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PRACTICE GUIDELINE

Management of paediatric ulcerative colitis, part 1: Ambulatory care—An updated evidence-based consensus guideline from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation

Eytan Wine[1,2,3] | Marina Aloi[4] | Stephanie Van Biervliet[5] | Jiri Bronsky[6] | Javier Martín di Carpi[7] | Marco Gasparetto[8] | Laura Gianolio[9] | Hannah Gordon[10] | Iva Hojsak[11] | Alexandra S. Hudson[3] | Séamus Hussey[12] | Johan van Limbergen[13] | Erasmo Miele[14] | Lorenzo Norsa[8] | Ola Olén[15] | Gianluca Pellino[16,17] | Patrick van Rheenen[18] | Lissy de Ridder[19] | Richard K. Russell[20] | Dror S. Shouval[21,22] | Eunice Trindade[23] | Dan Turner[24] | David C. Wilson[25] | Anat Yerushalmy Feler[26,27] | Amit Assa[24]

Correspondence

Eytan Wine, Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto, ON, Canada.
Email: eytan.wine@sickkids.ca

Amit Assa, Shaare Zedek Medical Centre, The Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Eisenberg R&D Authority, The Hebrew University, Jerusalem, Israel.
Email: dr.amit.assa@gmail.com

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Abstract

Objectives: Despite advances in the management of ambulatory paediatric ulcerative colitis (UC), challenges remain as many patients are refractory to therapy and some require colectomy. The aim of these guidelines is to provide an update on optimal care for UC through detailed recommendations and practice points.

Methods: These guidelines are an update to those published in 2018 and are a joint effort of the Paediatric IBD Porto group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation. An extensive literature search with subsequent evidence appraisal using the Oxford methodology was performed, followed by three online voting sessions and a consensus face-to-face meeting. Thirty-nine recommendations and 77 practice points were endorsed by the 25 experts with at least an 84% consensus rate.

Results: Robust evidence-based recommendations and detailed practice points are provided. In addition to reemphasising and updating the role of more

For affiliations refer to page 797.

CME module may be found at https://learnonline.naspghan.org/jpgn2

All authors contributed equally to this study.

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'traditional' UC therapies, these guidelines outline optimising the use of anti-tumour necrosis factor therapies and integrating newer biologics and small molecules, as well as supportive therapy, to improve outcomes and provide an updated management algorithm. Measurement and monitoring tools and decision aids are provided, and additional aspects, including nutritional support, extraintestinal manifestations, pouchitis, inflammatory bowel disease-unclassified and patient support, are discussed. Some aspects, including surgery and thromboprophylaxis, are covered in the acute severe UC guidelines.

Conclusions: These guidelines serve as an aid in managing children with UC through a combination of evidence-based recommendations and more practical practice points in the ambulatory setting.

KEYWORDS

biologics, children, inflammatory bowel disease-unclassified, Paediatric Ulcerative Colitis Activity Index, thiopurines

1 | INTRODUCTION

With the increasing global incidence of paediatric-onset ulcerative colitis (UC),[1–4] the burden of disease and impact on patients, families and society has grown.[5,6] Although paediatric UC is more extensive and more likely to be severe than adult-onset UC,[7,8] and despite recent introduction of advanced therapies,[9] therapeutic options are limited with significant regulatory barriers to paediatric drug approval.[10–12]

These guidelines are focused on the ambulatory setting and are an update from the previous European Crohn's and Colitis Organisation (ECCO) and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines published in 2018[13] and a 2nd revision of the original from 2012.[14] They are intended to serve as an evidence-based, but also practical and accessible resource for practitioners and trainees involved in treating children with UC in the ambulatory setting. They are designed to assist in decision making but are not intended to replace clinical judgement and experience, recognising the need to adjust guidelines to specific patients and healthcare settings.

In this paper, we review measures of assessing disease activity and severity, detail the array of therapies for UC (including 'less traditional' treatment options), discuss inflammatory bowel disease (IBD)-unclassified (IBD-U), management of extraintestinal manifestations (EIMs) of UC, and supportive care (including nutrition, anaemia, and cancer surveillance). The ESPGHAN-ECCO paediatric UC guidelines are divided into two parts, but should be seen as one complementary resource. Surgical aspects and thromboprophylaxis are discussed in the acute severe colitis (ASC) guidelines.[15] Some related areas are discussed in less detail as they are covered by other guidelines or position papers (including the diagnostic [Porto] criteria,[16] paediatric IBD subtypes,[17] very early onset [VEO]-IBD,[18,19] endoscopy,[20] surgery,[21] and liver involvement[22]].

Emerging areas of UC management that have especially evolved since the previous guidelines include the use of bowel ultrasound, the need for higher

What is Known

- The European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Crohn's and Colitis Organisation guidelines for management of ulcerative colitis were last published in 2018 and are updated herein.
- Ambulatory management of ulcerative colitis in children remains complex.

What is New

- Some of the main updates from the previous guidelines relate to the importance of close and frequent (especially non-invasive) monitoring, leading to therapy adjustments, along with suggested algorithms for managing patients in the ambulatory setting.
- New off-label drugs are discussed, as is optimisation of approved drugs, including appropriate dosing and use of therapeutic drug monitoring.
- Emphasis is made on minimising exposure to corticosteroids, use of bowel ultrasound and indications for cancer surveillance.
- Importantly, we stress the regulatory challenges of studying and approving new drugs for managing children with ulcerative colitis, which delay access to important treatments for affected children.

doses, and a role for therapeutic drug monitoring (TDM) with antitumour necrosis factor (TNF) therapy, and integrating advanced and combination therapies. Beyond providing guidance for management of ambulatory UC, we hope that this paper will serve as an educational resource and guide for advocacy (by serving as a standard of care, but also recognising variation in access and resources).

2 | METHODS

Following an open call by the Paediatric IBD Porto and Interest Groups of ESPGHAN and ECCO in April 2023, 25 international experts in paediatric IBD were selected by the steering committee (E.W., A.A., R.K.R., D.T.), including two early career members, an adult gastroenterologist and an adult surgeon. These guidelines follow the ESPGHAN Standard Operating Procedure (https://www.espghan.org/our-organisation/governance-and-regulation). The aim was to generate two distinct manuscripts, the first focused on ambulatory UC (part 1) and the second on acute severe UC (part 2), similar to the 2018 guidelines. Next, a systematic review of the literature was performed centrally by a librarian, guided by search terms developed by the study leads (E.W., A.A.). Electronic searches were performed on June 15, 2023, using PubMed, Ovid Medline, Embase and Cochrane databases (Supporting Information S1: Document S1). Clinical guidelines, systematic reviews, clinical trials, cohort studies, case-control studies, diagnostic studies, surveys, letters, narrative reviews, case series and highly relevant selected abstracts published after June 2016 (data lock date of previous guidelines) were all utilised if performed in children. We used the search results of the previous guidelines[13] to cover the literature from 1985 to June 2016. Although we aimed to base the adult literature on the recently updated ECCO UC guidelines,[9] leading adult randomised controlled trials (RCTs) and meta-analyses identified in the initial search were not excluded for perusal and referenced if found to be relevant. Following the elimination of duplicates, 12,121 abstracts were reviewed by the working groups for eligibility. A total of 11,223 abstracts were excluded, mainly for the following reasons: clear irrelevance to the pre-defined topics, review manuscripts and manuscripts focusing on Crohn disease (CD) or on molecular/genetic pathways. The decision regarding questionable eligibility was made by the lead authors (E.W./A.A.). Finally, 898 full-text manuscripts were retrieved and circulated to the relevant working groups for writing their sections (Supporting Information S2: Figure S1). Given the paucity of evidence for some topics, key papers published after the initial search and up to the final submission of the guidelines were also included.

The guidelines include both recommendations and 'practice points', which reflect common practice where evidence is lacking or provide useful technical details. Authors were instructed to focus mostly on key papers published since 2016 (which would not have been covered in the previous guidelines). The subgroup's text and recommendations were iterated by email with the guideline leads until refined. Each working group responsible for an intervention or diagnostic topic tabulated the sentinel paediatric and adult manuscripts used to support their text, with grading of evidence according to the Newcastle-Ottawa assessment scales for case control and cohort studies[23] and according to the Cochrane Handbook for clinical trials[24] (Supporting Information S4: Table S1). The entire group then voted on all recommendations and practice points in three online rounds, while adding specific comments using a web-based voting platform. The document was revised again based on the comments received, and the group met virtually three times to discuss key areas of disagreement.

After a 3rd round of electronic voting and revisions, a final set of statements was circulated, and the group met face-to-face for a final full-day consensus meeting during the ESPGHAN annual meeting (Milan, May 2024). Only statements and practice points supported by at least 80% of the group advanced to each next round of voting, with attempts to improve consensus by discussion and refinement between voting rounds. A list of statements that did not achieve 80% approval is included in Supporting Information S5: Table S2. Recommendations were graded according to the Oxford Centre for Evidence-Based Medicine.[25] An additional virtual meeting to discuss and vote on several minor adjustments took place in November 2024, with consensus reached on all remaining issues. The final versions of the two papers were reviewed by all authors and approved by the members of the Paediatric IBD Porto Group and sponsoring societies (ESPGHAN and ECCO), with input from representatives of the European Federation of Crohn's and Ulcerative Colitis Associations. Together with the accompanying paper on acute severe UC (this study), we provide a detailed outline for the management of paediatric UC, summarised in Figure 1.

For the current ambulatory manuscript, ten topic-guided working groups were formed to address 30 PICO (population, intervention, comparison, outcome) and 30 non-PICO questions, formulated by the steering committee (Supporting Information S1: Document S1). Elective surgery, despite being utilised in ambulatory patients, is discussed together with urgent surgery in the ASC manuscript.[15] A total of 37 recommendations and 76 practice points were endorsed, and the consensus rate was at least 84% for all statements.

