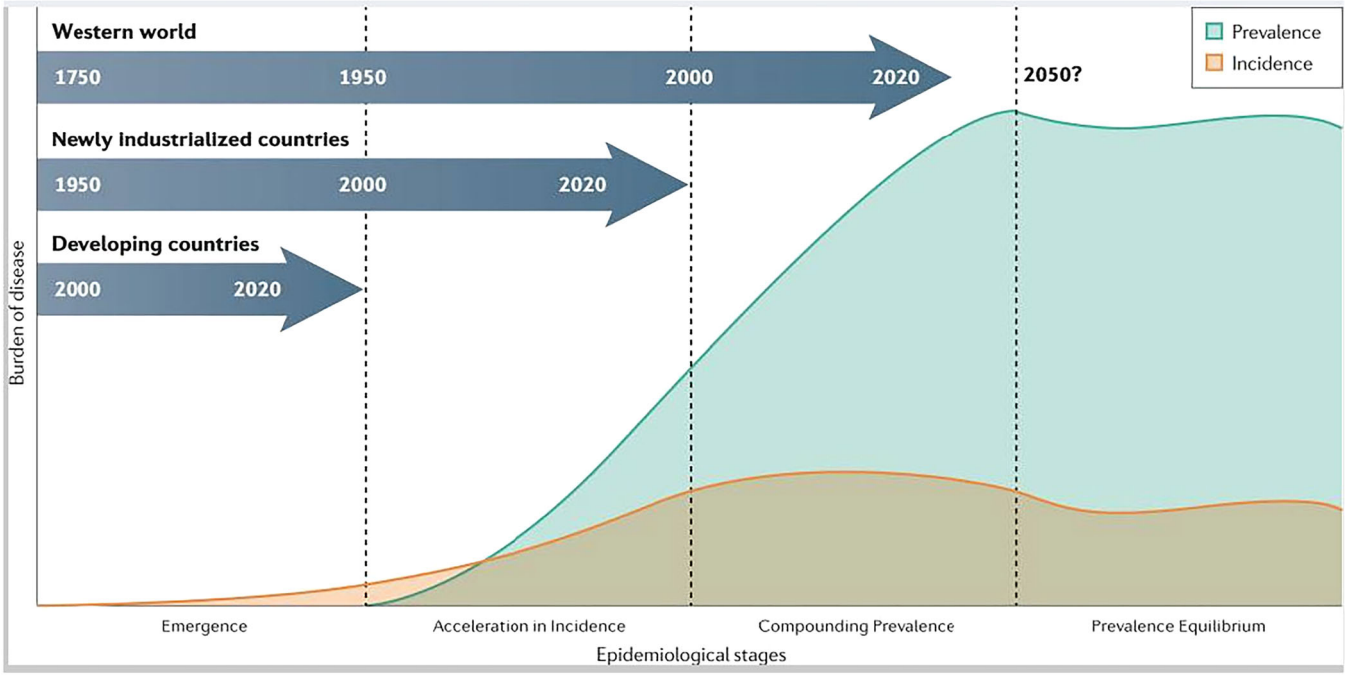

FIGURE 1 Four epidemiological stages of IBD evolution (Ref. [3]). IBD, inflammatory bowel disease.

resources, since PIBD may have a significant impact on morbidity, growth, bone health, nutrition, and quality of life. The present manuscript does not downgrade the previous guidelines, but merely tries to suggest alternative options where resources are limited, while prioritizing acceptable cost-effectiveness ratio.

2 | METHODS

Following an open call to the members of the "Paediatric IBD Porto Group" (Porto Group) and the IBD Interest Group of ESPGHAN, international specialists were invited to participate and selected based on content expertise. External pediatric IBD experts trained in IBD centers and with working experience in the LR setting were also invited to participate. A working group of 10 Porto Group members and 8 of these external IBD experts was established. The principal objective of this initiative was to prepare a practical clinical position paper with recommendations on how to diagnose and manage PIBD even when resources are limited. Regarding suspected Very Early Onset IBD (VEO-IBD), its evaluation follows the same basic protocol; however, its overall management requires further diagnostic and therapeutic modalities not specifically addressed here, as cooperation with expert centers is usually necessary.

After a preliminary face-to-face meeting, seven key topics most relevant to PIBD care in such setups were identified and allocated to author teams, consisting of one Porto Group member and one of the external IBD experts experienced in LR settings, assisted by one internal reviewer. In a second face-to-face meeting one Porto Group member (ACH) and one of the external IBD experts (MS) analyzed every recommendation of the three most recent ECCO-ESPGHAN guidelines and one ESPGHAN position paper on PIBD care (2020 Update of the ECCO-ESPGHAN guideline on Medical Management of Pediatric CD), both parts of the 2018 ECCO-ESPGHAN guideline on Management of Pediatric UC[7–9] and the ESPGHAN Position Paper on Endoscopy in PIBD,[10] respectively, for applicability:

As social indexes like the "Inequality-adjusted Human Development Index" (IHDI) reveal that there are considerable disparities in human development not only between countries, but also across populations within the same country (http://hdr.undp.org/en/content/what-purpose-inequality-adjusted-hdi-ihdi),[11] the most common divergences between existing PIBD guidelines and practicalities in such LR settings were used as the main structure for this position paper. The existence of advanced IBD centers in some of the countries with a lower IDHI, for example, a feature of disparity in health care structure, was considered in addition. The ensuing list of topics to be addressed was then approved by all authors.

Each author team conducted a systematic electronic literature search using Pubmed/Medline, Pubmed Cochrane, Embase, Web of Science and free search on Pubmed with as key words "Pediatric, Child/Children, Adolescents, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Unclassified IBD, and Low income/Middle income/Limited Resources (country/

setting/set-up)" and the last search date in September 2024. The limited pediatric literature precluded the use of the Oxford grading. With regard to this position paper's general concept of a resource-adjusted modification of current guidelines, we did not further detail the background of essential diagnostics (e.g., endoscopy) nor specify dosages of commonly used medications (e.g., steroids, azathioprine, and iron), whereas we provided specific information for the proposed alternatives.

3 | RECOMMENDATIONS VOTING

For each key topic, recommendations were developed via iterative e-mail and conference call discussions of assigned authors. A voting process was performed on each recommendation, with four levels of agreement (fully agree, partially agree, moderately disagree, and disagree), and it was approved if ≥80% agreement was reached. When approval was not reached, a new discussion ensued with revision until the needed approval was achieved. Each recommendation is followed by the result of the vote (percent agreement). In total, 90 recommendations were formulated (Table S1, with percentages of agreement), complemented by practice points that reflect common practice where evidence is lacking or provide useful pragmatic details, and should serve as alternatives in LR settings. The writing group voted on all statements and recommendations, while adding specific comments using a web-based voting platform. Revision and a second round of electronic voting on the final manuscript were performed for final approval.

1. Diagnostic work-up in suspected Pediatric Inflammatory Bowel Disease

An accurate diagnosis should be based on a combination of history, clinical and laboratory examination, as well as imaging, esophagogastroduodenoscopy (EGD), and ileocolonoscopy with histopathology (Table 1). In case of suspected VEO-IBD, more specific diagnostic (and therapeutic) modalities are needed, requiring the availability of specialized centers and, eventually, international cooperation. In LR settings, a high prevalence of intestinal infections that mimic IBD and the absence of a diagnostic gold standard for IBD have been shown to delay accurate disease assessment.[12]

TABLE 1 Investigations for PIBD diagnosis, routine monitoring, and suspected flare.

	Diagnostic workup	Monitoring	Suspected flare[a]
Symptom-oriented Clinical assessment incl. Activity Indices (wPCDAI/PUCAI, …)	**X**	**X**	**X** (self-assessment tools, use of dedicated Apps)
Blood inflammatory markers (CRP, ESR, CBC, …)	**X**	**X**	**X**
Microbiology (endemic countries: Serology, stool cultures, …)	**X**		**X**
TB: Mantoux TST, IGRA	**X**		**X**
Parasites	**X**		**X**
C. difficile (incl. toxin)	**X**		**X**
HIV	**X**		**X**
Pharmacologic tests and monitoring: Alternatives		**X (onset)**	
TPMT: Clinical assessment, WBC, MCV		**X**	
Therapeutic drug monitoring: Clinical assessment, biomarkers, imaging		**X**	**X**
Fecal inflammatory markers (FCal, lactoferrin)	**X**	**X**	**X**
Small bowel assessment (unless typical UC)—MRE/IUS	**X**		**X**
Endoscopy (EGD, IC)	**X**		**X**
Histopathology	**X**		**X**
Cancer surveillance		**X**	

Abbreviations: CBC, complete blood count; *C. difficile*, *Clostridioides difficile*; CRP, C-reactive protein; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IC, ileocolonoscopy; IGRA, interferon gamma releasing assay; IUS, intestinal ultrasound; MCV, mean corpuscular volume; MRE, magnetic resonance enterography; PIBD, pediatric inflammatory bowel disease; PUCAI, Pediatric UC Activity Index; TB, tuberculosis; TPMT, thiopurine S-methyltransferase; TST, tuberculin skin test; UC, ulcerative colitis; WBC, white blood cell; wPCDAI, weighted Pediatric CD's Activity Index.

[a]Choice of diagnostics depending on the individual clinical scenario.

1.1 Clinical assessment

Evidence

Growth, weight, and nutritional status must be assessed at each visit.[13,14] For evaluating the disease activity of pediatric UC, the Pediatric UC Activity Index (PUCAI[15]; allows a symptom-based assessment which correlates well with colonoscopy scores.[16,17] For Pediatric CD, the weighted Pediatric CD's Activity Index (wPCDAI), which combines clinical findings and results of basic and widely available laboratory tests, might be used, but its correlation with the degree of endoscopic inflammation is at best moderate.[18] For improved endoscopic correlation the Mucosal Inflammation Non-invasive Index (MINI) index may be used, which is based on fecal calprotectin, either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and the patient's stooling pattern.[19–22] MINI < 8 identified endoscopic healing with 88% sensitivity and 85% specificity, which was superior to the measurement of fecal calprotectin alone. The likelihood of moderate-severe inflammation with a MINI score of <8 is less than 5%.[19]

Recommendation 1.1:

a. Growth, weight, and nutritional status should be assessed at each clinical visit (agreement: 100%).
b. Disease activity should be measured by the PCDAI or wPCDAI for CD and PUCAI for UC (agreement: 100%).
c. Clinical indices (PUCAI in UC; PCDAI or MINI in CD) may be used to estimate non-invasively the degree of mucosal inflammation (agreement: 94%).

Practice point 1.1:

a. If locally developed growth charts are not available, the use of WHO growth charts is recommended.
b. PIBD disease activity indices should be translated into local languages to expand their usage as monitoring tools.

1.2 Laboratory diagnostics

1.2.1 CRP, ESR, and complete blood count (CBC)

Evidence

Although clinical symptoms have low correlation with endoscopic activity, their combination with simple blood tests, for example, CBC has been shown to improve their accuracy.[23] Leukocytosis might be indicative of acute inflammation, and anemia and thrombocytosis are associated with IBD diagnosis.[24] Hemoglobin levels and platelet counts were shown to add a fair diagnostic value in symptomatic children, with pooled areas under the curve (AUCs) of 76% and 79% respectively.[23] Platelet count may broadly help to differentiate between IBD and infectious processes, as thrombocytosis is relatively uncommon in intestinal infections.[25] Mean platelet volume (MPV) is influenced by the degree of mucosal inflammation and found to be particularly reduced in active UC, thus indicative of increased disease activity.[26] The neutrophil–platelet ratio (NPR) could be used as another surrogate marker, with significantly lower NPR values in UC patients in remission, compared to mild to moderate and severe disease (mean NPR values 14.02 vs. 16.4, 18.39, and 21.44, respectively; NPR cutoff vs. active UC: 14.94).[27] Another simple, inexpensive, and effective marker of inflammation is the neutrophil–lymphocyte ratio (NLR), which was shown to help differentiate CD patients from healthy controls.[28] In a recent pediatric study optimal cutoff values for NLR of 2.04 (sensitivity 82.1%; specificity 82.9%) and of 2.94 (sensitivity 77.8%; specificity 50.0%) were found to substantiate a diagnosis of IBD as well as differentiating IBD severity (remission vs. active disease), respectively[29] (Table 2).