3 | ASSESSING AND PREDICTING DISEASE ACTIVITY

3.1 | Recommendations

1. Disease activity should be monitored at each visit using the Paediatric UC Activity Index (PUCAI). Treatment should be evaluated and reconsidered when PUCAI ≥ 10, or when PUCAI drops by less than 20 points after a therapeutic change (evidence level [EL] 2) (Agreement 100%).
2. Faecal calprotectin should be regularly monitored in patients in clinical and biochemical remission; endoscopic evaluation or treatment change should be

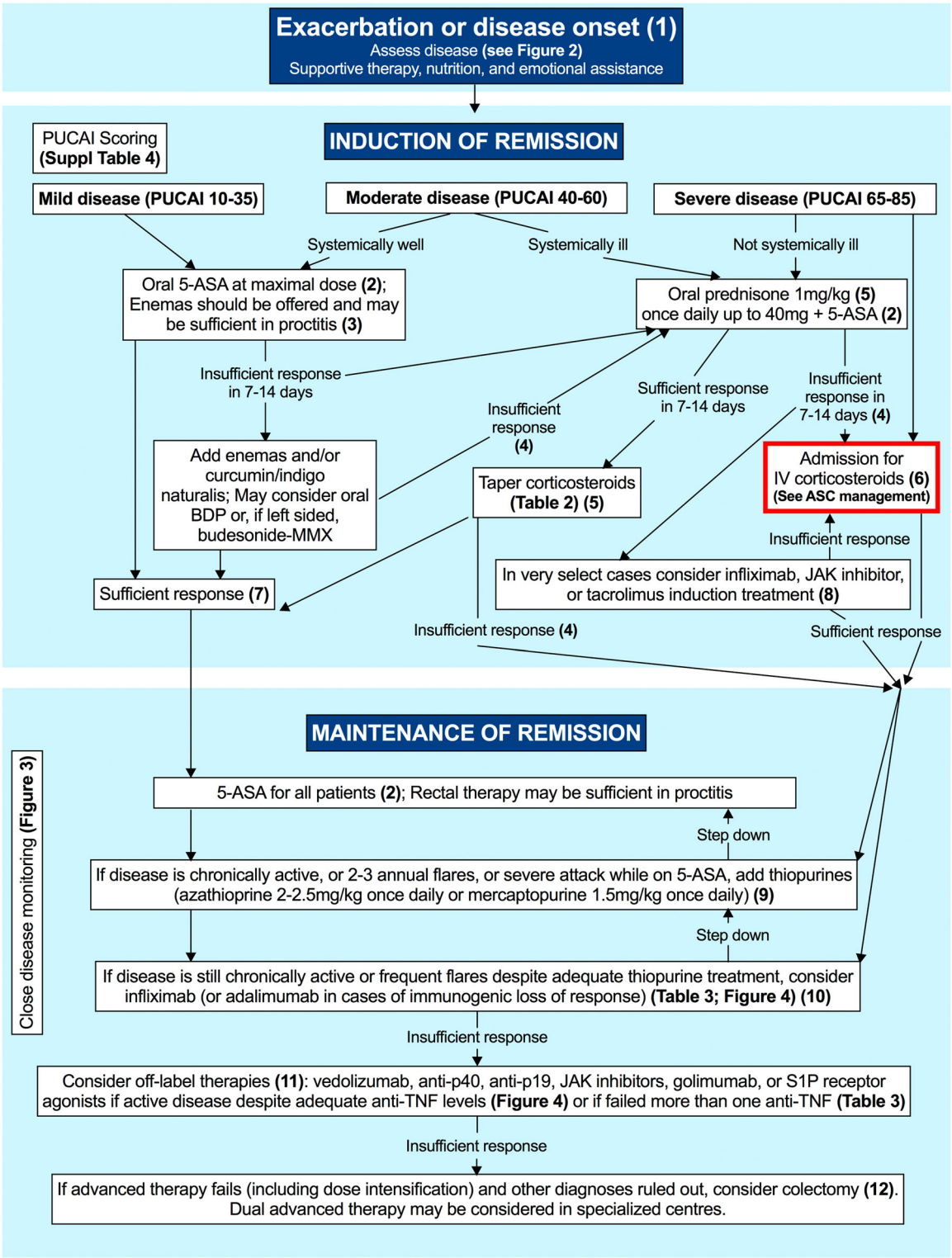

FIGURE 1 (See caption on next page).

considered in patients with sustained elevated faecal calprotectin values, as defined below [EL 2, adults EL2] (Agreement 100%).
3. Colonoscopy is recommended at diagnosis [EL4, adults EL4] and for cancer surveillance (detailed below) [EL5, adults EL3]; endoscopic evaluation is recommended before major treatment modifications [EL5, adults EL5] and when it is not clear if symptoms are disease-related [EL5, adults EL5] (Agreement 100%).

3.2 | Practice points

1. Clinical remission is defined as PUCAI <10 points, mild disease as 10–34 points, moderate disease as 35–64 points, and severe disease as ≥65 points (Supporting Information S5: Table S3) (Agreement 100%).
2. PUCAI at diagnosis can help predict the prognosis of children with UC. A PUCAI < 35 predicts a milder course and a lower rate of endoscopic disease extension, while a PUCAI ≥ 65 is associated with a higher risk of colectomy. Early clinical response to induction therapy predicts longer-term corticosteroid-free remission and avoids biologic escalation (Agreement 100%).
3. There is no clear cut-off value of faecal calprotectin to reflect mucosal inflammation and predict disease outcomes. Values differ substantially in different studies using different reference standards. A cut-off value <150 mcg/g is a surrogate marker of remission, while >250 mcg/g usually reflects mucosal inflammation. Values consistently above 250 mcg/g should prompt consideration of endoscopic evaluation or a therapeutic adjustment on an individual basis, especially when values increase over time and in the presence of clinical symptoms (Agreement 100%).
4. Given the high intraindividual (within-day and within-stool) and interindividual variability of faecal calprotectin values, uncertain results (e.g., between 150 and 250 mcg/g or unexpected results based on the clinical symptoms), should prompt repeat measurements (at least 2–4 weeks apart) before considering endoscopic evaluation or therapy change in an asymptomatic patient (Agreement 100%).
5. Blood tests (complete blood count [CBC], albumin, transaminases, gamma-glutamyl transferase [GGT], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) should be performed regularly, depending on symptoms and therapy and at least every 3 months while on immunosuppressive/biologic medications or at least every 6 months otherwise. Iron and vitamin D status should be monitored every 6–12 months and following a treatment course. In patients taking mesalamine, it is recommended to include testing for renal function/creatinine after 2–3 months of treatment, and annually thereafter, given the possible risk of mesalamine-induced acute interstitial nephritis (Agreement 100%).
6. Colonic ultrasound with the measurement of bowel wall thickness (BWT) and blood flow can be added to PUCAI and faecal calprotectin to monitor disease activity based on local availability and expertise. Although data are limited, a BWT < 2 mm is likely indicative of mild or no colonic inflammation (Agreement 100%).
7. In symptomatic patients, it is essential to rule out other potential causes, such as medical non-adherence, irritable bowel syndrome, medication-related adverse events, and infections (especially *Clostridioides difficile*, that is more frequent in active UC and cytomegalovirus [CMV] in patients treated with corticosteroids or other immune-suppressing agents) before treatment modification (Agreement 100%).

FIGURE 1 Summary flowchart of managing paediatric ulcerative colitis (UC). Medical therapies in UC are divided into those that induce remission (5-aminosalicylate [5-ASA], corticosteroids, antitumour necrosis factor [TNF] therapy and calcineurin inhibitors) and those that maintain remission (5-ASA, thiopurines, anti-TNF therapy and off-label therapies). (1) Assessment of active disease and differential diagnosis are detailed in the text and in Figure 2. (2) 5-ASA is usually dosed 50–70 mg/kg/day, up to 4.8 g daily. Once daily dosing may be as effective as twice daily dosing. (3) 5-ASA enemas (25 mg/kg; 1 g daily is as effective as higher doses) are usually more effective than steroid enemas. (4) Lack of improvement (i.e., Paediatric Ulcerative Colitis Activity Index [PUCAI] decrease of <20 points) after 7–14 days or increase in PUCAI ≥ 20 points at any time should prompt treatment escalation. (5) Effort should be made to reduce steroid exposure; start taper within 1–2 weeks if response is seen and limit taper to 7 weeks (Table 1). Steroid dependency should be avoided. (6) See guidelines on management of acute severe colitis. (7) Response is defined as a drop in PUCAI of at least 20 points. However, the ultimate goal of induction therapy is complete remission (Figure 3). (8) For example, previous intolerance or resistance to steroids, or when infliximab is indicated anyway for maintenance treatment after failing thiopurines. (9) Measuring thiopurine methyltransferase (TPMT; genotyping or enzymatic activity) should be tested at baseline; serum thiopurine metabolites (6-thioguanine [6-TGN] and 6-methylmercaptopurine [MMP]) assist in optimising thiopurine dosing. (10) Infliximab should be administered with an immunomodulator and usually at a higher dose of 10 mg/kg; the dose can be reduced after achieving remission, guided by serum trough concentration. Stepping down to thiopurine (in naïve patients) or 5-ASA may be considered in selected cases, and after a period of sustained deep remission. (11) Decisions on the use of off-label therapies should include the lack of approved indication in children and analysis of risk-benefit considerations; these are best provided in an experienced centre with monitoring based on adult guidelines. (12) Colectomy is always an option in refractory patients and should not be seen as a last resort. It is best practice to initiate informed, multidisciplinary discussions on surgery before decision time.

8. A standardised endoscopic activity index, including the Mayo endoscopic sub-score or Ulcerative Colitis Endoscopic Index of Severity (UCEIS), should be used during colonoscopy (Agreement 100%).
9. Histological activity scores (Nancy Index, Robarts Histopathology Index or Geboes Score) do not appear to predict disease course in the first 12 months. However, residual histological activity in otherwise healed mucosa (Mayo endoscopic score 0 and 1) might predict short-term disease relapse (Agreement 100%).
10. Quality of life (QoL) scores (e.g., IMPACT-III) and patient-reported outcome (PRO) measures (such as TUMMY-UC; Supporting Information S5: Table S4) correlate well with physician-based measures and are encouraged as part of disease assessment. They are also important for communication between patients and clinicians and can assist in patient engagement and empowerment (Agreement 100%).