CRP is one of the most widely used inflammatory markers in IBD to date: In children with CD, elevation of CRP (>0.8 mg/dL) has been associated with active mucosal inflammation on colonoscopy and moderate-to-severe clinical activity.[30] In Pediatric UC, CRP has a fair correlation with colonoscopic inflammation.[31] Changes in the values of CRP when monitored over time have been found to be useful reflecting disease activity at the more severe end of the spectrum. However, up to one third of children may have normal CRP even in the presence of active intestinal inflammation, more so if the initial levels were normal.[32] ESR, a cheaper test than CRP, serves as another surrogate marker of inflammation, since acute inflammation is associated with an increase in plasma proteins and viscosity and thus a prolonged ESR. Almost two thirds of PIBD patients had an elevated ESR at diagnosis, which was higher in CD than UC patients (72% and 23%, respectively), and, in Crohn's colitis, correlated with endoscopic and histologic activity.[32] In a recent Italian cohort, the combination of elevated white blood cells (WBCs), ESR, and CRP levels had a 65.2% and 88.5% sensitivity and specificity, respectively, in distinguishing PIBD from non-PIBD.[33] Albumin represents a negative acute phase reactant, as production is downregulated during acute inflammation; however, low albumin levels may not only reflect severe mucosal loss, but also malnutrition.[34]

Recommendation 1.2.1:

a. CBC, CRP, and/or ESR and albumin should complement clinical assessment (agreement: 100%).
b. The use of combined simple biochemical tests, such as platelet count, NPR, and NLR, may be helpful to further differentiate IBD from intestinal infections, or to characterize disease severity (agreement: 94%).

TABLE 2 Overview of hematological biomarkers in IBD.

Parameter	Clinical relevance	Normal range	Cutoff in IBD (CD and UC)	Diagnostic accuracy	Calculation example
MPV	Indicator of platelet activation and inflammation	7.5–11.5 fL	Lower MPV associated with active IBD (e.g., UC); exact cut-off varies	MPV is best used in combination with other biomarkers	MPV is a measured value in blood tests
NPR	Marker of systemic inflammation (and thrombosis risk)	Healthy individuals: 10–15	Active IBD (e.g., UC): ~20–25 Exact cutoff varies (~15–20); higher NPR may indicate active disease	Diagnostic accuracy varies; often used alongside other biomarkers; may aid disease severity assessment	**Formula:** $\text{NPR} = \frac{\text{Absoulte Neutrophil Count (cells/µL)}}{\text{Platelet Count (cells/µL), divided by 1000}}$ **Example:** Neutrophils: 6000 cells/µL Platelets: 300.000 cells/µL, divided by 1000 NPR = 6000:300 = 20
NLR	Reflects immune imbalance and inflammation severity	Healthy individuals: 1–2	a. Diagnosis of IBD: NLR > 2.04 (Sensitivity 82.1%; Specificity 82.9%)[a] b. IBD Severity: NLR > 2.94 (active disease) (Sensitivity 77.8%; Specificity 50.0%)[a]	a. Diagnosis of IBD: AUC = 0.74 b. IBD severity: higher NLR correlates with increased disease severity	**Formula:** $\text{NLR} = \frac{\text{Absolute Neutrophil count (cells/µL)}}{\text{Lymphocyte Count (cells/µL)}}$ **Example:** Neutrophils: 6000 cells/µL Lymphocytes: 2000 cells/µL NLR = 6000:2000 = 3

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; MPV, mean platelet volume; NLR, neutrophil–lymphocyte ratio; NPR, neutrophil–platelet ratio; UC, ulcerative colitis.
[a]Please see Ref.[29]

Practice point 1.2.1:

a. CBC, CRP (or ESR), and albumin are widely available in LR settings and at reasonable costs.
b. Levels at diagnosis may reflect the extent of acute inflammation:

Thrombocytosis is more common in IBD than in intestinal infections.
MPV may be reduced in active UC.
NPR values are significantly lower in UC in remission versus more active disease (Calculation: Division of the absolute neutrophil count by the platelets, divided by 1000). NLR values are higher in IBD versus healthy controls (Calculation: Division of the absolute neutrophil count by the absolute lymphocyte count, as determined by the CBC; NLR medians: 0.78 [healthy controls] vs. 3.04 [PIBD patients]).

1.2.2 Antineutrophil cytoplasmic antibodies (ANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA)

Evidence

In the largest study to date on their diagnostic value in differentiating PIBD subentities, ASCA+/ANCA– profile was shown to be more suggestive of CD, and ASCA –/ANCA+ profile of UC; however, diagnostic accuracy was too low to be used in isolation for distinguishing IBD-U from colonic CD or UC.[35] Importantly, rates of positivity seem to differ between populations: A study on ANCA/ASCA positivity in Arabs (Saudi Arabia) revealed a low rate in their PIBD patients,[36] and in a Chinese study, pANCA was found to be more sensitive in Caucasian than Chinese UC, with ASCA IgA having a low yield in Chinese CD as well.[37]

Recommendation 1.2.2:

ANCA and ASCA, as well as other serological markers, are costly and of limited diagnostic value and therefore should not be mandatory for routine evaluation in PIBD (agreement: 100%).

1.3 Microbiology

The ESPGHAN revised Porto criteria and the ECCO-ESGAR Guideline for IBD diagnostic workup both recommend the investigation and exclusion of an enteric infection as the cause of symptoms before endoscopy.[38,39] However, the presence of enteric pathogens does not always exclude a diagnosis of IBD because the first episode or flare of IBD can be triggered by documented enteric infection.[38]

1.3.1 Intestinal tuberculosis

Evidence

As no clinical, endoscopic, or laboratory finding is exclusive to either intestinal tuberculosis (ITB) or CD, a Bayesian model was developed, showing that gender, clinical manifestations, endoscopic features, and laboratory findings can accurately diagnose ITB in 92% of patients[40]: The model integrates significant findings and can calculate the probability of the diagnosis of ITB and CD (publicly available at https://www.pathology.med.umich.edu/shiny/tbcrohns/orbit.ly/ITBvsCD). In this context, at initial IBD diagnostic workup a screening test to identify latent tuberculosis infection (LTBI) and ITB that could mimic CD should be performed[39,41,42]: In agreement with the Red Book 2024-2027 either Mantoux tuberculin skin test (TST) or interferon gamma releasing assay (IGRA) testing is acceptable for children of any age. IGRA is preferred for children who have received a BCG vaccine or who are unlikely to return for the TST reading l.[43] An interesting option might be the use of the GeneXpert stool assay, an assay continuously being further developed, since its diagnostic yield, when considering mucosal biopsy with histopathology as diagnostic golden standard, was 39.1% and 85.7% (sensitivity and specificity, respectively.[44] Active TB must be excluded and screening for LTBI always performed before immunosuppressive therapy, in particular biologics (e.g., anti-tumor necrosis factor [anti-TNF] therapy).[6,45] According to the World Gastroenterology Organization (WGO) Global Guidelines, in endemic countries, a trial of anti-TB therapy for 2–3 months should be considered when initiating CD management.[46] Furthermore, weekly response assessment focusing on the resolution of clinical symptoms is suggested, since their complete resolution makes the diagnosis of ITB more likely.[47]

Recommendation 1.3.1:

Mycobacterium tuberculosis infection should be evaluated at initial diagnostic workup and before immunosuppressive therapy, particularly in endemic areas (agreement: 100%).

Practice point 1.3.1:

a. Both Mantoux TST and IGRA can be used to identify the presence of *Mycobacterium Tuberculosis* infection.
b. While the relatively cheaper Mantoux TST is still the most widely used test, false-positive results in BCG immunized children have to be considered.
c. The selection of TB diagnostics is based on availability and national recommendations.

1.3.2 Parasites

Evidence

The identification of an intestinal infection caused by a parasite does not necessarily exclude a diagnosis of IBD[38]: Of particular importance are infections with *Entamoeba histolytica* (EH), prevalent in many LR settings, in view of their bidirectional relationship with IBD.

In endemic countries, amebic colitis should therefore always be considered as an important differential diagnosis, both at IBD diagnosis and flares, and especially before starting immunosuppressive treatment. In addition, UC patients may be more prone to be infected by EH due to mucosal alterations.

However, the diagnostic modality, which is the most widely available, for example, stool microscopy, has only a low sensitivity (<60%). In contrast, stool PCR as the golden standard has sensitivities and specificities of 92%–100% and 89%–100%, respectively, but cannot replace stool microscopy for diagnosing amebiasis.[48] Despite its limitations (multiple stool samples needed, trained observer, time-consuming analysis), microscopic examination is easy and remains the only way to prove hematophagous trophozoites, and is diagnostic for amebiasis when found by two examiners.[49] The Centers for Disease Control recommend a minimum of three stool samples collected within 10 days to increase diagnostic sensitivity to 85%–95%.[50] According to WGO Global Guidelines, a course of anti-ameba therapy should be prescribed within initial UC and CD management in endemic areas and when there is limited access to diagnostic testing.[46]

Recommendation 1.3.2:
Parasite infection should be evaluated at initial diagnostic workup, particularly in endemic areas (agreement: 100%).

Practice point 1.3.2:
a. Microscopic stool examination is a widely available, cost-effective, and simple diagnostic tool for evaluating a parasitic infection, especially in endemic countries. A minimum of three stool samples is needed for diagnosis.
b. Multiple stool microscopy (stool analysis) should be performed at initial diagnostic workup, in cases of nonresponse to initial treatment and at IBD relapse.

1.3.3 Clostridioides difficile (C. difficile)

Evidence
IBD is an independent risk factor for *C. difficile* infection (CDI)[41] and screening for CDI is recommended at diagnostic workup for PIBD,[38] as well as in all patients with a suspected IBD flare and before treatment modification. However, as laboratory testing cannot distinguish between asymptomatic colonization and symptomatic CDI, detection of toxin and clinical correlation may be useful.[9,39,41,51] While metronidazole was traditionally regarded a first-line agent for CDI treatment, two comparative multinational trials showed vancomycin to be significantly more efficacious, even after adjustment for disease severity.[52] As a result, vancomycin is the recommended first line treatment for either non-severe or severe CDI. This is of particular interest, as some of the newer treatments, fidaxomicin,[53] are largely unavailable in LR settings. Metronidazole may be used when vancomycin is unavailable.[54]

Recommendation 1.3.3:
Diagnostic testing for CDI should be performed at the initial diagnostic workup (agreement: 100%).

Practice point 1.3.3:
In symptomatic patients with *C. difficile* toxin positivity, a course (10 days) of vancomycin or metronidazole may be considered.

1.3.4 Human immunodeficiency virus (HIV)

Evidence
Progressive decline in $CD4^+$ counts in HIV may improve and remit IBD activity.[55,56] Many of the opportunistic infections in HIV can mimic IBD and lead to misdiagnosis.[55] ECCO and British Society of Gastroenterology consensus guidelines recommend screening for HIV infection in all IBD patients before initiation of immunomodulatory therapy or biologics.[41,57] HIV antibody tests can provide definitive diagnosis of HIV infection in ≥18 months. In children aged <18 months, PCR is recommended to rule out HIV infection and should be performed at a minimum age of 4–6 weeks,[58] which needs to be considered in the rare case of suspected VEO-IBD.

Recommendation 1.3.4:
HIV infection should be evaluated at initial diagnostic work-up and before immunosuppressive therapy, in endemic areas (agreement: 100%).

Practice point 1.3.4:
a. Individuals at increased risk of acquiring HIV should seek effective HIV testing in line with current WHO recommendations (e.g., using simple and affordable rapid diagnostic tests, including self-tests).
b. The selection of diagnostics should be based on availability and national recommendations.

1.4 Fecal inflammatory markers

Evidence
While not specific for IBD,[38,39] fecal calprotectin's (FCal) high sensitivity has proven to be cost effective in distinguishing IBD from non-IBD in children.[59] FCal, as well as the slightly more specific lactoferrin, are both available as point-of-care tests (POCTs). Their use for diagnosing IBD in symptomatic children was studied prospectively in two cohorts of children with chronic GI symptoms, one presenting to primary, the other referred for specialist care. POCT FCal was shown to reduce the referral rate for specialist care by 76% and POCT lactoferrin by 81%; overall, one child

with an IBD diagnosis was missed (6%).[60] A retrospective single-center comparison of two large adult IBD patient cohorts (268 vs. 246 patients) with colonoscopy-only versus FCal as the first marker to assess IBD activity revealed that introducing FCal into routine IBD care aided changes in clinical management in a similar proportion, yet at potentially half of the total cost, compared to the historical colonoscopy-only cohort.[61] While a FCal cutoff of 50 µg/g was shown to reliably distinguish between IBD and non-IBD in pediatric populations (sensitivities: 95%–100%, specificities: 44%–93%), areas of uncertainty include the optimum management of children with borderline results (50–150 µg/g), most of whom do not have IBD. Repeat testing may be appropriate before referral.[62] The optimal timing for stool sampling is on debate, but recent data suggest that analysis of only one stool sample should be sufficient for adequate FCal evaluation.[63]

Recommendation 1.4:
In unclear cases, a fecal inflammatory marker (e.g., FCal) can be used to avoid unnecessary investigations, for example, endoscopies (agreement: 100%).