Initial investigation at diagnosis is not the focus of these guidelines (covered in depth in the revised Porto criteria),[15] but a general approach is summarised in Figure 2. The PUCAI score aligns well with endoscopic

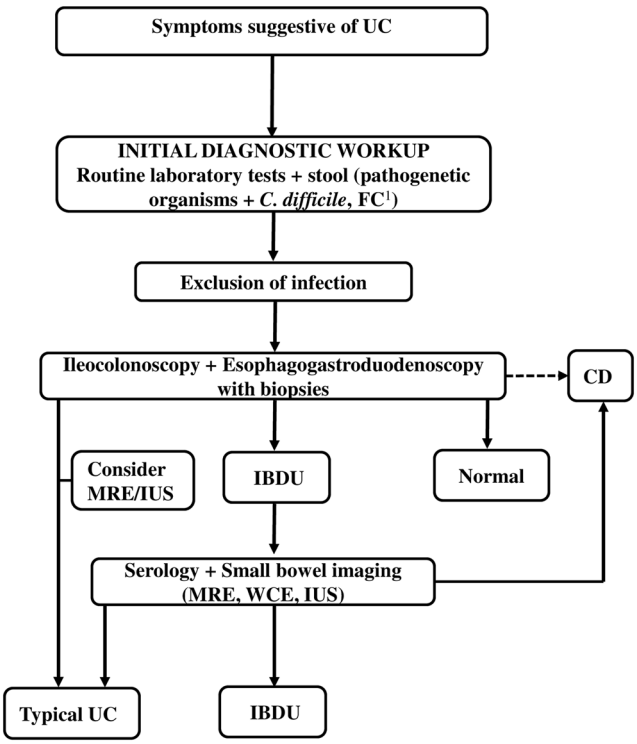

FIGURE 2 Diagnostic workup for suspected UC. [1]Useless in case of frank mucoid-bloody diarrhoea. CD, Crohn disease; FC, faecal calprotectin; IBDU, inflammatory bowel disease unclassified; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; UC, ulcerative colitis; WCE, wireless capsule endoscopy.

disease activity[26] and highly correlates with the Mayo score.[13,27,28] The cut-offs for remission, mild, moderate and severe disease activity have been validated in various cohorts.[27–29] Nevertheless, although most studies report a good correlation between clinical symptoms and endoscopic findings, some studies describe persistent mild-to-moderate endoscopic inflammation in more than half of the patients in clinical remission.[30,31] Furthermore, on an individual basis, one study reported a risk of about 20% for persistent endoscopic inflammation in patients with a PUCAI indicating complete remission.[31] This discrepancy is particularly relevant for patients with UC associated with primary sclerosing cholangitis (PSC-UC), in whom the lack of clinical symptoms may not reflect the absence of mucosal inflammation.[32] Therefore, non-invasive biomarkers and imaging investigations should be routinely performed in patients in clinical remission (Figure 3).

According to several studies, PUCAI at diagnosis and after induction can help predict the prognosis in children with UC.[33–35] In the multicentre PROTECT inception cohort, a PUCAI of less than 35, higher baseline levels of albumin among children <12 years, and achieving remission at Week 4 were predictors of corticosteroid-free clinical remission at 12 and 52 weeks, as well as reduced colectomy risk.[33,34] Corticosteroid-free clinical remission at 3 months but not at 12 months was also linked to better outcomes in a European prospective multicentre inception cohort study.[36] Several other studies linked higher PUCAI scores at the diagnosis to colectomy risk,[37,38] disease extension and hospitalisations.[39]

There is currently a trend toward assessing and monitoring PROs closely linked to patients' QoL.[40] Several studies indicate that patients' perception of their disease and symptom severity may differ significantly from that of their treating physician.[41] The recently developed and validated TUMMY-UC has been shown to be highly reliable and to correlate with PUCAI, endoscopic activity and IMPACT-III questionnaire (Supporting Information S5: Table S4).[42] TUMMY-UC has two versions: a patient-reported version for children older than 8 years and an observer-reported version for caregivers of children 8 years and younger.[42]

Faecal calprotectin is strongly associated with clinical activity as measured by PUCAI, as well as endoscopic and histological disease activity.[43] Although the specific thresholds for defining mucosal healing are not perfectly established, the American Gastroenterology Association (AGA) recommends a cut-off of 150 mcg/g to indicate the absence of endoscopic inflammation based on numerous studies conducted in adults and children.[44,45] With a cut-off of 150 ± 50 mcg/g, the sensitivity and specificity of faecal calprotectin are 71% (95% confidence interval [CI]: 62%–78%) and 69%

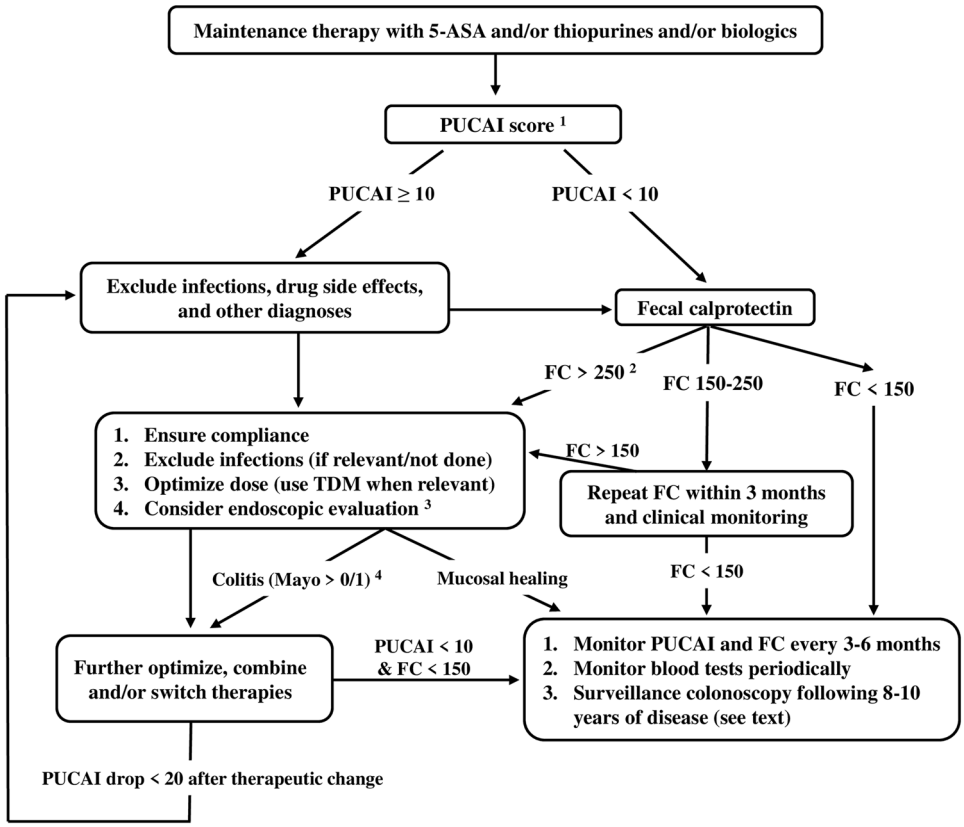

FIGURE 3 Algorithm for monitoring paediatric ulcerative colitis (UC) during the maintenance phase. [1]Quality of life scores and patient-reported outcomes (PROs), such as TUMMY-UC, are encouraged as part of disease assessment. [2]In asymptomatic patients, consider repeating FC measurements (at least 2–4 weeks apart) before endoscopic evaluation or therapy change. [3]Proceeding to sigmoidoscopy/colonoscopy should preferably be based on at least two independent calprotectin measurements. Endoscopic re-evaluation is also recommended before major treatment modifications and when it is not clear if symptoms are disease-related. [4]The decision whether to escalate therapy based on a Mayo 0 or 1 endoscopic findings should be individualised, based on the current treatment (e.g., it is easier to increase mesalamine dose or add rectal therapy than starting thiopurines), symptoms, and extent (short Mayo 1 segment may be closely monitored whereas extensive disease may require escalation). FC, faecal calprotectin; PUCAI, paediatric ulcerative colitis activity index.

(95% CI: 62%–75%), respectively. In patients who have recently achieved clinical remission following a therapeutic change in the previous 1–3 months, a 50 mcg/g cut-off may be more indicative of endoscopic improvement.[44]

The prognostic role of faecal calprotectin was acknowledged in the previous version of the UC guidelines, with references coming from adult UC patients. Evidence of this role in children has been published since then. Faecal calprotectin levels over 350 mcg/g together with elevated CRP were demonstrated to predict disease relapse in the following 6 months in children with quiescent UC.[46] Furthermore, a more than 75% decrease in faecal calprotectin in the first 4–12 weeks of treatment was found predictive of corticosteroid-free clinical remission at Week 52.[47] These findings were incorporated into the PROTECT prediction model together with baseline PUCAI, albumin and haemoglobin.[34,36]

Routine laboratory tests (haemoglobin, CRP, platelets, albumin) can be normal in UC patients, particularly those with mild-to-moderate disease.[48] Specifically, compared to patients with CD, those with UC can have a modest or even absent CRP response, likely related to the fact that in many UC cases, the inflammation is limited to the mucosa.[49] However, if abnormal, inflammatory indexes (CRP > 20 mg/L[50] and higher ESR[35]) are markers of severe disease and increased colectomy risk. Furthermore, low albumin and haemoglobin, and higher PUCAI at diagnosis, predict higher colectomy rates and biologic use at 18 months.[34] In particular, lower albumin levels were also confirmed to increase the risk of colectomy in another prospective cohort study.[51] Assessment should also include a review of immunisation records, preferably at the time of diagnosis. This is reviewed in detail elsewhere, but in some cases, specific vaccines should be provided if possible before starting immunosuppressive therapy to mitigate infectious risks.[52,53] Live vaccines are generally contraindicated with immunosuppressive therapy, especially corticosteroids.