Practice point 1.4:

a. As FCal is increased in case of bleeding, its use may be questionable in the presence of visible blood in stools.
b. Intra-individual variability should be considered in the interpretation of measurement results.
c. Alternative diagnoses (e.g., irritable bowel syndrome, or intestinal infections, e.g., giardiasis) should be considered in the face of a low level of FCal (<150 µg/g).

1.5 Radiology

1.5.1 Small bowel assessment

Evidence
To maximize differentiation between CD and UC at diagnosis, small bowel evaluation should be performed depending on available resources, except for typical UC. Therefore, in LR settings, small bowel imaging may be avoided if the presentation is typical of UC, based on clinical presentation, endoscopy and histology.[38] Small bowel evaluation should be performed in CD if possible, to assess the degree and the extent of the inflammation and define the presence of disease-related complications.[64,65] Moreover, in those patients whose ileum could not be intubated, imaging may help to reach correct diagnosis and monitor disease.[38]

The choice of which test to perform depends on local availability and expertise and includes preferably magnetic resonance enterography (MRE) and intestinal ultrasound (IUS), but when unavailable computed tomography enterography (CTE) could be used. In the absence of all other modalities, small bowel follow-through (SBFT) may serve as an alternative. Video capsule endoscopy (VCE), a newer technique of significance with an accuracy comparable to MRE and IUS,[66] is largely unavailable in LR settings. However, if available, VCE may follow the above-mentioned tests in selected cases, after excluding bowel stenosis.

Recommendation 1.5.1
The small bowel should be evaluated, as available, in all children newly diagnosed with CD, atypical UC, or IBDU, but this is not needed in typical UC (agreement: 100%).

1.5.2 Imaging techniques

Evidence
MRE is the preferred imaging modality at diagnosis and during follow-up as it allows to evaluate both the changes of the bowel wall, and thus the degree of transmural inflammation, stricturing, and penetrating disease, with no radiation exposure. In many LR settings, MRE scanners are currently not widely accessible, especially in the smaller and more peripheral centers.[67] In addition, anesthesia may be required for small children, taking up more resources.

Despite the inherent radiation exposure, CTE is still widely used in the diagnosis and evaluation of CD in both adults and children.[68] Various techniques and strategies to reduce CTE radiation dose are currently available with no significant negative impact on the test's accuracy.[69] CTE has shown a high and significant correlation coefficient with "Crohn's Disease Endoscopic Index of Severity" for small bowel lesions[70] and demonstrated similar sensitivity and specificity when compared to MRE.[71] In a subgroup analysis of a comparative prospective study, MRE was more sensitive for mild CD lesions than CTE (76.5% vs. 60.3%), while the sensitivities for moderate-severe CD were similar between these two modalities (96.8% for MRE and 93.5% for CTE). Overall specificities were similar.[72] Nevertheless, as children are likely more susceptible to the potentially harmful effects of ionizing radiation, repeated evaluation of the small bowel using CTE should be avoided due to cumulative radiation exposure.[73] Despite the radiation exposure and limited information (low sensitivity compared with MRE) provided, performing SBFT may still be an option if all other alternatives for small bowel evaluation and assessment of disease activity and extent are not available.[39]

However, mounting evidence has begun to demonstrate the accuracy of IUS as compared to the gold standard of endoscopy in children with suspected IBD, with a sensitivity for diagnosing de novo IBD of 48-93%, as shown in a systematic review of 14 studies.[74] For

the diagnosis of CD as well as for the evaluation of established disease, published data report an even better performance (79.7% sensitivity, 96.7% specificity and 89% sensitivity, 94.3% specificity, respectively)[75]: Bowel wall thickness (BWT, ≥3 mm) and hyperemia are the best IUS parameters for defining active inflammation. The highest sensitivity is for ileal, right and left colon lesions with less sensitivity in detecting the upper small bowel and rectal lesions.[76] Other signs of bowel inflammation also include regional lymph nodes, mesenteric hypertrophy, mural stratification, vascularity, fibrofatty proliferation as well as evaluation of complications, e.g. stricture, fistulae or abscesses.[76–78] A comparative evaluation of endoscopy and IUS in PIBD patients revealed BWT and mesenteric inflammatory fat as the most important sonographic parameters for predicting disease activity.[79] When combined with hyperemia (as assessed by color doppler) into a simple score, there was accurate detection of inflammatory activity,[79] allowing for standardization of the use of IUS in children.

Based on these data, considering the wide availability, the low costs, and non-invasiveness for patients, IUS may substitute MRE in LR settings for evaluating the (small) bowel in IBD. Its main limitation is that its performance is operator-dependent, requiring adequate training for the gastroenterologist or radiologist. Implementing IUS as an alternative to MRE should be paralleled by nationwide training programs, facilitated through applying, for example, to the International Bowel Ultrasound Group (www.IBUS-Group.org).

Recommendation 1.5.2:

a. MRE is currently the imaging modality of choice in pediatric CD at diagnosis, but intestinal US in experienced hands may be a suitable alternative (agreement: 94%).
b. When MRE and intestinal US are not available, CTE or small bowel follow-through may be used (agreement: 94%).

Practice point 1.5.2:

a. For IUS, a linear transducer (5–15 MHz) according to patient size should be used.
b. Doppler ultrasound is useful to check for intramural enhanced perfusion.
c. If licensed, intravenous US contrast media are helpful for the assessment of perfusion.
d. Sonographic signs for transmural healing are normalization of values of BWT (<3.0 mm) and of Doppler perfusion.

1.6 Endoscopy

Evidence

The ESPGHAN Revised Porto Criteria recommend EGD and ileocolonoscopy as the most essential part of the initial workup for the diagnosis of PIBD in nonemergency situations. The choice of endoscopes should depend on the child's weight and age.[80] Ideally, the endoscopy should be performed by a pediatric gastroenterologist after an age-appropriate bowel preparation, under general anesthesia or deep sedation in a setting suited for children, and by personnel with training and expertise in PIBD.[38] When pediatric gastroenterology facility is lacking, adolescents may be evaluated by adult gastroenterologists, if they have appropriate experience in pediatric IBD; however, this should be avoided whenever possible.

In LR settings, however, pediatric endoscopy services can be performed by adult gastroenterologists in collaboration with pediatricians.[81–83]

There is a striking difference between LR settings and HICs in the number of formally trained and certified pediatric gastroenterologists.[6] In some developed-world countries, there could be one pediatric endoscopist for every 100,000 to 200,000 inhabitants, whereas in countries with more LRs, for example, in Bangladesh, there are only two or three pediatric endoscopists for a population of approximately 150 million.[84,85] As per the WGO Global guidelines in adults, full-length ileocolonoscopy should be performed in suspected IBD, also in children, and even in LR settings, including biopsies, if available.[46] It is crucial, that endoscopists and pathologists should agree on a minimum of required biopsies to provide accurate diagnosis, based on available local resources (see Section 4.7).

Practice point 1.6:

If the pediatric endoscopy service is unavailable, gastrointestinal endoscopy in children and adolescents may be performed by adult gastroenterologists, but in close collaboration with pediatricians.

1.6.1 Anesthesia

Evidence

ESPGHAN Revised Porto Criteria recommend endoscopy to be performed under general anesthesia or deep sedation in a setting suited for children, but the choice of sedation is still debatable, regardless of age.[38] In LR settings, expertise and technological limitations may require adjustments to this guidance, but some basic rules must be kept: (1) the patient safety and welfare; (2) minimization of physical discomfort and pain; (3) lessening of anxiety and psychological trauma and maximizing the potential for amnesia; (4) control of patient behavior for safe completion of the procedure; and (5) safe discharge of the patient.[86,87] Pre-sedation risk assessment using the American Society of Anesthesiologists-Physical Status (ASA-PS) classification is recommended.[87] In LR settings, anesthesiologist-administered sedation is preferred in

children with ASA Class III–V. In ASA Class I–II, conscious (moderate) as well as deep sedation may be performed safely by non-anesthesiologists, for example, by a pediatrician with competence in advanced pediatric life support.[88,89]

Recommendation 1.6.1:

a. A health professional with experience in managing airways should be in charge of the monitoring of the patient apart from the endoscopist (agreement: 100%).
b. Endoscopists performing pediatric procedures should be certified for pediatric advanced life support and familiar with resuscitation protocols, including airway management (agreement: 94%).

1.6.2 Endoscopic assessment

Recommendation 1.6.2:

Simple Endoscopic Score for CD (SES-CD) and UC Endoscopic Index of Severity (UCEIS) or Mayo Score for UC, respectively, are recommended for assessment of endoscopic remission (agreement: 100%).

Practice point 1.6.2:

a. Standard adult gastroscopes can be used in children with a body weight ≥ 10 kg or age ≥ 1 year.
b. Gastroscopes ≤ 6 mm, if available, should be used for EGD in children with body weight < 10 kg or age < 1 year.
c. Standard adult colonoscopes can be used in children > 10 kg if a pediatric colonoscope is not available. For children between 2.5 and 10 kg, adult gastroscopes can be used for colonoscopy.
d. Recording the endoscopy in a video format eases any discussion with a (P)IBD expert regarding further management.

1.7 Histopathology

Evidence

Standardized histologic examination of endoscopic biopsies is an essential component of initial IBD diagnosis, and monitoring asymptomatic IBD patients using endoscopy remains the gold standard as a marker of disease activity with respect to validity (correlation with gold standard) and responsiveness to changes in disease activity.[39]

Because accurate phenotype classification is mandatory for individually tailored management, additional "PIBD-classes" criteria have been developed that standardize the differentiation of PIBD into five categories.[35,90] Furthermore, the dynamic features of PIBD phenotype, that is, changes in disease location and behavior over time, should be captured adequately to ensure the universal therapeutic goal of "mucosal healing." To define such phenotypes in a standardized manner, the evidence-based "Paris classification" of clinical, imaging, and endoscopic findings should be used worldwide, as this also bears long-term predictive properties (e.g., ileal location at CD diagnosis indicating a long-term worse outcome,[91] and be complemented by histology to allow for definitive classification.

However, recent surveys from countries with LR settings have shown significant shortages of pathology services (e.g., statistics enumerating one pathologist per 1,555,000 patients in Sub-Saharan Africa), and technical or structural problems that may further limit response capacity. In view of the global recommendation for gastrointestinal endoscopy with biopsies and histology, even in countries with LRs,[46] minimal requirements as to the histologic examination must allow a reliable diagnosis of PIBD.

Although localized symptoms of the upper gastrointestinal tract (UGT) are not correlated with UGT involvement in PIBD,[92] histological UGT involvement is noted in approximately half of PIBD patients, most frequently involving the stomach (67%), less so the duodenum (22%)[93] or esophagus (7% in UC, 12%–28% in CD).[94] Specific histologic findings, such as granulomas, were found in a significant proportion of children with CD only in the UGT biopsies, emphasizing the importance of EGD in this population.[94,95] According to the revised Porto criteria, EGD should therefore be performed in all children at the initial evaluation of IBD, with two or more biopsies obtained from each site, irrespective of the UGT manifestations and endoscopic appearances.[10]

For suspected IBD and a reliable diagnosis of UC and CD, ECCO-ESGAR guidelines as well as Porto criteria recommend ileocolonoscopy with a minimum of two biopsies from the terminal ileum, cecum, transverse colon, sigmoid colon and rectum.[38,39] Tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution before transport.[96]

Identifying histologic changes in areas of normal endoscopy to stage the extent of disease is particularly important with regard to CD diagnosis, as is the assessment of non-caseating granulomas. Differentiating CD from ITB is mandatory in developing and newly industrialized countries, some of which are endemic for ITB, and where the disease burden of IBD is rising. In these regions large or confluent/caseating granulomas would be indicative for ITB and caseation necrosis on biopsy is even regarded as the only exclusive feature, further emphasizing the importance of histology in LR settings.[97] Similarly, histopathologic findings such as crypt architecture distortion, "crypt runting," and basal plasmocytosis are features of chronic colitis and would be atypical in acute infectious colitis.[46]

Digitizing 40,000–200,000 slides per month is feasible, although to date, in HICs only. While this system is not yet extended enough for clinical use, such digitization makes a specimen more reproducible, with digital whole-slide imaging (WSI) allowing capture and

visualization of the entire tissue on a slide.[98] WSI modalities (i.e., scanners, software, clouds, communication systems), the digital products already available, will allow for migrating the entire workflow of pathologists from the manual to the digital. Thus, WSI could ultimately reduce barriers between hospitals, regions, and countries facilitating consultations and referrals. However, the costs of adequate scanning systems are still substantial. While providing virtual pathology services at remote sites might eventually facilitate international consultations, it is certainly mandatory for now to focus on explicitly training histopathologists in LR settings, particularly regarding IBD diagnosis, and facilitate direct cooperation between institutions with LRs and those in HICs.