Endoscopy is the gold standard for assessing mucosal inflammation.[54] In paediatric UC, the Mayo endoscopic score, which ranges from none to severe (0–3 points), along with the number of affected colonic segments (rectum, sigmoid, descending, transverse and ascending colon), can be used for evaluation.[13,54] Although not validated, the modified Mayo endoscopic score is a simple tool that combines disease extent with the Mayo Endoscopic score.[55] The UCEIS is a validated index that assesses vascular pattern, bleeding and ulcers at the most severe site (Supporting Information S5: Table S5).[54,56]

While mucosal healing is associated with favourable disease outcomes in adult and paediatric UC,[57] the prognostic role of histology is still debated. A meta-analysis including more than 2500 adult patients showed that persistent histological activity was associated with a higher risk of UC relapse.[58] A paediatric UC cohort study showed a 15% rate of mucosal abnormality (with colonic intestinal gland histological abnormalities), associated with a higher risk of relapse and need for medical escalation and colectomy in the first 2 years of follow-up.[59] Conversely, two smaller paediatric cohort studies indicated that histological scores at diagnosis do not affect colectomy risk at 90 days[60] and long-term prognosis.[61] Other promising biomarkers that might predict UC prognosis are different targeted gene expression,[62] microRNA 35[63] or N-glycan expression in the mucosa,[64] and stool and serum interleukin (IL)-1β and IL-1ra.[65]

There is increasing interest in using colonic ultrasound for monitoring disease activity in paediatric UC.[66] Two recent meta-analyses from the same Dutch team were conducted in healthy children[67] and children with IBD[68] and reported a cut-off of BWT above 2 mm for the definition of colonic inflammation, although a cut-off of 3 mm is more specific. Based on this evidence, a small cohort preliminary validation study on ultrasound score for paediatric UC was designed and published.[69]

Data supporting colorectal cancer (CRC) surveillance recommendations are available in adult guidelines[70,71] and the 2018 position paper of Porto Group of ESPGHAN on endoscopy in paediatric IBD.[54] According to the latter, cancer surveillance should be performed after 8–10 years of disease, with intervals based on risk factors (extensive colitis, high burden of the colitis over time, and family history of CRC; patients who also have PSC are at highest risk, as discussed below). High-risk patients (>2 factors) need annual endoscopy, intermediate-risk patients (>1 factor) every 3 years, and those with no risk factors every 5 years.[54] It is worth noting, however, that although childhood-onset UC has been related to a higher risk of developing CRC later in life compared with matched reference individuals without IBD,[72,73] only a few cases of dysplasia and CRC in UC patients under 18 years old have been reported to date.[74–76]

4 | ORAL 5-AMINOSALICYLATE (5-ASA) AND TOPICAL (SUPPOSITORY/ENEMA) THERAPIES

4.1 | Recommendations

1. Oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-to-moderate UC [EL2, adults EL1] (100% agreement).
2. Combined oral and rectal 5-ASA therapy is more effective than oral 5-ASA monotherapy [EL2, adults EL1] (100% agreement).
3. Rectal monotherapy should be reserved for mild-to-moderate ulcerative proctitis [EL2, adults EL1] (100% agreement).
4. When rectal therapy is used, 5-ASA is preferred over corticosteroids for both induction and maintenance [EL5, adults EL1] (100% agreement).

4.2 | Practice points

1. No mesalamine delivery system has proven clearly superior for induction or maintenance of remission. There is no efficacy difference between once daily and twice daily dosing of mesalamine. Only sulfasalazine is available in liquid formulation and may also be effective for arthritis, but it is associated with more adverse events (Agreement 96%).
2. Suggested dosing: *oral mesalamine* usually 50–70 mg/kg/day (up to 100 mg/kg/day or 4.8 g daily); *rectal mesalamine* 25 mg/kg up to 1 g daily; *sulfasalazine* 40–70 mg/kg/day up to 4 g daily. Higher rectal mesalamine doses up to 4 g are being used, but evidence suggests that it is no more effective than 1 g (Agreement 96%).
3. Suppositories are useful for limited proctitis, while foam and liquid mesalamine enemas are suitable for more extensive colitis (Agreement 100%).
4. Gradual sulfasalazine dose augmentation over 7–14 days may mitigate dose-dependent side effects. If evidence of sulfasalazine hypersensitivity (fever, rash) occurs, the sulfasalazine should be stopped immediately (Agreement 100%).
5. The effective induction dose should also be continued as the maintenance dose. After several months of sustained biochemical remission, a dose reduction within the suggested dose range may be considered (Agreement 96%).
6. Treatment modification should be considered in patients who do not show an initial meaningful response to mesalamine within 2–3 weeks of therapy, as most children with mild-to-moderate UC will

not achieve remission with oral mesalamine monotherapy alone. Addition of mesalamine enemas should be considered after oral mesalamine failure before progressing to oral corticosteroids (Agreement 100%).
7. Acute mesalamine intolerance could present as an exacerbation of the UC, usually within the first month of treatment. Symptoms resolve within days of cessation. Recurrence on rechallenge is diagnostic and precludes its future use. Symptoms usually recur following rectal administration (Agreement 100%).

Strong evidence supports the use of 5-ASA for induction and maintenance of remission in mild-to-moderate UC at all ages.[77–83] According to the PROTECT inception cohort study, corticosteroid-free clinical remission on mesalamine was obtained in 38% after 1 year in children with mild-to-moderate UC after standardised induction with mesalamine (with or without corticosteroids).[34]

The MUPPIT trial demonstrated no difference in outcomes comparing once daily (clinical response 60%, remission 30%) versus twice daily (clinical remission 63%, remission 40%) oral mesalamine.[84] Improvement was observed in almost all responders by Week 2 without additional benefit after Week 3. A once-daily mesalamine RCT in children demonstrated an efficacy and tolerability of high-dose oral multimatrix mesalamine in inducing clinical response (65%) in mild-to-moderate UC comparable with the reported adult results.[77,78,82] There was no difference in maintenance of clinical response between the once daily high and low dose (53% vs. 54%, respectively).[82] Clinical improvement in mild-to-moderate UC was seen in nearly twice as many children randomised to sulfasalazine (22/28, 79%) compared to olsalazine (11/28, 39%).[79]

Although there are no paediatric maintenance comparative trials of 5-ASA, the North American PROTECT study confirms a 38% corticosteroid-free remission rate on mesalamine, with 32% reported in the Northern French EPIMAD registry.[34,85] The prospective Italian paediatric IBD registry (SIGENP) reported remission in 46% of UC patients on 5-ASA at 5 years after diagnosis.[86] Meta-analyses in adult UC showed that no specific 5-ASA compound was superior for inducing remission, although sulfasalazine was statistically superior to other 5-ASA compounds for maintenance of remission.[77,78,87]

The pharmacokinetics of 5-ASA are comparable between children and adults.[88–90] Adult trials have shown somewhat greater efficacy of higher induction mesalamine dose in patients with severe or extensive disease, phenotypes more commonly seen in children.[91–93] However, in a multicentre RCT, 81 children with mild-to-moderate UC randomised to high dose (53–118 mg/kg/day) or lower dose (27–71 mg/kg/day) delayed release mesalamine demonstrated similar PUCAI-defined remission rates after induction (55% and 56%, respectively).[83]

Oral mesalamine may be better tolerated than sulfasalazine (relative risk [RR] of adverse effects: 0.48, 95% CI: 0.36–0.63), but the latter is cheaper, as effective, and remains the only 5-ASA available in liquid formulation, making it attractive for young children.[78,79] Sulfasalazine also has a direct effect on nuclear factor kappa B, which may add to its mode of action.[94] Sulfasalazine suspension was safe and effective in a retrospective study of 57 children with UC (mean [standard deviation (SD)] age 5.3 ± 3.3 years) with inability to swallow tablets.[95] Moreover, except for the uncommon allergic reaction (<0.1%), the vast majority of adverse events are mild (e.g., headache and gastrointestinal symptoms) and uncommon.[96] Serious adverse events with 5-ASA treatment are rare and include renal, pancreatic, pulmonary and cardiac complications.[97–101] Sulfasalazine hypersensitivity presents with fever, rash and eosinophilia, which should trigger immediate treatment cessation[102]; folic acid deficiency has been reported with sulfasalazine.[103] In adult studies, withdrawal due to intolerance ranges from 2% to 5%.[77,78] Intolerance to 5-ASA medications may mimic a UC flare, and when clinically proven by rechallenge, it precludes further use of 5-ASA compounds.[104] Regular laboratory monitoring of CBC, renal function and urinalysis remains the practice of many clinicians, though not supported by evidence. Poor adherence is always a possible cause of non-response to therapy.[105]

Stopping maintenance therapy is tempting in the management of a chronic disease such as UC, but data guiding this action are lacking. In a nationwide study of paediatric and adult UC patients, 18% (12% of paediatric UC) were on no maintenance therapy; a propensity score-matched analysis showed similar outcomes for those not adherent to those on 5-ASA with mild disease.[106] RCTs exploring stopping 5-ASA and the risk of relapse in UC have yet to be published. However, the long-term risk of developing CRC and the chemoprotective effects of 5-ASA shown in adults[107] should be considered in any discussion on stopping 5-ASA as the sole UC therapy.[108]

In patients with a limited extent of disease (proctitis or left-sided colitis) topical monotherapy (suppositories or enemas) is logical, although supportive data are lacking and paediatric ulcerative proctitis has high rates of treatment escalation with proximal disease extension.[93,109–111] Suppository use should be restricted to active proctitis, whereas both foam and liquid enemas are useful for distal and left-sided colitis. Proctitis comprises 3%–10% of incident paediatric UC patients, but extension has been reported in up to 47%.[93,109–111] An increase in topical 5-ASA therapy use over 2008–2015 in paediatric UC was reported in the Swiss IBD cohort.[112]

Mesalamine suppositories (0.5 g daily) improved disease activity at 3 and 6 weeks in children with mild-to-moderate proctitis.[113] Combining oral and rectal 5-ASA therapy further improves clinical outcomes.[114,115] Remission was gained in 16/38 children (42%) unresponsive to oral high dose mesalamine in a prospective uncontrolled trial of 3 weeks' rectal mesalamine.[116] Adult studies with larger numbers, summarised in Cochrane reviews, show that rectal mesalamine foam, gel or liquid enema formulations are effective for induction and maintenance of remission in distal colitis; all formulations have comparable tolerance, safety and outcomes.[117–120] Once daily rectal therapy is as effective as divided daily dosing.[121] In adults, more than 1 g daily of rectal mesalamine did not enhance clinical, endoscopic and histological remission.[117,118] Once clinical remission and mucosal healing are gained, enemas may be stopped at the patient choice and maintenance attempted with oral mesalamine. Rectal corticosteroid preparations are useful for patients who are 5-ASA intolerant; novel budesonide suppositories were shown in an RCT to be non-inferior to budesonide foam enema in adult ulcerative proctitis.[122] Although corticosteroid preparations are superior to placebo in inducing proctitis remission at all ages, meta-analyses consistently support the superiority of rectal mesalamine over rectal corticosteroids (symptomatic remission odds ratio [OR]: 1.65, 95% CI: 1.1–2.45).[118]

Rectal tacrolimus can be a successful third-line treatment of ulcerative proctitis at all ages[123,124] as shown in an adult placebo-controlled RCT.[125] Availability is however very limited outside of research studies and although usually well tolerated, rare toxicity episodes have been reported.[124]

5 | ORAL CORTICOSTEROIDS

5.1 | Recommendations

1. Oral corticosteroids should be used as a second-line induction treatment for mild-to-moderate UC not responding to 5-ASA (oral and/or rectal). Corticosteroids may be considered as first-line induction treatment for moderate-to-severe disease based on clinical and endoscopic characteristics [EL3, adults EL1] (Agreement 100%).
2. Second-generation oral corticosteroids with lower systemic effect such as beclomethasone dipropionate (BDP) [EL2, adults EL1] and budesonide-MMX [EL5, adults EL2] may be considered in patients with mild-to-moderate disease refractory to 5-ASA (Agreement 100%).
3. Corticosteroids should not be used for maintaining remission, and the need for repeated courses should prompt a change in therapy; corticosteroid-sparing strategies should be applied [EL5, adults EL4] (Agreement 100%).