Recommendation 1.7.1:

a. Number of biopsies per patient may be adjusted according to personal and structural resources (agreement: 82%).
b. In endemic countries, a special focus should be directed on histopathologic differentiation between IBD and ITB (agreement: 100%).

Practice point 1.7.1:

a. Although a minimum of 7–8 biopsies from the UGT is recommended, 2–3 biopsies only may suffice (1 duodenal, 1–2 gastric). There is no need to routinely biopsy the esophagus, unless there are macroscopic changes.
b. To further reduce costs, two jars to collect UGT biopsies are sufficient (one for duodenum, 1 for gastric specimens) and four jars for the lower GI tract (1 × terminal ileum, 1 for ascending and descending colon, respectively, 1 for rectum).
c. If no histopathology service is available, hospital laboratory technicians should be taught adequate preparation of specimens and slides shipped for analysis in an HIC institution.

2 Disease Monitoring

Evidence

The target of IBD treatment includes the resolution of symptoms and intestinal inflammation; therefore, regular monitoring of inflammatory activity is essential for the optimization of IBD treatment (Table 1). For PIBD follow-up, clinical evaluation including growth monitoring remains essential, and the need for easy-to-use and noninvasive objective markers is important to minimize repeated endoscopic evaluation. Importantly, at 1–3 months after the initiation of induction therapy, biomarkers, such as CRP, hemoglobin, or neutrophil counts correlate with intestinal inflammation and can predict the response to treatment allowing for early assessment of treatment efficacy.[99] However, the heterogeneity of countries with LR settings, both ethnically and economically, test availability and costs represent major challenges in generalizing recommendations on PIBD care.

For monitoring a known CD, clinical evaluation including a disease activity index (e.g., PCDAI) along with laboratory markers (e.g., CRP and FCal) should be used, and in patients with clinical remission, performed periodically, initially every 3 months. These biomarkers can be further used to assess treatment response, since normalization of CRP and FCal, for example, at Weeks 10–14 of treatment with biologics, is associated with improved outcomes of clinical remission and mucosal healing.[100] As far as UC is concerned, previous data show that the clinical activity monitored by PUCAI score reflects the degree of mucosal inflammation in most patients,[17] and thus it can be effectively used during routine visits to monitor patients, in combination with FCal when available. Reassessment of the disease status should be strongly considered in cases of relapse, persistent disease activity, new unexplained symptoms and before significant switch of therapy, using any of the above measuring methods.[39]

2.1 Clinical assessment

Recommendation 2.1:

a. Clinical evaluation, including growth monitoring and assessment of disease-specific activity indices, is mandatory for follow-up, both at routine controls and when a flare is suspected (agreement: 100%).
b. The use of self-assessment tools or dedicated Apps should be considered to monitor clinical evolution (agreement: 94%).

2.2 Blood inflammatory markers

Recommendation 2.2:

Clinical assessment should be paralleled by analysis of blood inflammatory markers (CBC, CRP, and ESR) and albumin, particularly in suspected flare (agreement: 100%).

Practice point 2.2:

a. Blood inflammatory markers should be repeated initially every 3 months.
b. When in clinical remission, repeated assessments of blood inflammatory markers can be spaced at the treating physician's discretion.
c. In suspected flare, blood inflammatory markers can help to decide on the need for endoscopic reassessment.

2.3 Microbiology

Recommendation 2.3:

Diagnostic testing for CDI should be performed in symptomatic patients and in all flares associated

with diarrhea, but not as a routine examination (agreement: 100%).

2.4 Pharmacologic monitoring

2.4.1 Testing for thiopurine S-methyltransferase (TPMT) activity and metabolites

Evidence

A deficiency in TPMT activity may potentiate thiopurine-related side effects, thus testing for its activity (genotype or phenotype) may identify patients at risk of early myelosuppression. However, this is not a standard of practice in many countries and when not available in LR settings, frequent WBC testing after initiation of thiopurines may suffice. Additionally, ethnic-related variation of TPMT genetics, like mutations in the Nudix hydrolase 15 (NUDT15) gene in South East Asians, may also guide the utility of this testing, as genome-wide association studies, in Korean patients with CD, revealed non-synonymous single-nucleotide polymorphisms in NUDT15 that are strongly associated with thiopurine-induced early leukopenia. In clinical application, NUDT15 genotyping is therefore a good candidate for predicting thiopurine toxicity in East Asian populations,[101–105] test availability provided. Importantly, cytopenia can still occur despite normal TPMT activity.

Measuring thiopurine metabolites (6-thioguanine nucleotide [6-TGN] and 6-methylmercaptopurine [6-MMP] levels) may assist in dose adjustments and reduce adverse events, while considering 6-TGN level of 235–450 pmol/8×10^8 RBCs and 6-MMP level <6700 pmol/8×10^8 RBCs as optimal. A recent review of these pharmacokinetic data indicated a somewhat limited value of their translation into clinical outcome[106] and due to limited availability and high costs of these tests, the therapeutic monitoring of TGNs is not practical for every clinic.[107] If thiopurine metabolites are unavailable, clinical symptoms and regular routine blood tests can be used to guide dosage changes: Monitoring WBC is needed to control for leukopenia, while liver enzyme levels should also be regularly assessed, for early detection of hepatotoxicity.[7] If mean corpuscular volume (MCV) is elevated, 6-TGN is unlikely to be subtherapeutic.[108]

Recommendation 2.4.1:

When initiating thiopurines, frequent monitoring of WBC and liver enzymes is always mandatory and may replace testing for TPMT-activity and thiopurine metabolites (if these are not available; agreement: 100%).

Practice point 2.4.1:

a. Testing for TPMT activity phenotypically may be more cost-effective than genetic testing.
b. Actual values for TPMT activity are not reliable in case of recent blood transfusions.
c. An elevated MCV (≥101 fL) may be used as a surrogate marker to rule out subtherapeutic thiopurine metabolites.

2.4.2 Therapeutic drug monitoring (TDM) in biologics

Evidence

TDM, including detection and titration of anti-drug antibodies, has been suggested as a useful tool to manage patients on anti-TNF treatment, including monitoring for dose escalation, de-escalation, or to switch treatment.[109] While TDM may be cost-effective,[110] access to TDM is limited in many parts of the world, and even in areas with access the results of TDM can take up to several weeks to become available, thus causing a delay as to the corrective action. Clinicians have therefore developed alternative strategies that include standardized symptom-oriented clinical assessments (no/partial/complete symptom resolution) and make use of biomarkers or imaging modalities.[111]

Recommendation 2.4.2:

Clinical and biological markers should be used to optimize immunomodulatory/biologic treatment (e.g., FCal or alternative, CRP, serum albumin, MINI, and if relevant, cross-sectional imaging and endoscopy; agreement: 100%).

Practice point 2.4.2:

For routine monitoring, when a patient is in clinical remission, such biomarkers can be assessed every 6 months, and when a flare is suspected upon discretion of the treating physician, availability, and cost.

2.5 Fecal inflammatory markers

Evidence

An increase in FCal in the absence of identified infection may warrant therapeutic adjustment or re-evaluation.[9] In pediatric UC, clinical activity indices are reliable signs; therefore, PUCAI combined with monitoring FCal allows an adequate assessment of disease activity without the need for endoscopy.[112,113]

Recommendation 2.5:

If available, a fecal inflammatory marker should be used for monitoring and to evaluate treatment efficacy (agreement: 100%).

Practice point 2.5:

For routine monitoring, when a patient is in clinical remission, a fecal inflammatory marker can be measured every 6 months, and when a flare is suspected, upon discretion of the treating physician, availability and cost.

2.6 Imaging for monitoring

Evidence

While MRE is currently the imaging modality of choice for monitoring pediatric CD, IUS has emerged as a valuable real-time, point-of-care biomarker, akin to the current use of CRP or FCal. Importantly, IUS has the benefit of real-time results for treatment optimization, potentially without the need for additional invasive testing.[114] In children with ileal CD, changes in BWT, color Doppler signal, and bowel segment length were visualized as early as 2 weeks after the initiation of infliximab (IFX) therapy, and a strong correlation between bowel wall color Doppler signal and FCal shown.[115] Another study demonstrated resolution of bowel wall hyperemia post-induction at Week 14, as the first IUS parameter to normalize,[116] while a decrease in BWT by 18% by Week 8 was predictive of mucosal healing of the ileum with an AUC of 0.995 [95% confidence interval: 0.98–1.00; Dolinger et al.; personal communication; DDW 2023].

Recommendation 2.6:

MRE is currently the imaging modality of choice in pediatric CD during follow-up and should be the preferred option whenever available, but IUS is a valuable technique for monitoring an established PIBD and should be used as an alternative to MRE (agreement: 94%).

2.7 Endoscopy—Follow-up

2.7.1 Disease monitoring

Recommendation 2.7.1:

When clinical symptoms and biochemistry suggest moderate disease activity or relapse, use of endoscopy for disease monitoring and/or reassessment of mucosal healing should be considered (agreement: 100%).

2.7.1 Cancer surveillance

Recommendation 2.7.1:

Cancer surveillance screening should be performed in accordance with the ECCO/ESPGHAN guidelines, if endoscopy and histopathology services are available (agreement: 100%).

3 Pharmacological treatment (non-biologics)

Infections may mimic IBD or complicate management; therefore, antibiotic use is often an important part of treatment, taking into account the local epidemiology (amebiasis, tuberculosis). Empiric antibiotic treatment may be considered in the management of CD and UC, regardless of positive infectious origin.[7–9,46]

In LR settings, many of the recommended non-biologic IBD medications, such as steroids, mesalazine, methotrexate, and azathioprine, are available. However, several drugs or preparations of drugs, such as budesonide, mercaptopurine, tacrolimus, and some enemas, are not generally available. Lastly, therapeutic optimization tools for safety and effectiveness are often unavailable, such as pharmacogenomics (TPMT genetics) and drug level measurement.

3.1 Empiric treatment of (intestinal) infection

Recommendation 3.1:

a. In endemic countries, antituberculosis therapy should be considered before IBD treatment, governed by testing (agreement: 88%).
b. In endemic countries, anti-ameba therapy should be considered before IBD treatment (agreement: 88%).

3.2 Mesalazine and sulfasalazine

Evidence

Oral mesalazine (5-aminosalicylic acid, 5-ASA) compounds are used as first-line induction and maintenance therapy for mild-to-moderate UC, and their effectiveness can be augmented by combining oral and rectal administration formulas. Sulfasalazine may be somewhat superior to mesalazine for maintenance of remission, as shown in adult studies, effective for arthritis, and cheaper than the other formulation.[8] Although associated with somewhat more adverse events, severe reactions have not been translated to a meaningful difference on a group level, and the Cochrane review summarized that given the lower cost sulfasalazine should be prioritized over other formulation.[8]

Recommendations 3.2:

In pediatric UC, sulfasalazine is cheaper than the other mesalazine compounds and thus may be prioritized in LR settings (agreement: 100%).

Practice point 3.2:

As Sulfasalazine is available in liquid formulation in some countries, it should be used in younger children and those who cannot swallow mesalazine tablets or granules.

3.3 Steroids

Evidence

Oral corticosteroids should be used as second-line treatment for mild-moderate UC not responding to 5-ASA and may be considered as first line in the higher end of the moderate disease range.[8] Chronic active UC which becomes severe and acute severe UC (ASUC) are treated initially with intravenous steroids.[8,9] Rectal steroid therapy (suppositories plus liquid and foam enemas) is less effective than rectal mesalazine therapy in UC, but has a role in cases of mesalazine intolerance. In active luminal CD, oral steroids can also be considered

for inducing remission when "Exclusive Enteral Nutrition" (EEN) is not an option or failed,[8] but they are not used for maintenance of remission.[8,9] Steroid tapering regimens should be implemented,[117] alternate day tapering over 2–4 weeks,[118] but even abrupt steroid discontinuation has been practiced in randomized controlled trials (RCTs). There are also apps available that may guide timing for clinical and biochemical remission,[117] ESPGHAN App: ESPGHAN Guidelines https://espghan.info). If the rectum is inflamed, in CD rectal steroids are used before rectal mesalazine.[119]

So far, oral steroid courses are more frequently used in LR settings for both UC and CD, given the issues with availability, cost, and feasibility of EEN. The lack of availability of medications, for example, some mesalazine preparations and topical steroid enemas, leads to novel solutions such as the use of intravenous steroid ampoules to prepare enemas.[120] Biologic therapy is expensive and not prioritized by the providers in some LR settings, and reliance on systemic steroid usage as the mainstay of medical treatment is still an issue.[120] In addition, mitigating the steroid burden by using second-generation oral steroids (e.g., beclomethasone dipropionate [BDP] and budesonide-MMX[121]) proves difficult due to high costs and unavailability in many LR settings.