5.2 | Practice points

1. The recommended daily dose for oral prednisolone/prednisone is 1 mg/kg/day (max 40 mg) once daily in the morning for 1–2 weeks (in any case not >4 weeks) followed by a tapering period of up to 7 weeks (Table 1) (Agreement 100%).
2. In patients >30 kg, the dosing schedule of BDP is 5 mg once daily for 4 weeks, and for budesonide-MMX 9 mg for 8 weeks. Dosing for children <30 kg has not been established. No liquid formulation is available. There is no evidence to support whether and how to taper either drug. While abrupt discontinuation has been practiced in RCTs, alternate day tapering over 2–4 weeks may be considered (Agreement 100%).
3. The term 'corticosteroid-dependency' applies to patients who are unable to stop corticosteroids within 3 months due to ongoing disease activity, or who have a relapse requiring corticosteroids within 3 months of stopping corticosteroids (Agreement 100%).
4. Alertness to symptoms of adrenal suppression (e.g., weakness/fatigue, malaise, nausea, vomiting, diarrhoea, headache, arthralgia and abdominal pain) is needed for all patients on corticosteroids, particularly in those recently exposed to high doses and repeated exposures/long duration. When these symptoms are present while weaning corticosteroids below physiological threshold (approx. 0.2 mg/kg/day of prednisone), adrenal insufficiency should be excluded (Agreement 100%).

Oral corticosteroids represent the second-line therapy to induce remission in children with extensive mild-to-moderate active UC, who fail to respond to oral and/or topical mesalamine.[13] Studies on the natural history of children with active UC receiving an initial course of corticosteroids report short-term (1–3 months) remission rates of 45%–64%[33,50,126–129]; at 1 year 49%–61% had prolonged response; however, 14%–49% were corticosteroid-dependent and 4%–33% required surgery.[50,127–132] While we recognise the efficacy of corticosteroids, efforts to reduce corticosteroid exposure need to be a priority, as also reflected in the tapering approach in Table 1 and discussed throughout the guidelines.

As for mucosal healing, in a non-randomised study after 8 weeks of corticosteroids or 5-ASA, 87% of children had clinical remission, 40% endoscopic remission and 15% histological remission, with no significant difference in outcomes between the 2 therapies.[133] Modestly lower rates of clinical remission and higher rates of corticosteroid resistance and

TABLE 1 Steroids tapering schedule (doses are in mg/day prednisone equivalent): The goal is to discontinue steroids by Week 7.

Starting dose	Taper week 1	Taper week 2	Taper week 3	Taper week 4	Taper week 5	Taper week 6	Taper week 7
40	35	30	25	20	15	10	5
35	35	30	25	20	15	10	5
30	25	20	15	15	10	10	5
25	20	20	15	15	10	5	5
20	15	15	12.5	10	7.5	5	2.5
15	12.5	10	10	7.5	7.5	5	2.5

Note: Avoid steroid dependency by timely escalation of maintenance therapy when needed. The risk for exacerbation is smaller with prednisone doses >20 mg, but the risk for adverse events is then higher, thus a more rapid tapering to <20 mg is desired. Shortening each stage from 7 to 5 days or any other tapering modification may be considered individually, as many factors come into play when weaning off steroids. Consider the possibility of adrenal insufficiency, even many months after tapering off steroids.

dependence have been reported in VEO-IBD compared to older children.[134] Strategies to avoid corticosteroid dependency include timely optimisation of maintenance treatment such as 5-ASA, adjuvant therapy with enemas, or escalation to thiopurines or biologics.[13]

Corticosteroids designed to act locally in the gut or with first pass effect in the liver, reducing systemic exposure (low systematic bioavailability) with less severe side effects, have been developed. These medications, including budesonide and BDP, may be considered before systemic corticosteroids in selected patients.[135] BDP has anti-inflammatory effects in patients with UC with low systematic bioavailability and with a predominantly colonic action.[135] A systematic review and meta-analysis showed that BDP 5 mg and BDP 10 mg were more effective than placebo in achieving clinical remission or improvement (OR: 2.36, 95% CI: 1.37–4.08; OR: 2.23, 95% CI: 1.02–4.87), in adult patients with UC. However, in comparison with 5-ASA, no differences were found between 5-ASA and BDP 5 mg or BDP 10 mg in achieving clinical remission or improvement (OR: 0.90, 95% CI: 0.51–1.57; OR: 1.54, 95% CI: 0.42–5.64).[135] One paediatric RCT in 30 children (weight > 30 kg) with mild-to-moderate UC showed that oral BDP, 5 mg/day for 4 weeks, was well tolerated and more effective than 5-ASA in achieving both clinical remission (80% vs. 33%, $p < 0.025$) and endoscopic remission (73% vs. 27%, $p < 0.025$), respectively.[80]

Adverse effects of glucocorticoid use include immunosuppression, impaired growth, osteoporosis, myopathy, altered glucose homoeostasis and, less frequently, cataract formation and pancreatitis.[136,137] Increased ocular pressure is a potential concern with prolonged use of corticosteroids, but is unlikely with most exposures.[138] Glucocorticoid-induced adrenal insufficiency (GIAI) is caused by hypothalamic–pituitary–adrenal axis (HPA) suppression by high dosages or prolonged use of corticosteroids, followed by abrupt discontinuation or rapid tapering. GIAI may present with nonspecific symptoms (including abdominal pain, malaise, weakness/fatigue, nausea, anorexia, diarrhoea, headache, arthralgia) or rarely adrenal crisis (hypotension up to hypovolemic shock, lethargy, collapse, decreased consciousness/coma, hyponatremia, hypoglycaemia and seizures).[137]

Diagnostic criteria for nonspecific GIAI symptoms are preferentially based on cortisol evaluation.[139] However, there are still no published consensus guidelines that advise who should be screened for GIAI. Nevertheless, if glucocorticoids have been used for 2 weeks or longer, assessment of the integrity of the HPA axis may be suggested if a clinical concern is raised when weaning off corticosteroids, but the optimal time to test for HPA axis recovery remains controversial.[140] Consultation with or referral to a paediatric endocrinologist should be considered in cases with longer duration of corticosteroid exposure, weaning challenges and suspicion of adrenal insufficiency. Early morning (8 AM) cortisol level is a useful screening test. A morning serum cortisol <3 mcg/dL in combination with low/normal adrenocorticotropic hormone (ACTH) is considered suggestive of adrenal insufficiency, while morning cortisol values >16–18 mcg/dL, depending on the assay, rule out GIAI.[141] If morning cortisol concentrations range between 3 and 15 mcg/dL further investigation such as ACTH or short synacthen stimulation tests are needed.[142] Children with confirmed GIAI should receive daily hydrocortisone replacement (6–8 mg/m^2/day), until HPA axis recovers.[143–145] Awareness of the risk for GIAI should continue even after completing hydrocortisone replacement (until the ACTH stimulation test is normal) when affected individuals are still at risk of becoming ill. In a study of consecutive children with IBD on low-dose corticosteroids (i.e., on physiological doses of oral corticosteroids, meaning 5–10 mg daily prednisolone), 20% had biochemical GIAI using a value <69 nmol/L and of these, half had

an undetectable cortisol.[146] Higher glucocorticoid dose and longer duration of the therapy were associated with increased risk.[146]

6 | IMMUNOMODULATORS (IMMS)

6.1 | Recommendations

1. Thiopurines should not be used to induce remission in children with UC (EL5, adults EL2) (Agreement 100%).
2. Thiopurines are recommended for maintaining remission in children who, despite optimal 5-ASA treatment, are corticosteroid-dependent or have frequent relapses (≥2 relapses per year) or in 5-ASA-intolerant patients; thiopurines should be considered following discharge from ASC episodes (EL4, adults EL3) (Agreement 100%).
3. Measuring thiopurine metabolites should be considered in all patients and is recommended in patients with an incomplete response on a stable thiopurine dosage, in patients who present with leukopenia or elevated transaminases, or if poor compliance is suspected (EL2, adults EL2) (Agreement 100%).
4. Methotrexate is not recommended for inducing or maintaining remission in UC (adults EL3) (Agreement 100%).