Recommendation 3.3:

a. Steroids are recommended for severe pediatric UC, and in moderate-severe CD for induction of remission, when formula for enteral nutrition is not available (agreement: 100%).
b. BDP and budesonide-MMX may be considered before oral prednisolone in patients with mild disease refractory to oral mesalazine (5-ASA; agreement: 100%).).
c. For maintenance treatment, steroid-sparing strategies should be applied, with thiopurines (agreement: 94%).

Practice point 3.3:

a. In patients > 30 kg the dosing schedule of BDP is 5 mg once daily for 4 weeks and for budesonide-MMX 9 mg once daily for 8 weeks.
b. BDP dosing for children < 30 kg has not yet been established. While standardized liquid formulations are not commonly available, compounding pharmacies might prepare BDP oral liquids.

3.4 Thiopurines

Evidence

Thiopurines are commonly used to maintain remission of UC and CD (especially if steroid-dependent), and in the context of issues with availability, cost, and feasibility of biologic use.

The limited access to pharmacogenomic testing (TPMT genotype or phenotype before thiopurine start) and optimizing thiopurine use by measuring thiopurine metabolites may affect both effectiveness and safety: Determination of TPMT genotype or phenotype (i.e., TPMT activity), if available, is encouraged, to identify patients at greater risk of profound myelosuppression. Dose should be reduced in heterozygous patients or in those with low activity. Thiopurines should not be used in children homozygous for TPMT or those with very low TPMT activity, as defined at each laboratory. A further key concern with thiopurines is the risk of hepatotoxicity and pancreatitis, which also require regular assessment.[7] Nevertheless, thiopurines can be widely and comfortably used without TDM, based on clinical response (no symptom improvement, partial symptom resolution, clinical remission, within 16 weeks) and biomarkers, for example, monitoring WBC and MCV.[111]

3.4.1 Indications

Thiopurines (azathioprine and mercaptopurine) are recommended for maintaining remission in children with UC who are corticosteroid-dependent or relapsing frequently (≥2 relapses per year) despite optimal mesalazine treatment as well as in mesalazine intolerant patients.[8] Given that thiopurines may take up to 16 weeks to have full therapeutic effect, they should be introduced at full dose.[9] They can also be used to maintain remission in pediatric patients with CD who have reached remission, with deep remission rate of 20% in pediatric CD.[7,122]

Recommendation 3.4.1:

a. In pediatric UC, thiopurines are recommended for maintaining remission in children who are steroid-dependent or relapsing frequently (>2 relapses per year) despite optimal oral mesalazine (5-ASA) treatment and in 5-ASA-intolerant patients (agreement: 100%).
b. Thiopurines should be considered following discharge from ASUC episode (agreement: 100%).
c. In pediatric mild-moderate CD, thiopurines are recommended as a first-line maintenance therapy (agreement: 94%).

Practice point 3.4.1:

a. Thiopurine dose may need to be lowered or stopped if there is evidence of myelosuppression.
b. For maintenance therapy in CD, and particularly in male adolescents, methotrexate may be considered as an alternative to thiopurines.

3.4.2 Initiation, monitoring and withdrawal of medication

Clinical symptoms and regular routine blood tests are used to guide dosage changes, as mentioned above.

Recommendation 3.4.2:

a. When initiating thiopurine medication, frequent monitoring of WBC (e.g., every 2 weeks for

4 weeks) to identify patients at risk of profound myelosuppression is recommended, even if NUDT15-genotyping and TPMT-enzyme assay are available (agreement: 100%).
b. Patients with Leukocytes $< 2.5 \times 10^9$/L or elevated aminotransferases (>100 U/L) should have dose reduction or temporary cessation (depending on clinical assessment and laboratory values; agreement: 100%).
c. Thiopurines should be discontinued in clinically significant myelosuppression or pancreatitis (agreement: 100%).
d. Thiopurine withdrawal could be considered in patients in sustained clinical remission following long-term treatment (up to 4 years) after ideally ensuring complete mucosal healing and preferably histological remission (agreement: 100%).
e. If endoscopic, histopathological, and radiological reassessment is not possible, serial fecal biomarker measurements can be helpful to follow mucosal healing before and after withdrawal (and may help to decide which patient should undergo invasive investigations; agreement: 100%).
f. In the case of thiopurine withdrawal, oral mesalazine (5-ASA) treatment may assist in maintaining remission in UC (particularly in patients naïve to 5-ASA; agreement: 100%).

Practice point 3.4.2:

a. Thiopurines may take 10–16 weeks to have full therapeutic effect, and a decision on effectiveness should be made then.
b. Regular monitoring of WBC and liver enzymes is mandatory in all patients (of WBC e.g. weekly at initiation, and of liver enzymes at clinical discretion, depending on severity of abnormality or clinical context). Once thiopurine dose is stable, then monitoring can be spaced to every 3 months.
c. Several options for patients with azathioprine intolerance (e.g., nausea) can be considered:
   – Split dosing from once to twice daily.
   – Temporary cessation for 2 weeks with subsequent repeat of azathioprine trial.
   – Switch to mercaptopurine.
d. If pancreatitis is suspected, pancreatic enzymes and abdominal ultrasound have to be checked.
e. Reintroduction of thiopurines after leukopenia (but not usually pancreatitis) can be considered at a lower dose (using clinical reviews and regular WBC check to guide reintroduction).

3.5 Methotrexate

Evidence

Methotrexate (MTX) can be considered for maintenance of clinical remission in pediatric CD in case of unavailability and/or failure or intolerance of thiopurines.[7] While MTX had usually been administered via subcutaneous (SC) injection in an induction course of 16 weeks and a switch to oral methotrexate only considered in case of steroid-free remission by 16 weeks, some recent data indicate similar outcomes for oral administration.[123] Because nausea and vomiting are major problems right from the start of MTX use and during the maintenance phase, ondansetron is often used to reduce nausea and improve drug durability. However, access to ondansetron to prevent and/or treat these side effects, is limited in LR settings and thus metoclopramide may be used.

Recommendation 3.5:

In CD, MTX can also be considered as primary maintenance therapy as well as in thiopurine intolerance or thiopurine nonresponse (agreement: 100%).

Practice point 3.5:

a. Administration of ondansetron/metoclopramide 1 h before taking MTX and for 1 day [occasionally more days] may reduce nausea and improve tolerance.
b. Taking weekly MTX just before sleeping at night may be helpful.
c. MTX had usually been administered via SC injection, at least for induction, but oral administration is also possible.

3.6 Calcineurin inhibitors

Evidence

Topical tacrolimus enemas may be used for refractory ulcerative proctitis. For ASUC, cyclosporine, if available, can be used as an alternative second-line therapy to IFX. Tacrolimus is less likely to be available, but if so, then dosing and target levels should be observed as recommended.[9] Further, availability issues plus the need for frequent TDM means that calcineurin inhibitor use for chronic active pediatric UC and CD is rare in LR settings. Therefore, in many such settings, colectomy can be a more likely option than second-line medical therapy for ASUC.

Recommendation 3.6:

a. Calcineurin inhibitors (tacrolimus and cyclosporine) can be considered as an alternative second-line medical therapy (to biologics) in UC, and only if TDM monitoring is available (agreement: 94%).
b. Rectal tacrolimus may be considered in patients with ulcerative proctitis who are either refractory or intolerant to mesalazine and steroid topical therapies (agreement: 100%).
c. Oral tacrolimus may be considered a short-term agent in steroid-refractory cases of UC (agreement: 94%).
d. Oral tacrolimus may be considered as rescue therapy in ASUC as another option to steroids for bridging to thiopurines or biologics (agreement: 94%).

Practice point 3.6:

a. Cyclosporin may be considered as the first alternative, given the lower cost (a) i.v. dosing: For induction 2 mg/kg/day via continuous infusion; initial trough level 150–300 ng/mL; oral dosing: 4–8 mg/kg/day; trough level 150–300 ng/mL).
b. At initiation, high target tacrolimus serum trough levels (10–15 ng/mL) should be achieved, with a gradual titration to lower trough levels (5–10 and eventually 2–5 ng/mL) to avoid serious adverse events.
c. Selected patients may benefit from a long-term, low-dose treatment (i.e., drug level target of 2 ng/mL), considering potential toxicity and limited supportive evidence.

3.7 Thalidomide

Evidence

Thalidomide is rarely available in LR settings. Due to numerous potential side effects (sedation [32%]; peripheral neuropathy [20%]), and its teratogenicity, thalidomide use as induction therapy is restricted to a very selected cohort of pediatric CD patients, for example, those intolerant to parenterally administered therapies despite psychological support or refractory to several biologics, and must be managed in experienced centers.

3.8 Antibiotics

Evidence

Antibiotics have a potential role across all IBD beyond their key role during bacterial infection in IBD,[7–9] with most consistent evidence as first-line pouchitis therapy.[8] In ASUC, vancomycin is recommended as the first-line antibiotic for CDI, but an antibiotic cocktail may also be used with benefit, in addition to i.v. steroids.[9] In CD, Levine et al have shown that antibiotic combination may be useful for induction of clinical remission.[124] In case of perianal fistulizing CD, antibiotics (e.g., ciprofloxacin, metronidazole), are vital in the three-pronged approach to induce and maintain remission together with surgical intervention and anti-TNF usage.[7] In regard to IBD-PSC (primary sclerosing cholangitis), vancomycin is used as an add-on for IBD induction and maintenance of remission, in severe cases.[8,125]

Recommendations 3.8:

a. In hospitalized children with ASUC, an oral antibiotic quadruple therapy (amoxicillin, metronidazole, doxycycline/ciprofloxacin, and vancomycin, if available) can be considered as rescue treatment in addition to intravenous steroids (agreement: 88%).
b. A combination of antibiotics (azithromycin and metronidazole) can be used for induction of remission in mild-to-moderate pediatric CD, particularly where nutritional therapy is not an option or has failed (agreement: 94%).
c. Antibiotics may also be used in CD when small bowel bacterial overgrowth is suspected and for active perianal disease (agreement: 88%).

Practice point 3.8:

Oral vancomycin should be considered as first-line therapy for CDI, but oral metronidazole may be used in the absence of oral vancomycin.

3.9 Probiotics

Evidence

Having been evaluated for induction and maintenance of remission in UC and CD, the main use of probiotics in IBD is in UC, in particular for pouchitis after colectomy. There are both major cost and availability issues for probiotics (particularly those discussed in IBD guidelines, including a mixture of 8 bacterial strains and *E. coli Nissle*) in most LMICs. Therefore, for practical reasons, no recommendation can be made on its use.

3.10 Curcumin

Evidence

Recently, a small case series on the tolerability of curcumin added to standard therapy in pediatric IBD has been published, reporting an acceptable tolerability and a possible signal of benefit.[126] Moreover, in a placebo-controlled trial in adults, endoscopic remission was observed in 38% (8/22) patients treated with curcumin, compared with 0% (0/16) in the placebo group.[127] In the latest systematic review on efficacy and safety of supplemental curcumin therapy in UC, including six randomized trials with 385 patients in total, authors reported that supplemental curcumin treatment for UC was safe without any severe side effects and effectively induced clinical remission, albeit no endoscopic improvement, hence further well-planned studies are suggested.[128] Given the availability of curcumin in many LR settings, there is no issue with the recommendation on curcumin use in the ambulatory care of pediatric UC. While neither the formulation nor dosage of curcumin is established for children, evidence suggests that it can be safely used up to 4 g/day for induction and up to 2 g/day during maintenance. The induction dosing of an ongoing pediatric trial is as follows (all doses are daily, prescribed as two divided doses): 2 g 2 times daily for children over 30 kg, 1.5 g 2 times daily for 20 to 30 kg and 1 g 2 times daily for those under 20 kg (safety has not been established in infants). Doses may be halved for maintenance treatment.

Recommendation 3.10:

Curcumin may be considered in the ambulatory care of UC as an add-on therapy for inducing and maintaining

clinical remission of mild-to-moderate UC (agreement: 100%).

4 Pharmacological treatment (biologics)

4.1 Anti-TNF-agents

Anti-TNF agents such as IFX and adalimumab (ADA) may be available for patients with refractory disease or for specific indications such as Crohn's perianal fistulizing disease, while other more recent agents like vedolizumab, ustekinumab, golimumab, risankizumab, mirikizumab, S1P receptor modulators, or anti-JAK small molecules may be less available.– Given the immunosuppressive effects of anti-TNF agents, careful reevaluation before their initiation is essential to assess the risks of opportunistic infections,[7] which may be more prevalent in LR settings (i.e., screening for LTBI, see 1.3.1). Anti-TNF treatment escalation may be feasible in non- or partial responders.

4.1.1 Anti-TNF administration: SC versus intravenous

Evidence

Biologics approved for treatment of PIBD are also available in SC form, their benefits including self-administration by the patient, shorter time of application process with fewer infusion-related adverse events, and consequently lower healthcare costs. With appropriate education and support, patients are able to administer their treatments at home. This leads to improvement of quality of life, reduction of time needed to travel to the healthcare institution, and consequently reduces costs for the patient.[129] Importantly, SC administration has been proven to be effective, safe, well-tolerated, generally preferred by patients and healthcare providers, and it results in reduced drug delivery-related healthcare costs and resource use.[130] As citrate additives are mostly related to injection site pain, citrate-free formulation should be preferred, if available.

In regard to pediatric CD, a retrospective study of 115 patients with ileocolonic CD showed IFX and ADA to have comparable outcomes by 52 weeks,[131] a notion substantiated by a prospective study based on a propensity score analysis, also demonstrating comparable efficacy and safety of these two anti-TNF agents.[132]

SC-IFX has been approved in Europe for the treatment of adults with CD and UC allowing patients to switch from IV to SC-IFX outside clinical trials. Growing real-world experience demonstrates that SC-IFX offers clinical advantages in terms of an improved pharmacokinetic profile and potential efficacy, immunogenicity, and health-related quality-of-life benefits compared with IV-IFX, as shown in a recent multicenter cohort study in adult patients with IBD.[133] Importantly, the feasibility of an elective switch to SC-IFX was also demonstrated for PIBD as maintenance with potential advantages concerning medical resources and patient satisfaction.[134]

Under low resources considerations, de-escalation of ADA intervals to every 3 or even 4 weeks may seem an interesting option: In 2 retrospective trials, the reported success rate of de-escalation to every 3 weeks was 60%–65%.[135,136] In a recent open label RCT, adults with luminal CD with stable corticosteroid-free clinical remission, -were randomized (1:2) to either conventional treatment (40 mg every 2 weeks) or de-escalation to every 3 weeks and even 4 weeks, if successful. At Week 48, the de-escalation group was non-inferior to the control group (3% vs. 0% of persistent flares, respectively).[137] Pediatric data that support de-escalation of ADA are still lacking and since children often require higher anti-TNF levels, this practice cannot yet be recommended in children, especially if TDM is not available.

Recommendation 4.1:

a. Anti-TNF agents should be considered in patients with refractory disease or Crohn's perianal fistulizing disease; subcutaneously, self-injectable, as a preferential option (agreement: 100%).
b. In the absence of TDM, treatment effectiveness should be monitored closely through regular clinical assessments and blood inflammatory and fecal biomarkers (agreement: 94%).
c. In ASUC, subsequent to steroids, up-front intensified induction with IFX should be considered until complete response is achieved lagreement:94%).
d. In ASUC, once a complete response is achieved, a cautious de-escalation to standard dosing can be considered under close monitoring (100%).

Practice points 4.1:

a. In LR settings, access to ADA is reported to be easier and SC formulations have the advantage of requiring fewer frequent visits to clinics and being less invasive than IV administration.
b. In patients with sustained corticosteroid-free clinical remission, normal serum biomarkers, and preferably low FCal (<150 µgr/gr), ADA intervals may be spaced to every 3 or 4 weeks, under close monitoring
c. If ADA biosimilars are used, citrate-free preparations should be preferred.

4.2 Loss of response (LoR) to anti-TNF agents

Evidence

TDM is recommended for anti-TNF-treated patients at the end of induction and during LoR.[7] However, the evidence for proactive TDM is not strong and thus in LR settings, reactive testing may suffice, meaning, testing

only when clinical remission is not complete (based on clinical indices, serological and fecal biomarkers).

In the complete absence of TDM, empirical escalation of anti-TNF treatment in patients with LoR is the only viable option. A lack of initial response or a LoR over time is principally caused by inadequate drug levels and the presence of antibodies.[138] Dose-escalation, interval shortening, or both were shown to improve treatment efficacy in adults[139] and children.[140] Despite uncontrolled evidence,[141,142] two RCTs did not show that empirical escalation of IFX is inferior to TDM-based escalation[143,144] in adult patients with CD.

The addition of an immunomodulator to patients with IBD who lost response due to development of anti-drug-antibodies is an established strategy for regaining response while salvaging the anti-TNF agent on board.[145] In view of the increased risk of opportunistic infections, careful patient selection and monitoring during treatment are especially important when considering such a combination therapy.[7]

There are scarce data and controversy on the efficacy of intensified IFX induction and maintenance for ASUC,[146] and the ESPGHAN guidelines specify this strategy may be considered.[9] This recommendation mainly derives from studies showing that IFX trough concentrations during induction were lower in patients with ASUC than in those with moderate colitis, possibly due to a higher inflammatory burden and/or increased IFX clearance.[147,148] In the absence of TDM, upfront intensified IFX induction as a salvage therapy for ASUC is advised. A regimen of 10 mg/kg at Weeks 0, 2, and 6 or even within 4 weeks (0, 1, 4 or 0, 2, 4) is a reasonable choice, but adjustments should be performed according to clinical and biochemical response (including de-intensification when remission is achieved.[9]

In patients with ongoing symptoms despite adequate drug levels, a switch to a different class of biologics is warranted: The second-line biologics to be considered in pediatric patients with anti-TNF refractory CD are anti-IL 12/23 or anti-IL 23 agents,[7] whereas in non-ASUC, the preferred second-line agent is vedolizumab. These recommendations are based on the observation that patients with pharmacodynamic failure (adequate trough concentration) have a much better chance to respond to "out of class" medication, whereas patients who are intolerant or experience immunogenic failure have a high rate of response when switching "in class."[149,150]

Nevertheless, recent studies have highlighted the option of switching from ADA to IFX in this context, even if ADA trough concentrations are high.[151] This strategy (that could be explained by different pharmacokinetics of IV vs. SC drugs) may be employed, particularly when other classes are not available. It was clearly shown that most patients with nonresponse or LoR to anti-TNF agents have either high titer of anti-drug antibodies or subtherapeutic trough concentrations.[152]

Standard induction can be used for the second anti-TNF agent. However, early escalation during or post-induction is warranted in the case of inadequate response as patients switching to a second anti-TNF agent were shown to require more frequent treatment escalations than naïve patients.[153]

In UC, ADA was shown to be a valid option following IFX failure. In a cohort of 60 patients, clinical response and remission at Week 12 were 60% and 27%, respectively.[154] ADA failure in IFX exposed patients was significantly higher for secondary IFX failures (odds ra 2.79), but not in primary failures and intolerant patients.

Recommendation 4.2:

a. If anti-TNF TDM is not routinely available, reactive testing may suffice, testing only when remission is not complete (based on clinical indices, blood and fecal biomarkers; agreement: 94%).
b. If anti-TNF TDM is not available for a patient with LoR, an empirical escalation of anti-TNF treatment (e.g., dose increase/interval decrease) is recommended (agreement: 100%).
c. If anti-TDM is not available and given the limited options of newer biologics in LR settings, an immunomodulator may be added to ADA or IFX to optimize treatment (even from the beginning; agreement: 100%).
d. In the absence of anti-TNF TDM, when a patient is not responding or losing response to one anti-TNF agent after treatment optimization (dose adjustment and an addition of an immuno-modulator), a switch within class (IFX to ADA or vice versa) is an option (agreement: 94%).

Practice point 4.2:

a. In IFX-treated patients, dose can be escalated up to 10 mg/kg every 4 weeks and in ADA treated patients, treatment can be escalated to 40 mg every week (even in patients < 40 kg) and up to 80 mg every week, if only partial response is regained following escalation to 40 mg weekly.
b. In patients losing response while on anti-TNF monotherapy, oral thiopurines (azathioprine, 6-mercaptopurine) or SC methotrexate in their recommended doses should be added in parallel to anti-TNF escalation.
c. In the absence of TDM while lacking "out of class" options probably some patients may develop anti-drug antibodies, leading to non-improvement. In this situation switching "in class" may be a pragmatic option.

4.3 Absence of alternative biologics to anti-TNF therapy

Evidence

Intestinal resection for limited CD can offer excellent short-term and long-term results even in treatment-

naïve patients.[155] A pediatric study showed clinical remission rates of 79% at 1 year and 56% at 2.5 years post-resection[156] with a significant effect on linear growth. In the recent LIR!C trial which compared laparoscopic ileocecal resection and IFX treatment in noncomplicated patients with CD,[157] the long term outcome of patients in the surgical arm was excellent, with only 26% of 69 patients requiring anti-TNF therapy and none requiring a second resection.[158]

Nutritional intervention (formula based enteral nutrition with an exclusion diet) induced clinical remission in 62% out of a mixed cohort of 21 children and adults who had lost response to at least one biologic agent.[159] Interestingly, an RCT of adolescents and young adults showed that the CD exclusion diet (CDED) was as effective even without the formula: Herein patients received the CDED with phases 1 and 2 as previously published,[160] followed by the more individualized phase 3. This is an approach that may be easily implemented in LR settings without any cost.[161]

There is conflicting evidence regarding the efficacy of cyclosporine for induction of remission in CD,[162] but one study demonstrated benefit in terms of colectomy free survival in patients with refractory Crohn's colitis.[163]

In UC, cyclosporine and IFX demonstrated similar short-term efficacy to corticosteroids in refractory and ASUC in four RCTs.[164,165] Cyclosporine treatment after IFX failure for severe UC was shown to be safe and effective in a retrospective cohort of 40 patients, with 42% colectomy-free survival at 1 year.[166] Adverse events were not associated with high IFX trough concentration before cyclosporine initiation.

Recommendation 4.3:
In the absence of biologics other than anti-TNF agents, ileo-cecal resection is recommended for limited ileal segmental CD (agreement: 100%).

Practice point 4.3:

a. In case of LoR to a biologic, exclusive enteral nutrition could be used as a nutritional intervention and should be given for 6–8 weeks. Polymeric formula is preferred over elemental formula (please see nutrition section).
b. Another nutritional intervention in this context is CDED, which may be attempted without partial enteral nutrition (PEN; formulas) for inducing and maintaining remission in CD.

5 NUTRITION

ESPGHAN guidelines cover a wide variety of nutritional topics related to IBD in children[7–9,167] with various issues deserving special attention: Clinical assessment of the nutritional status, treatment of selective deficiencies (e.g. micronutrients, vitamins) and the use of exclusive enteral nutrition (EEN) or PEN and special formulas to support the nutritional status of these patients. However, in LR settings limitations regarding availability of EEN/PEN are substantial and there are important cost and health insurance issues, including the lack of trained dietitians/nutritional therapists (NT) as well as laboratory (e.g., measurement of vitamin levels) or imaging methods (e.g., dual-energy x-ray absorptiometry [DEXA]).

According to the ESPGHAN position paper on Nutrition in IBD, a regular nutritional assessment should be an integral part of the follow-up in PIBD patients.[167] If neither dietitians nor NT are available, a trained physician or nurse can partially replace this position.

5.1 Alternatives to EEN and PEN in pediatric CD management

Evidence
If EEN is not available, other effective induction therapies may be used, such as corticosteroids or a Crohn's disease exclusion diet (CDED) in combination with PEN. Regarding CDED + PEN, recent pediatric data show that the formula type (cow's milk based, rice based, soy based) does not affect the treatment efficacy,[168] and in a small, open-label, pilot, randomized trial in adults, CDED seemed to be effective even without using concomitant PEN.[161]

Based on meta-analyses, steroids are equally effective as EEN,[169,170] but have lower rates of mucosal healing.[171,172] Furthermore, there are data suggesting that azithromycin and metronidazole may lead to clinical remission,[124] and the good tolerability of CDED[173] in induction of remission of mild-to-moderate luminal CD in children is of additional interest. In view of the risk of steroid side effects, maximal efforts should be made to minimize the exposure of children to steroids[174,175]; therefore, all other possible alternatives, particularly a nutritional approach, must be strongly considered:

A recent study across two centers compared outcomes of two proprietary polymeric formulas (one specialized, one a generic oral nutritional supplement) in 171 children with mild to moderate active CD in regard to treatment effectiveness, along with practical aspects of formula delivery and differences in estimated treatment costs. While no differences were demonstrated in remission rate or reduction of biochemical disease markers, there was substantial cost-saving if the generic oral nutritional supplement was used.[176] This result is in so far of great interest since it is known that the composition of formulas used as EEN varies greatly,[177] to date no formula has shown any benefits over any other formula in inducing clinical remission in CD.[176] In case CDED + PEN is used, the specific protocol should be followed as published, and,

if possible, under supervision by dietitians or trained physicians.