6.2 | Practice points

1. Thiopurine methyltransferase (TPMT) genotype or phenotype (i.e., TPMT activity) should be tested based on local accessibility and variant frequency before starting thiopurines to identify patients at greater risk of profound myelosuppression. The dose should be reduced in heterozygous patients or those with low activity. Thiopurines should not be used in children with homozygous mutations for TPMT or those with very low TPMT activity, as defined by each laboratory (Agreement 88%).
2. Regular monitoring of blood counts and liver enzymes is recommended in all cases, including patients whose enzyme activity (TPMT or NUDT-15) was assessed: during the first week, every 1–2 weeks during the first month, and then monthly up to 3 months, followed by every 3 months thereafter (Agreement 100%).
3. Patients/families should be instructed to use sun protection with the use of thiopurines and other immunosuppressive drugs (Agreement 100%).
4. Given its excellent safety profile, it is reasonable to continue 5-ASA with thiopurines, at least initially, despite the lack of firm evidence. 5-ASA inhibits the enzyme TPMT, thus increasing the active metabolite 6-thioguanine (6-TGN) (Agreement 96%).
5. The maximal therapeutic effect of thiopurines may not be evident until 10–14 weeks of treatment (Agreement 100%).
6. Thiopurine dose as monotherapy should be approximately 2–3 mg/kg of azathioprine and 1–1.5 mg/kg of mercaptopurine, in a single daily dose in patients with a normal TPMT (Agreement 100%).
7. Measuring thiopurine metabolites may assist in further dose adjustments and reduce adverse events while considering the 6-TGN level of 235–450 pmol/8×10^8 red blood cells (RBCs) and 6-methylmercaptopurine ribonucleotides (6-MMP) < 5700 pmol/8×10^8 RBCs as optimal (based on the Lennard method). Cut-off values may vary between labs and methods (Agreement 100%).
8. Patients with gastrointestinal intolerance or flu-like reaction attributed to one thiopurine compound may tolerate lower doses, split dosing, or a switch to another thiopurine (azathioprine to mercaptopurine and vice versa) (Agreement 100%).
9. Thiopurines should be discontinued in cases of severe leukopenia (<2×10^9/L) or pancreatitis and discontinued or reduced in cases of moderate leukopenia (2–3×10^9/L). Reintroduction of thiopurines after leukopenia can be considered at a lower dose after carefully assessing the risks and benefits and after measuring thiopurine metabolites. Thiopurines should not be reintroduced following thiopurine-associated pancreatitis (Agreement 100%).
10. In cases of hyperactive TPMT resulting in high 6-MMP (often associated with elevated transaminases) and low 6-TGN, concomitant use of allopurinol may provide a valid therapeutic option, in suitably experienced units. The suggested allopurinol dose is 50 mg once daily in patients <30 kg and 100 mg once daily in patients ≥30 kg with a reduced dose of azathioprine (to approximately 25%–30% of the initial dose). Children must be closely monitored, given the increased risk of toxicity (Agreement 96%).
11. The benefits of thiopurine withdrawal should be carefully weighed against an increased risk of UC relapse. Thiopurine withdrawal could be considered in patients in sustained clinical remission following long-term treatment (at least 1 year) after ensuring complete mucosal healing and preferably histological remission. In the case of thiopurine withdrawal, 5-ASA treatment may assist in maintaining remission, and patients should be followed closely (Agreement 100%).
12. Oral tacrolimus (initial dose of 0.1–0.2 mg/kg/day divided into two daily doses) may be considered to induce remission while bridging to maintenance therapies in selected patients, including those with corticosteroid-dependent or refractory disease.

Levels should be measured on Days 3–4, with the dose adjusted accordingly. High target serum trough levels (10–15 ng/mL) in the first 2 weeks should be sequentially lowered (initially 5–10 ng/mL; eventually to 2–5 ng/mL) to avoid toxicity (Agreement 96%).

13. A course of rectal tacrolimus (if available) may be considered in patients with ulcerative proctitis who are either refractory or intolerant to mesalamine and corticosteroid topical therapies (suggested dose 0.07 mg/kg/day; maximum dose in adult trials 3 mg/day) (Agreement 100%).

Thiopurines (azathioprine and mercaptopurine) are a mainstay of paediatric UC maintenance management. Meta-analyses of placebo-controlled RCTs affirm that azathioprine is more effective than placebo in preventing relapse but not in inducing remission.[147–149]

Paediatric data support the efficacy of thiopurines in maintaining remission and reducing the need for corticosteroids.[150–156] The median time to achieve steady thiopurine levels is 55 days.[156] A prospective dose optimisation study including 33 patients with UC reported 1-year corticosteroid-free remission in 39%, with corticosteroid-free remission plus normal CRP and ESR in 27%.[157] A retrospective study from the 'biologic-era' reported a 56% 1-year corticosteroid-free remission in children on thiopurines without previous or concomitant biologic therapy, with a probability of not requiring rescue therapy of 83% at 1 year, 62% at 2 years, 45% at 3 years and 37% at 4 years.[158] However, earlier introduction of thiopurines neither benefits clinical nor endoscopic outcomes, nor reduces the ultimate risk of colectomy in children.[154,159]

Despite a single negative small-scale study in adults, combining 5-ASA with thiopurines may be considered due to the excellent safety profile of the former and potential additive effects, including chemoprotection.[160] 5-ASA may partially inhibit TPMT activity, increasing 6-TGN levels.[161,162] A decision to add 5-ASA should balance between the additive efficacy and chemoprevention with maintaining mesalamine while on thiopurines and the better expected adherence profile when the patient is on monotherapy.

In adults, azathioprine is typically administered at doses of 2.5 mg/kg, and mercaptopurine at 1–1.5 mg/kg. For children under 6 years, higher doses of azathioprine per body weight, up to 3 mg/kg/day, might be necessary.[163,164]

Patients with genetic variants causing reduced TPMT or nudix hydrolase 15 (NUDT15) enzyme activity are more susceptible to side effects such as myelosuppression, due to increased levels of active thiopurine metabolites, that is, 6-TGN. Thiopurines should be avoided in patients with very low TPMT activity or those homozygous for variant TPMT and NUDT15 alleles. Clinicians should bear in mind the distribution of inter- and intra-ethnic variants in their treatment population when considering and interpreting pharmacogenomic assays.[165] Variants in TPMT and NUDT15 are more prevalent but not exclusive to European and Asian ethnic populations, respectively.[166]

Lowering dosages in patients with low enzyme activity significantly reduces haematologic adverse events in adults.[167] Paediatric data are conflicting, with one study reporting myelosuppression in 15% of carriers, and another finding no association between TPMT polymorphisms and thiopurine-related adverse events.[168,169] Monitoring of CBC and liver and pancreatic enzymes, especially during treatment initiation, remains mandatory, irrespective of genomic or functional testing.

In cases of hyperactive TPMT causing elevated 6-MMP and reduced 6-TGN, concurrent allopurinol with a lowered dose of azathioprine may be a viable therapeutic option, but caution is advised.[170,171] Appropriate dose reduction and regular CBC and 6-TGN/6-MMP monitoring are necessary to prevent myelosuppression-related side effects. Adult trials utilised allopurinol at 100 mg once daily,[170,172] while in a few paediatric case series, lower doses (50 or 75 mg once daily) were employed in younger children.[171,173]

TDM of thiopurines in children may improve dosing accuracy and clinical outcomes, including a higher likelihood of clinical remission and fewer exacerbations.[174–176] Elevated 6-MMP levels correlate with hepatotoxicity, while low thiopurine metabolite levels are associated with noncompliance or underdosing.

Several methods measure red-cell levels of the metabolites 6-TGN and 6-MMP, each with corresponding reference ranges. Levels presented herein are based on the Lennard and Singleton method.[177] The links between 6-TGN levels, clinical response and myelotoxicity have been established in prospective adult studies[178,179] and smaller retrospective paediatric studies.[180–182] In children, 6-TGN levels >250 pmol per 8×10^8 RBCs correlated with a higher clinical response (OR: 4.14), whereas remission was lower in children with subtherapeutic levels.[180,183] Metabolite testing may prompt therapeutic change, with 6-TGN levels >405 pmol/8×10^8 RBCs, during active disease, predicting azathioprine resistance (OR: 10.8) in a study of 78 children.[184]

The RR of adverse events from thiopurines in adults is 2.82.[149] Withdrawal rates of 15%–30% are reported in large paediatric cohorts.[185–188] Dose-independent reactions include fever, pancreatitis, rash, arthralgias, nausea, vomiting and diarrhoea. Dose-dependent phenomena include leukopenia (~5%), thrombocytopenia, infections and hepatitis.[189,190] Specific infections are not well documented with thiopurines, so recommendations for infectious screening are lacking; these

should be considered on an individual basis and may include those detailed below in the anti-TNF section.

Thiopurine rechallenge following adverse events requires careful consideration, with options including intra-class switching, dose reduction and dose splitting. A meta-analysis of adult studies reported mercaptopurine tolerance in 68% of 455 azathioprine-intolerant patients.[191] Traditionally, switching in the case of pancreatitis is not recommended, although one adult study presented favourable data.[191] In one paediatric retrospective study, 50/233 children had thiopurine-related adverse events; 18/26 patients tolerated rechallenge; 10/16 tolerated an alternative thiopurine agent.[187] Evidence supporting dose-splitting to manage non-dose-related effects stems from retrospective observational adult data, while this approach was also used to manage children with preferential 6-MMP metabolism.[192,193]

The evidence supporting thioguanine use in children with UC is limited, with past concerns raised about liver toxicity and non-cirrhotic portal hypertension.[194,195] One recent paediatric study included 36 patients with past azathioprine failure and reported 31% discontinuation.[195]

Thiopurine treatment for IBD harbours a higher RR of developing lymphoma (standardised incidence ratio [SIR] = 6.99) in patients under 30 years, especially males, though the absolute risk approximates 1 in 4000–5000.[196] The absolute risk is much higher in the elderly. In a meta-analysis of four studies including 261,289 adult patients, the incidence rate ratio for lymphoma was 2.23 for patients exposed to thiopurine monotherapy compared to unexposed patients.[197] A comparable RR (1.8, 95% CI: 0.6–6.1) of lymphoma in paediatric IBD was recently reported.[198]

Hepatosplenic T-cell lymphoma (HSTCL) represents an exceptionally rare yet life-threatening complication associated with thiopurine therapy. Among the reported cases of HSTCL related to IBD, nearly all individuals had undergone treatment with thiopurines, either alone or in combination with anti-TNF.[199] Most affected individuals were males, and most cases had CD rather than UC. Three HSTCL cases were identified in a prospective study of malignancy and mortality in 25 countries over 42 months; one patient had UC, and all cases had thiopurine exposure.[76]

The decision to withdraw thiopurines following sustained remission requires careful consideration. Limited data guide monotherapy withdrawal. In a systematic review and meta-analysis of available RCT data, withdrawal of thiopurine monotherapy did not result in a significantly higher risk of relapse within 24 months of follow-up compared to ongoing therapy in UC (RR = 1.39, CI: 0.85–2.26), though UC studies were limited.[200] Retrospective adult cohort data reported 1–2-year relapse rates of 26%–36%.[201–203] Longer-term outcome studies of thiopurine monotherapy withdrawal are lacking, so any decision on withdrawal needs to be individualised to the case with shared decision making.