Recommendation 5.1:

a. If EEN is not available, steroids can be used as an effective induction therapy in mild-to-moderate luminal CD (agreement: 88%).
b. If specialized formulas (indicated for EEN) are not available or too costly, their replacement by generic oral nutritional supplement (i.e., non-specialized polymeric formula) may be considered (agreement: 94%).
c. If CDED is used, food fortification and/or supplemental formula could be added, but the diet's effectiveness may be maintained even without formula at all (agreement: 94%).

Practice point 5.1:

If generic oral nutritional supplement is used for EEN, the specific protocol should be used as published.

5.2 Nutritional management in ASUC

Recommendation 5.2:

In ASUC, body weight, caloric intake, and hydration status should be monitored daily (agreement: 100%).

5.3 Monitoring (laboratory and imaging methods)

Evidence

Monitoring of some micronutrients, iron, vitamin D, folic acid, and vitamin B12 status is recommended in selected patients,[167] as well as DEXA in high-risk patients, those with severe disease, prolonged malnutrition, amenorrhea, delayed puberty, and/or steroid dependency.[8]

Based on the current ECCO and ESPGHAN guidelines, i.v. iron is recommended as preferred first-line treatment in patients with clinically active IBD. This is also emphasized for children with IBD in LR settings.[178] Further indications are previous intolerance to oral iron and need for erythropoietin stimulating agents. On the other hand, oral iron is recommended in patients with mild iron deficiency anemia whose disease is clinically inactive. As the i.v. iron may not be available in all centers taking care of children with IBD in LR settings, oral iron (possibly combined with iron-rich food) should be used instead of i.v. iron in patients needing iron supplementation. In mild anemia, oral iron may be as effective as intravenous iron in correcting hemoglobin. After starting oral iron, hemoglobin levels should be monitored over the first 4 weeks and treatment should be continued for a period of ~3 months after normalization of hemoglobin. To maximize absorption and minimize side effects, one morning dose on alternate days should be given.[179]

In LR settings, less common laboratory methods (measurement of vitamins or trace elements) or imaging (e.g. dual energy x-ray absorptiometry, DEXA) may not be covered by health insurances and low dose oral vitamin D supplementation (e.g., 400 IU daily) can be useful in IBD patients with low risk of toxicity. There is evidence on use of Peripheral Quantitative Computed Tomography (pQCT) in PIBD patients, which can be used, if DEXA is not available,[180–182] but assessment of bone fragility and surveillance by conventional lateral thoracolumbar radiographs has also been shown as an alternative: This technique is even more cost-saving and should be prompted by bisphosphonate therapy.[183]

Recommendation 5.3:

a. If laboratory measurements are not available, supplementation of vitamin D, folic acid, or vitamin B12 should be based on dietary and clinical assessment (agreement: 100%).
b. To assess bone fragility and if DEXA is unavailable, surveillance by conventional lateral thoracolumbar radiographs may be considered as an alternative (agreement: 100%).

Practice point 5.3:

a. In patients with clinically active disease and if i.v. iron is not available, oral iron in one morning dose on alternate days and iron-rich food can be used in IBD patients with iron deficiency.
b. Hemoglobin should be closely monitored and treatment continued for approx. 3 months after its normalization.

6 Surgery

Global data on PIBD surgery in LR settings are scarce, but some Asian reports are indicative for a potential need for IBD surgery, particularly in view of difficult access to biologics[184]: Stenosis as well as stricturing disease were reported as common complications in South-East Asian children with CD, with rates as high as 34%–45% in newly diagnosed patients.[185,186] The same applies for perianal CD, with rates of perianal involvement in Chinese and South Korean pediatric cohorts as high as 42.4% and 47.1%, respectively[185,187]). However, actual rates of PIBD surgery are so far only documented in one Chinese study on 143 children with an IBD diagnosis between 2003 and 2016, of whom 15 (10.5%; 14 CD) underwent abdominal surgery, including intestinal perforation surgery in 7 out of 15.[185]

6.1 Ulcerative colitis

6.1.1 Total colectomy and pouch

Evidence

According to the ECCO-ESPGHAN guidelines on management of UC, restorative proctocolectomy with

Ileal Pouch Anal Anastomosis (IPAA; J pouch) and a covering loop-ileostomy is the recommended elective surgery in refractory patients.[8,9] Preferably, experienced pediatric or adult surgeons in high volume centers (at least 10 pouches/year) should perform such a procedure.[8] In a multicentre retrospective ESPGHAN study, surgeon experience of <10 pouch surgeries/year (regardless of whether pediatric or adult surgeon) was the only factor associated with increased rate and time of pouchitis and chronic pouchitis.[188] A survey of pediatric surgical centers in a HIC revealed a substantially lower experience with IPAA, resulting in arrangements for joint operating with adult surgeons.[189]

Recommendation 6.1.1:
If experienced surgeons (at least 10 pouches/year) are not available in the area, the option of travel of an experienced surgeon from another center (national/country nearby/HICs) should be actively promoted (agreement: 100%).

Practice point 6.1.1:
a. Children with UC who require IPAA should be operated on in a pediatric care environment. Collaboration of pediatric and adult surgeons is imperative.
b. Creation of a network of at least one IBD Referral Centre per country, or in the closest country nearby or of visiting programs could be beneficial.
c. Experienced surgeons from IBD centers could advise during surgery by means of live video-communication.

6.1.2 Postoperative monitoring

Evidence
The ECCO-ESPGHAN guidelines recommend pouchoscopy at the first suspected episode of pouchitis.[8] However, growing evidence suggests that FCal may serve as a surrogate marker for pouchitis when pouchoscopy is less available.[190–194]

Recommendation 6.1.2:
In limited endoscopic availability, elevated FCal may be sufficient to diagnose pouch inflammation (i.e. pouchitis, cuffitis, or Crohn's like disease of the pouch), in the appropriate clinical setting and after excluding intestinal infections (agreement: 100%).

Practice point 6.1.2:
a. Anastomotic stenosis could be evaluated by digital rectal examination, but ulcers require endoscopic evaluation.
b. Serial measurements of fecal biomarkers in asymptomatic patients can help predict the occurrence of pouchitis.

6.1.3 Refractory pouchitis and cuffitis

Evidence
Total proctocolectomy with ileal pouch formation may be associated with a high risk of recurrent and chronic pouchitis, but only in 8% subsequent Crohn's like disease of the pouch and 4% pouch failure were found.[195] Various treatments have been suggested to treat pouchitis including antibiotics, probiotics, budesonide, thiopurines and biologics.[8]

Recommendation 6.1.3:
a. In refractory pouchitis not responding to antibiotic therapy or in the presence of budesonide dependence, and if no anti-TNF agents are available, oral thiopurines or tacrolimus enemas could be used (agreement: 100%).
b. Topical mesalazine is recommended for treating cuffitis (agreement: 100%).

6.2 Crohn's Disease

6.2.1 Elective surgery

Evidence
Surgery for CD is not curative and limited resection is the key principle, thus preserving bowel length. Surgical resection in children with CD is usually reserved for those who are refractory to anti-TNF therapy, have stricturing [B2] disease with prestenotic dilatation, or penetrating [B3] disease.[7] However, in adults with non-stricturing CD, the multicentre LIR!C randomized controlled open-label trial compared laparoscopic ileocecal resection and IFX treatment at disease onset. During a median follow-up of 4 years, 26% of patients in the resection group received IFX and 37% patients in the IFX group had resection.[157] Laparoscopic ileocecal resection was a cost-effective treatment and provided quality-of-life outcomes similar to those of treatment with IFX.[158] Another recent adult study in this category of patients also found that costs were significantly lower for early surgery versus biologic treatment, and the quality of life was significantly better.[196] Pediatric data are scarce, and no RCTs are available. A retrospective multicentre pediatric study showed clinical remission rate of 79% at 1 year and 56% at 2.5 years after resection, with a significant effect on linear growth. One year after surgery, there was no significant difference between recurrence rates between open vs laparoscopic approach.[156] As summarized in the ESPGHAN Guidelines, pediatric studies have shown that growth and nutritional status improved significantly after surgery.[197]

Recommendation 6.2.1:
Elective surgical segmental resection may be a reasonable alternative in children with limited ileal segmental CD, even as an induction, and also in those

in whom immunomodulators (e.g., azathioprine or methotrexate) have failed or in those with growth delay, if anti-TNF therapy is not available (agreement: 100%).

6.2.2 Post-surgery follow-up

Evidence

ESPGHAN guidelines recommend postoperative endoscopic evaluation at 6–9 months after bowel resection[7,10,197–200]: No clinically relevant factors were found to be associated with endoscopic recurrence rate at the sixth month.[201] FCal, as well as IUS and MRE can be considered as noninvasive alternatives to detect early postoperative recurrence,[7,39] with FCal <100 µg/g as the accepted cutoff for early versus late follow-up scope when measured at 3 months in CD.[202]

In LR settings, consecutive elevated levels of fecal markers could dictate the timing of endoscopic assessment rather than at fixed time points, and possibly even of treatment modification. Continued low FCal levels indicate continuous remission.[203]

Recommendation 6.2.2:

a. If endoscopy is not available, patients should be monitored by a fecal inflammatory marker and/or IUS or MRE, 6–9 months following ileocecal resection and repeatedly thereafter (agreement: 100%).
b. If fecal biomarkers are not available, regular clinical assessments and blood inflammatory markers should be used (agreement: 94%).

6.2.3 Post-surgery treatment protocols

Evidence

According to the ECCO-ESPGHAN guidelines postoperative use of anti-TNF agents is recommended in patients with high risk of recurrence.[7] Relevant risk factors for postoperative disease progression include growth failure, delayed puberty, short duration from diagnosis to surgery, extensive resection (>40 cm), penetrating behavior, active disease beyond resected site[197] as well as a combination of ulcer depth and circumference at the anastomosis at 6 months.[204] However, a smaller prospective study also showed endoscopic remission in 13 out of 21 children treated postoperatively with azathioprine monotherapy. Thus, even if the evidence is weak to support the use of thiopurines, or of methotrexate or 5-ASA/sulfasalazine, they could represent an option in LR settings.[205,206] Also, a 3-month course of metronidazole is supported by older studies[197] and a more recent one,[205] in which metronidazole was associated with lower endoscopic recurrence (20%) versus the control group (54%), within 12 months. Maintenance enteral nutrition (MEN) may be an option if available.[7] Low-risk patients may be given 5-ASA if there are signs of colonic involvement.[197]

Recommendation 6.2.3:

a. In high-risk patients who underwent surgical resection, and if anti-TNF agents are not available, full-dose thiopurines are recommended shortly after surgery (agreement: 100%).
b. Metronidazole and maintenance enteral nutrition (e.g., PEN) can also be considered if anti-TNF agents are not available (agreement: 94%).
c. In CD patients, oral mesalazine (5-ASA) may be considered if ongoing colonic disease after resection (agreement: 94%).
d. Endoscopic recurrence on thiopurine monotherapy should trigger a step-up to anti-TNF therapy (agreement: 100%).

7 Education and counselling (of patients, caregivers and health professionals)

7.1 Avoidance of diagnostic delay: Disease awareness

Evidence

Diagnosing IBD involves distinct longitudinal periods from first symptoms to primary care assessment, tertiary care referral, and then endoscopic confirmation. However, an analysis of the pediatric cohort ($n = 294$ patients) from a large Indian IBD registry revealed more than 75% of patients with a diagnostic delay > 6 months (median > 12 months), excluding the VEO-IBD cases. Ileal disease (L1) was predictive of longer diagnostic delay in CD.[207] Around 20% of the children had received antitubercular therapy before the diagnosis of CD, further delaying the diagnosis. This was in sharp contrast to the French population-based EPIMAD study with 1412 pediatric cases, where diagnostic delay >6 months was seen in 30% patients.[208] Since diagnostic testing to effectively identify children with IBD without the need for endoscopy is not yet available, a recent narrative review summarized evidence on specific presenting symptoms, testing, and risk factors of PIBD which may aid the identification of children requiring timely referral for specialist care, thereby reducing the chance of a delayed diagnosis.[209] It was shown that the most common metrics include rectal bleeding, weight loss, family history of IBD, and perianal disease, and the addition of FCal testing to an alarm symptom algorithm increases the diagnostic accuracy of IBD.[23] Finally, a simple clinical algorithm, the IBD-REFER criteria, was recently developed and validated for children with IBD to guide early referral for suspected IBD.[210] It includes 10 items: 3 major and 7 minor (Figure 2). In the external validation, the IBD-REFER criteria had a sensitivity/specificity of 96%/96% in children to correctly identify children who eventually were diagnosed with IBD. Nurses can be trained to

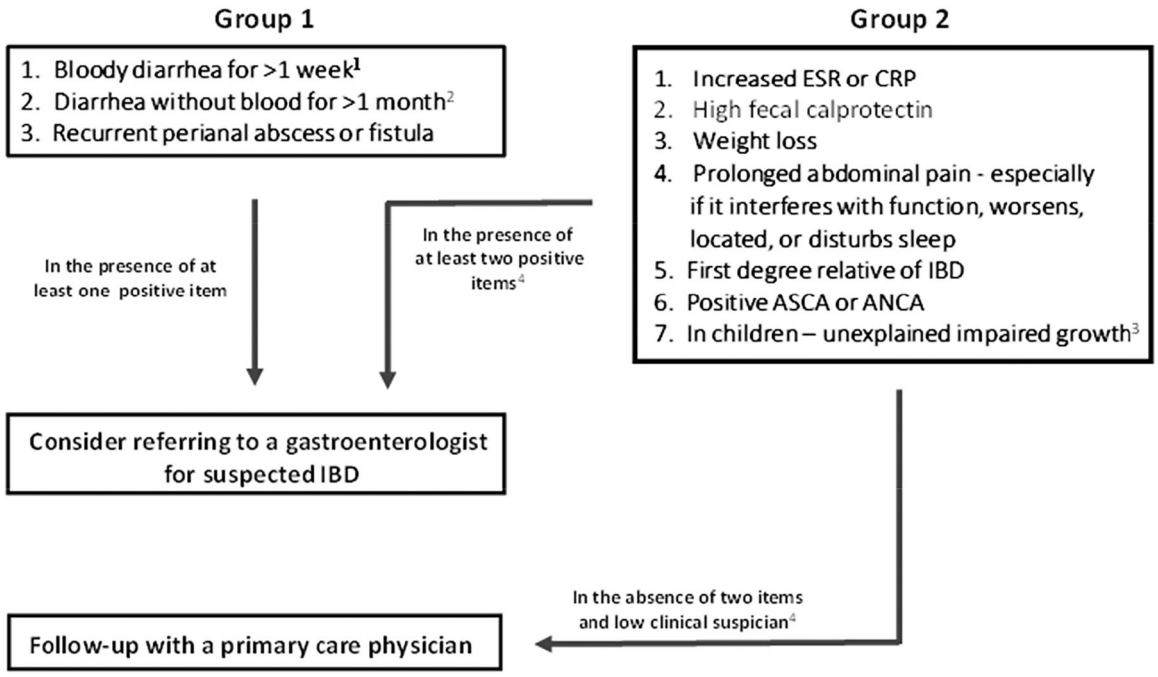

FIGURE 2 The final IBD-REFER criteria (Ref.[194]). IBD, inflammatory bowel disease.

use this algorithm in places without PIBD specialists to prioritize referrals.

Recommendation 7.1:

a. To decrease diagnostic delay primary care physicians and general pediatricians should be trained in recognizing the most common clinical alarm symptoms indicative for PIBD and using the validated IBD-REFER criteria (agreement: 100%).
b. Early testing for FCal or an alternative fecal biomarker is recommended in suspected PIBD when available (agreement: 100%).
c. Upon initiation of antituberculosis therapy, careful PIBD diagnostic workup should be performed, with a focus on (ileal/ileocecal) CD as the most important differential diagnosis of intestinal TB in LR settings (agreement: 100%).

Practice point 7.1:

In primary care setting, FCal testing is useful for its negative predictive value of excluding IBD at normal levels.

7.2 Disease-specific information and promotion of self-management

Evidence

Both parents and children, especially adolescents, experience difficulties understanding and complying with the necessary treatment regimens and dietary recommendations at different stages of the disease. This is particularly relevant in LR settings where literacy levels may be low and where is limited awareness of IBD. The use of popular but unproven therapies can adversely affect disease outcomes. Furthermore, the lack of professional dietary or psychological support often results in excessive restrictions of the diet and age-appropriate activity for the young patient.

Many studies have shown that understanding the principles of PIBD management results in improved adherence to therapeutic recommendations and improved quality of life (QoL).[211,212] Pre-assessment of the baseline knowledge by standardized and validated questionnaires can further enable proper education of patients and caregivers on the principles of management[213] and, given the ongoing lack of PIBD-related knowledge, is much needed.[214]

The recent creation of the validated IBD-KID as well as IBD-KID-2 questionnaires could in fact assess the impact of education and self-management initiatives directed at children with IBD as well as identifying topics, which require detailed discussion.[215,216]

Education and counseling of the pediatric patient is an important but often unidentified or overlooked problem of PIBD management, with inadequate standardized recommendations and protocols.[217] However, various studies have shown the benefit of targeted educational programs for patients and their families, especially in chronic diseases.[218,219] Self-management strategies in adult IBD patients have been found successful, especially regarding health-related QoL, and self-management programs including telemedicine and

web-based interventions appear to have the potential to produce better outcomes in this population.[220]

Recommendation 7.2:

a. Individualized information on PIBD diagnosis and disease management must be provided to both the patient as well as parents and caregivers to ensure treatment adherence, the development of self-management skills and overall improved quality of life (agreement: 100%).
b. Educative formats and informative platforms (in local languages) should be implemented and used to ensure individualized self-management information on specific Apps re disease activity scores as well as IBD management (e.g., App for PUCAI, ESPGHAN App for IBD management; agreement: 100%).
c. Assessment of IBD-related knowledge in both patients and parents or caregivers should be considered, using validated questionnaires such as IBD-KID-2 (agreement: 100%).
d. IBD care centers should implement multidisciplinary teams dedicated to ensuring patient and family training on PIBD (agreement: 100%).

Practice point 7.2:

a. Disease specific Apps for improvement of self-management (e.g., "CEDMO", personal communication: J. de Laffolie) may need modifications according to relevant aspects of the given LR settings, as well as translation into the local language.
b. Similarly, PIBD-specific questionnaires may need such modifications, in particular securing correct sources of information, and translation of questionnaires into the local language.

7.3 Mental health

Evidence

Mental health is an important yet most neglected part of pediatric IBD care.[221–223] Higher rates of illness-related anxiety as well as depression were found to be particularly severe in the pediatric population and significantly associated with negative illness perceptions in adolescents with IBD.[224] Certain perceptions such as catastrophizing (negative prediction of the future) and rumination are common and have also been implicated in worse pain perception in the PIBD population.[225,226]

However, in LR settings, the probability of misconceptions and lack of communication is expected to be even higher, thus further affecting disease management adversely. Psychological wellbeing becomes a non-priority for parents and caregivers in the process of providing adequate and affordable treatment, although an "ideal IBD service" should involve significant roles of psychologists and run in specialist clinics (to be easily accessible to patients and publicly funded.[227]

In a recent questionnaire-based survey of mental health from consecutive IBD patients, including pediatric cases from eight centers in six countries (Nepal, Bangladesh, India, Thailand, Myanmar, Malaysia, and Iran), depression and anxiety were found in 72% and 67% of patients, respectively. (Banerjee R., Personal communication).

Recommendation 7.3:

Long-term psychological support should be implemented for patients with PIBD, using local health care structures (agreement: 94%).

7.4 Caregiver burden

Evidence

Another important aspect is the caregiver burden of these patients including QoL: In an Indian survey more than two thirds (67%) of caregivers reported a high caregiver burden (Zarit Burden Interview (ZBI) score ≥21), which correlated with poor QoL ($r = -0.373$, $p < 0.001$), while coping strategies had not yet been evaluated. As expected, the caregiver burden ($p = 0.028$) was lower with higher socioeconomic status (Banerjee R., personal communication).

Recommendation 7.4:

Long-term administrative and psychological support should be considered for caregivers of patients with PIBD, using local health care structures (agreement: 94%).

7.5 Transition

Self-management behaviors are generally influenced by sociodemographic and socioeconomic factors, including family support, education level, and employment status[211,212] and are of particular interest in view of a transition to adult care. A standard one-step transition plan may not be acceptable or feasible in the developing world, where the social dynamics are different. There are numerous cultural, family, and economic hurdles to overcome. However, a stepwise approach to the transition process can enhance the patients' knowledge and self-management skills, with children gradually transferred to adult care once a pre-transition is completed.[228]

Because the healthcare network in LR settings, particularly in the rural settings, is inadequate for specialized IBD care in general,[229,230] in most of these settings transition of care models do not exist at all. There are often no Electronic Medical Records and official handover to adult care is therefore not performed. An overhaul of this process will need active support of the administration together with improved healthcare policies.

Recommendation 7.5:

a. The transition plan should be established through periodic interviews between the patient

and family and the relevant health care providers (agreement: 100%).

b. The transition process should be planned and started in advance of the actual handover moment so that patients and families become progressively aware of it (agreement: 100%).

4 | CONCLUSION

Incidence and prevalence of PIBD are rising worldwide, particularly in the highly populous LMICs of the Asian subcontinent,[231] which are home to 4·6 billion people and constitute more than half of the world's population.[229] Here, as in other LR settings, healthcare resources are limited, with low gross domestic product (GDP) per capita and very low spending on healthcare. A large proportion of this population still lives below the global poverty line, and with many patients not having any health insurance, out-of-pocket spending is common.[230] In these resource-limited settings standard validated guidelines regarding IBD from HICs are thought not completely relevant or suited.[230,232,233] The increase in IBD prevalence in such settings combined with poor physician and patient awareness of the disease are additional challenges.[234,235]

Diagnosing and managing Pediatric IBD is an ever-changing topic with new additions of diagnostic tools and medications. This means an ever-increasing cost that may not be met in many countries. Despite up-to-date guidelines, one often needs to consider compromises between desirable and achievable resources.

The present document tries to provide guidance on alternative methods to manage PIBD, even if not all resources are available. Patients diagnosed in childhood or adolescence are expected to have a long-lasting disease, and all efforts to provide the best management and quality of care must be made.

This should be achieved through continuous negotiation between official scientific and clinical bodies (such as local Societies for Pediatric Gastroenterology, Hepatology and Nutrition with support of e.g. ESPGHAN), health insurance companies, and governments. In the meantime, other financial resources may be temporarily used in selected IBD centers to ensure availability of resources, such as grants, supplies provided by industry, and financial support from foundations or families willing to cover, e.g., the nutritional therapy for their children. One must concentrate on the long-term outcome of these patients, as the prognosis will worsen if an improper diagnosis and control of the disease are not made early enough.

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CONFLICT OF INTEREST STATEMENT

Almuthe Christine Hauer—Speaker's fee from Sanofi; Advisory Boards: Sanofi, Mirium; Research Grant: Janssen. Andy Darma—Speaker's fee: Nestlé. Daniela Elena Serban—Speaker's fee: Montavit; Support for participation at ESPGHAN AM: Nestlé; Advisory Board: AbbVie. Claudia Patricia Sánchez Franco—Senior Medical Manager for Abbott Nutrition (since 2022). Lissy de Ridder—Speaker's fees: Medtronic, Janssen, Pfizer; Advisory Boards: Alvotech; Research Grants: Pfizer, ECCO. Jiri Bronsky—Speaker's/Congress fees and/or Advisory Boards: Nutricia, Nestlé, MSD, AbbVie, Sanofi, Vitabalans. Marina Aloi—Speaker's fee: Dicofarm, Nestlé; Advisory Boards: AbbVie, Pfizer, Takeda. Vaidotas Urbonas—Speaker's fee: Nutricia, Mayoly, Nestlé, AbbVie, Takeda. Dan Turner—Consultation fees, research grants, royalties, or honoraria from Janssen, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, Ferring, AbbVie, Takeda, Prometheus Biosciences, Lilly, Sorriso-Pharma, Boehringer Ingelheim, Galapagos, BMS, Alfa-Sigma. Jorge Amil-Dias—Speaker's fee: Danone; Advisory Boards: Bristol-Myers Squibb, Danone. The remaining authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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