Epstein-Barr virus (EBV) is associated with an increased risk of developing virally driven hemophagocytic lymphohistiocytosis (HLH) and EBV-associated lymphoma, especially in patients with CD and during thiopurine treatment.[204,205] Routine serology testing should be considered before commencing immunosuppressive therapy, especially thiopurines.[206] Paediatric data are limited, but EBV serology is not routinely performed in the majority of children with IBD.[207,208] Of children tested before starting thiopurines, 53%–63% have negative EBV serology.[207–209] In a retrospective paediatric study of 409 patients, thiopurines would have been withheld in 47% of patients and 30% of males based on their negative serology status.[209] In that study, nine children developed proven EBV infection, without significant complications. This issue remains controversial with no clear recommendation on the use of thiopurines in EBV-naïve patients, but some have advocated that using methotrexate (only as a concomitant IMM, not as primary therapy in UC) may be preferred in EBV-negative cases.[210]

Paediatric data on calcineurin inhibitor use in UC are limited, in practice being more often used as a short-term bridge to another maintenance therapy rather than for maintenance itself. A Cochrane review of oral and rectal tacrolimus found superiority over placebo for inducing remission in UC (pooled RR [pRR]: 4.47, 95% CI: 2.15–9.29), despite low-quality evidence.[211] A meta-analysis of tacrolimus therapy in 166 children reported a pooled initial response rate of 84% (95% CI: 73%–93%) in corticosteroid-refractory or dependent UC, irrespective of high (>10 ng/mL) or low trough levels (85% vs. 75%, $p = 0.3$).[212] The most prevalent adverse events were tremors (13%) and hypertension (16%). In an adult RCT, response rates were better in those with higher (10–15 ng/mL) versus lower (5–10 ng/mL) trough levels (68% vs. 38%, respectively).[213]

There is no evidence supporting the use of methotrexate in UC management (outside of its use as a concomitant therapy to anti-TNF, discussed below). Meta-analysis of adult RCTs shows no benefit of methotrexate over placebo for inducing or maintaining remission in UC.[214] In the METEOR double-blind placebo-controlled trial of 111 adults with corticosteroid-dependent UC, methotrexate and placebo had comparable outcomes for corticosteroid-free remission and endoscopic healing at Weeks 16 and 24.[215] In the subsequent MERIT-UC trial involving 179

patients with active UC, methotrexate was no better than placebo at preventing relapse, achieving mucosal healing or maintaining corticosteroid-free clinical remission by Week 48.[216]

7 | BIOLOGICS AND SMALL MOLECULES

7.1 | Use of approved biologics in UC

7.1.1 | Recommendations

1. Infliximab should be considered, preferably in combination with an IMM, as the first-line biologic agent in chronically active or corticosteroid-dependent UC, uncontrolled by 5-ASA, and in most cases also thiopurines, for both induction and maintenance of remission [EL1, adults EL1] (Agreement 96%).
2. Adalimumab could be considered in those with immunogenic loss of response to infliximab, based on serum trough concentrations (TCs) and antibodies (Figure 4). Adalimumab may also be considered as a first-line biologic in non-severe cases; combination therapy is generally not warranted [EL2, adults EL2] (Agreement 96%).
3. Adalimumab has no role in patients with primary, pharmacodynamic nonresponse to infliximab [EL5, adults EL5] (Agreement 100%).

7.1.2 | Practice points

1. For most ambulatory UC cases, a step-up maintenance approach should be implemented, starting with 5-ASA (in mild-to-moderate cases), followed by thiopurines, and if both fail, advancing to infliximab (Figure 1). Exceptions to this could include corticosteroid-refractory disease (not requiring admission for IV corticosteroids), corticosteroid-dependent cases, specific patient safety concerns, ongoing symptoms, or extra-intestinal findings indicating an anti-TNF (Agreement 100%).
2. Screening for latent tuberculosis with a combination of patient history, chest X-ray, tuberculin skin test or interferon-gamma release assays (QuantiFERON) is essential before initiating anti-TNF. The QuantiFERON test is preferred in patients under immunosuppressive therapy and in Bacille Calmette-Guérin immunised patients. Screening for hepatitis B (HBV) and C viruses (HCV), varicella zoster virus (VZV) and human immunodeficiency virus (HIV) when appropriate, is also recommended (Agreement 100%).
3. In most cases, higher doses of infliximab (e.g., 10 mg/kg/dose at Weeks 0, 2 and 6, followed by 10 mg/kg every 4–8 weeks for maintenance) are required to provide the best chance of reaching the desired clinical and endoscopic outcome. The

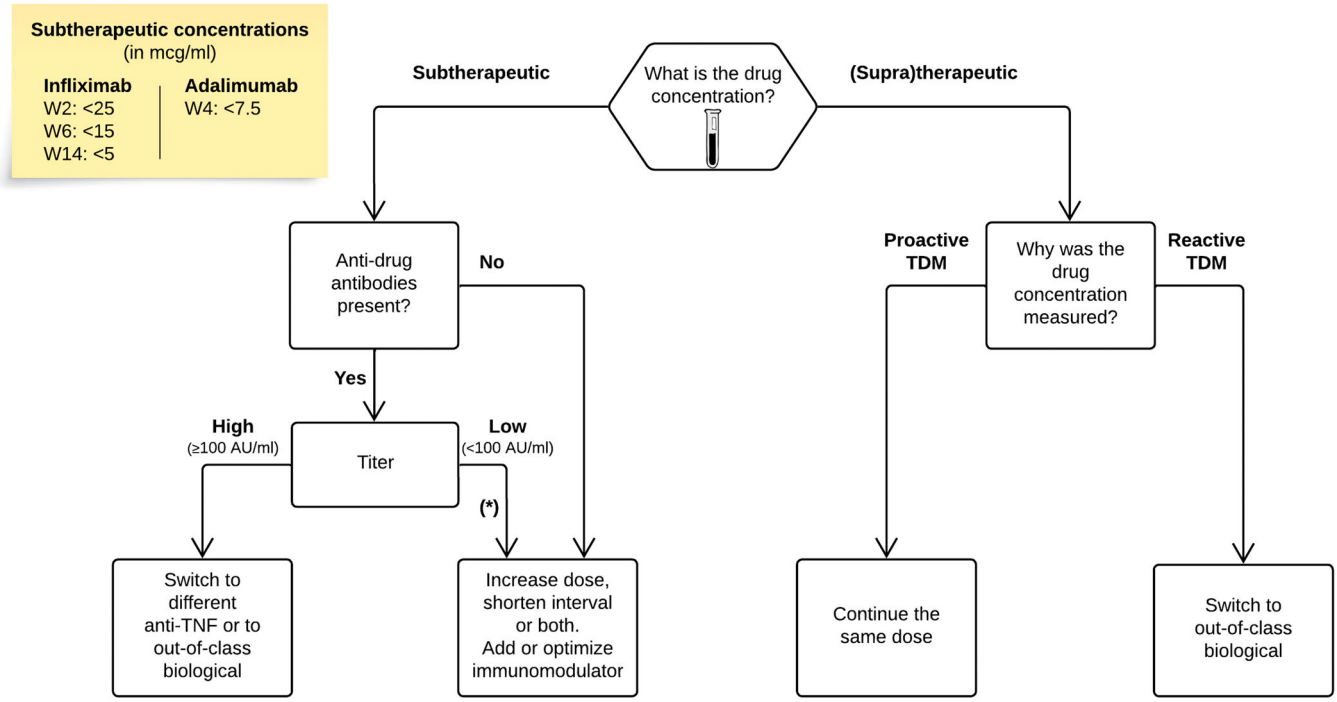

FIGURE 4 TDM decision tree for infliximab treatment. Note that at Week 14 or later, higher trough concentrations (>8 mcg/mL) may be needed to fully respond. *Remeasure anti-drug antibodies shortly before the next administration to differentiate between transient and persistent antibodies.

dose can be subsequently reduced, guided by TDM. Lower dosing (5 mg/kg) can be used in less severe cases. In cases in which IV infliximab treatment is switched to subcutaneous injections, the recommended dosing schedule (established only for >40 kg) is 120 mg every 2 weeks. See Table 2 for dosing details (Agreement 100%).

4. Infliximab is recommended to be used preferably in combination with an IMM (with the most evidence in UC being for thiopurines) to reduce the likelihood of developing antibodies to infliximab (ATIs) and in thiopurine-naïve patients, to enhance effectiveness. Methotrexate may also be used to mitigate ATIs. For immunogenicity prevention, lower doses of azathioprine (1–1.5 mg/kg) may be used. Data on methotrexate dose in this setting are scarce, but low total doses of 7.5–12.5 mg weekly are reported. Proactive TDM is recommended, particularly when infliximab is prescribed as monotherapy (Agreement 96%).
5. Stopping IMM may be considered after several months (at least 6) of combination treatment if endoscopic healing or normal calprotectin levels have been reached. Note that infliximab TC may decrease on average after stopping IMM, and thus TCs in the higher range (preferably ≥5 mcg/mL) should be ensured before stopping the IMM (Agreement 100%).
6. Adalimumab should be started at 160 mg, followed by 80 mg after 2 weeks and then 40 mg every other week in adolescents with weight ≥40 kg; some patients will require higher maintenance doses. Optimal dosing in younger children with UC has not been well defined, but body surface area (BSA)-based dosing could be considered (i.e., induction with 90 mg/m^2 followed by 45 mg/m^2 followed by 25 mg/m^2 every other week, which is the equivalent dosing of a typical adult with BSA of 1.73 m^2) (Agreement 100%).

In contrast to CD, time to initiation of biologics is not associated with risk of colectomy, as shown in population-based UC cohorts in adults[217–219] and one in paediatrics.[220] Therefore, children with UC should be managed based on the step-up approach, meaning that biologics should usually be initiated after failure or intolerance to both 5-ASA and thiopurines. An exception would be corticosteroid-refractory/dependent cases, where infliximab can be used without failing azathioprine first. In these cases, stepping down to thiopurines may be considered once deep, sustained remission has been achieved. Under this paradigm, the use of biologics in paediatric UC was 31% at 1 year in the PROTECT cohort[34] and 40% at 3 years in the paediatric nationwide epi-IIRN cohort.[221]

Current evidence supports the use of anti-TNF regimens as first-line biologics in children with UC, with infliximab likely more effective than adalimumab, especially when prescribed in combination with IMMs.[222] Nine RCTs that compared anti-TNF agents (i.e., infliximab, adalimumab and golimumab) with placebo in adult UC showed high effectiveness in inducing remission and endoscopic healing.[9]

In the T-72 paediatric trial, 45/60 (75%) enroled children with ambulatory moderate-to-severe UC responded to infliximab.[223] Clinical remission and complete endoscopic healing were each achieved in 33% at Week 8. Dose escalation to 10 mg/kg was required in 44% of the patients during the maintenance phase, which randomised responders to q8 versus q12 weeks infusions. Week 54 remission rate was 38% of responders in the q8 weeks arm. In other studies, higher per/kg dosing of infliximab has been suggested in younger children[224,225] and in children with high inflammatory burden and hypoalbuminemia.[226] However, a recent study found that of 52 children with moderate-to-severe UC initiating biologics in clinical practice, only 40% would have been eligible for inclusion in the registration trial of that biologic. Of concern, the potentially eligible children had 2.3-fold higher likelihood of therapeutic success versus non-eligible children.[227] Indeed, different real-world studies have shown a pooled long-term success rate in infliximab-treated children with UC of 64%,[228] and a corticosteroid-free remission of 38% and 21% at 12 and 24 months, respectively.[229] A relationship between the increased use of anti-TNF agents and the reduction of surgery risk for UC children has also been suggested.[230] Subcutaneous infliximab is available for induction and maintenance of remission, but paediatric data are limited, and it remains off-label for use in children.[231–233]

The double-blind ENVISION I trial randomised 93 children with moderate-to-severe UC into high-dose versus standard-dose induction adalimumab.[234] At Week 8, clinical remission was noted in 33% on standard dose and 47% in the high-dose group. Clinical remission by the PUCAI in the standard- and high-dose groups at the end of the maintenance phase was 45% and 58%, respectively, of Week 8 responders. Adalimumab blood levels were naturally higher in the high-dose group, and in general, higher doses have been suggested in younger children receiving adalimumab.[235] This suggests that a BSA-adjusted dosing is more appropriate than weight-based. In a real-world retrospective analysis of 32 children with UC failing or intolerant to infliximab, adalimumab induced corticosteroid-free remission in 41% at 52 weeks and endoscopic healing in 28%.[236] Ample studies now confirm that the use of biosimilars of adalimumab and infliximab is as effective and safe as the originators and may be switched.[237]

TABLE 2 Dosing of advanced therapies in UC.

Drug and route	Adults/adolescents		Paediatric	
	Induction	Maintenance	Induction	Maintenance
Infliximab IV	5–10[a] mg/kg at Weeks 0, 2, and 6	5–10 mg/kg every 4–8 weeks	5–10 mg/kg at Weeks 0, 2, and 6	5–10 mg/kg every 4–8 weeks
Infliximab SC	120 mg weekly for 4 weeks	120 mg every 2 weeks	N/A	[b]
Adalimumab SC	160 mg, followed by 80 mg and 40 mg every 2 weeks	40 mg every 2 weeks	Children < 40 kg: 90 mg/m^2 followed by 45 and 25 mg/m^2 every 2 weeks	25 mg/m^2 every 2 weeks
Vedolizumab IV	300 mg at Weeks 0, 2, and 6	300 mg every 8 weeks starts from Week 14[c]	Children < 30 kg: 200 mg/m^2 or 10 mg/kg (max 300 mg) at Weeks 0, 2, and 6	200 mg/m^2 or 10 mg/kg (max 300 mg) every 8 weeks starts from Week 14[c]
Golimumab SC	200 mg at Week 0, followed by 100 mg at Week 2	100 mg every 4 weeks starts from Week 6	Children < 45 kg: dose based on BSA (115 and 60 mg/m^2 at Weeks 0 and 2)	60 mg/m^2 every 4 weeks starts from Week 6
Ustekinumab IV → SC	IV (260 mg <55 kg; 390 mg 55–85 kg; 520 mg >85 kg)	SC 90 mg every 8 weeks starts from Week 8[c]	IV 6 mg/kg rounded to 130 mg (maximum 520 mg)	BSA-adjusted dose every 8 weeks (generally either 90 or 45 mg) starts from Week 8[c]
Risankizumab IV → SC	Three IV doses of 600–1200 mg at Weeks 0, 4, and 8	SC 360 mg every 8 weeks starts from Week 12	[b]	[b]
Mirinkizumab IV → SC	Three IV doses of 300 mg at Weeks 0, 4, and 8	SC 200 mg every 4 weeks starts from Week 12	[b] IV 5 mg/kg at Weeks 0, 4, and 8	[b]
Guselkumab IV → SC	Three IV doses of 200 mg at Weeks 0, 4, and 8	SC 200 mg every 4 weeks starts from Week 12	[b]	[b]
Tofacitinib PO	10 mg BID for 8 weeks	5 mg BID	[b]	[b]
Upadacitinib PO	45 mg OD for 8 weeks	15 or 30 mg OD	[b]	[b]
Filgotinib PO	200 mg OD	200 mg OD	[b]	[b]
Ozanimod PO	0.92 mg OD, after a 7-day titration schedule	0.92 mg OD	[b]	[b]
Etrasimod PO	2 mg OD	2 mg OD	[b]	[b]
Tacrolimus	Start at 0.05–0.1 mg/kg BID (target level 10–15 ng/mL)	Adjust dose to target level 5–10 ng/mL and then 2–5 ng/mL	Start at 0.05–0.1 mg/kg BID (target level 10–15 ng/mL)	Adjust dose to target level 5–10 ng/mL and then 2–5 ng/mL
Cyclosporin	Continuous IV 2 mg/kg/day (up to 7 days or until response)	2.5 mg/kg BID	Continuous IV 2 mg/kg/day (up to 7 days or until response)	2.5 mg/kg BID

Abbreviations: BID, twice daily; BSA, body surface area; IV, intravenous; OD, once daily; PO, oral; SC, subcutaneous.

[a]Most UC cases will require a higher dose of 10 mg/kg; see practice point and text.

[b]Lower dosing regimen may be required for younger children, but the exact dosing is yet to be determined.

[c]Shortening of interval to every 4 weeks may be attempted in children who have partial response.

7.1.3 | Comparative effectiveness of anti-TNFs

Studies that directly compare the anti-TNF agents are not available. Five adult-based network meta-analysis of RCTs, two administrative studies and one real life cohort, compared infliximab with adalimumab in UC, mostly reporting higher success rate with infliximab and the minority similar effectiveness.[222,238–245] Data supporting a switch from infliximab to adalimumab are limited.[246,247] Nevertheless, in case of infliximab immunogenic failure, a switch to adalimumab can be considered.

7.1.4 | Safety

Safety concerns with anti-TNF include acute infusion reactions, delayed hypersensitivity reactions (beyond 4 h and up to 14 days), infections, and a potential risk of skin cancer; evidence to date does not indicate that anti-TNF is associated with lymphoma if prescribed as monotherapy, but a recent study challenged this concept.[248] Psoriasiform skin reactions are adverse class effects of anti-TNF, but are usually mild and controllable with topical therapy; unresponsive cases may require referral to dermatology or addition of systemic therapy, and rarely cessation of anti-TNF therapy is needed.[249] Other very rare adverse events, such as demyelination and optic neuritis, have been reported.[250] There is no clear evidence that premedication with any drug prevents the development of acute infusion reaction[251,252]; however, treatment and prevention of infusion reactions are reasonable in some cases, and could avert the need for stopping anti-TNFs.[253,254]

Required infectious screening before initiation of anti-TNF treatment includes testing for HBV, HCV, HIV, VZV and tuberculosis according to local prevalence and national recommendations. A systematic review of 49 RCTs of >14,000 biologics-treated patients concluded that their use has a modest risk of any infection (OR: 1.19, 95% CI: 1.1–1.29) and moderate risk of opportunistic infections (OR: 1.90, 1.21–3.01).[253] In another study, the estimated risk of severe infections with anti-TNF has been 2%.[255] Concomitant immunosuppressants, particularly corticosteroids, are an additional risk for opportunistic and other infections. Surprisingly, a meta-analysis[40] found a reduced risk of serious infections (OR: 0.56, 0.35–0.9) and no increased risk of malignancies (OR: 0.9, 0.54–1.5), but for the latter, data were insufficient in terms of follow-up period. Studies report conflicting results regarding the risk of anti-TNF and the risk for melanoma and non-melanoma skin cancer.[256,257]

DEVELOP is a prospective post-marketing industry-initiated safety registry for paediatric IBD, which includes patients exposed and never exposed to infliximab.[258] In 5766 patients (29% UC; 24,543 patient years follow-up; median 4.5 years per patient follow-up), there were 15 malignancy events (13 exposed to thiopurines [10 with infliximab; 3 thiopurine only]; 1 only to infliximab; 1 to neither biologics nor thiopurines). Comparison with rates from the SEER database of healthy controls indicated a SIR for neoplasia of 2.43 (95% CI: 1.29–4.15) for thiopurine exposure (with or without biologic exposure), but no significant increase in neoplasia with infliximab exposure in the absence of thiopurine exposure (SIR: 1.49, 95% CI: 0.04–8.28). Five children in total experienced HLH, four with primary EBV infection, one with CMV infection, and all during thiopurine monotherapy.

7.2 | Therapeutic Drug Monitoring (TDM) of anti-TNFs

7.2.1 | Recommendations

1. Proactive TDM is recommended for both infliximab and adalimumab, particularly at the end of induction (before the 4th infliximab infusion and after 3 adalimumab injections) [EL4] (Agreement 100%).
2. Reactive TDM testing is recommended in all children with UC who experience loss of response to infliximab or adalimumab (including elevated faecal calprotectin) [EL3] (Agreement 100%).

7.2.2 | Practice points

1. Indications for more frequent TDM (e.g., during early induction and throughout maintenance) include conditions with increased infliximab clearance: body weight <30 kg, low serum albumin, high inflammatory burden and high BMI (Agreement 100%).
2. To achieve endoscopic healing in UC, target infliximab TCs at Weeks 2, 6 and 14 at approximately ≥25, ≥15 and ≥5 mcg/mL, respectively (i.e., before the 2nd, 3rd and 4th infusion, respectively). Levels >8 mcg/mL are often needed to achieve endoscopic healing. See Supporting Information S5: Table S6 for infliximab target drug levels (Agreement 100%).
3. Target adalimumab TCs are less well established. A concentration ≥7.5 mcg/mL from Week 6 onwards is associated with clinical remission, but levels >12 mcg/mL are often required to achieve endoscopic healing (Agreement 100%).

A retrospective cohort study from Canada among 125 children with UC showed better remission rates after an intensified infliximab induction scheme.[226]

Typically, higher drug concentrations are required during the induction phase as compared to the maintenance phase, for children who weigh <40 kg, and especially <30 kg,[259] and for endoscopic remission compared with clinical remission. The Week 6 TC required for endoscopic remission at 6 months is >15 µg/mL (see Supporting Information S5: Table S6).

Reactive TDM is used in patients who have not achieved remission or lost response (either clinically or by using biomarkers) during the maintenance stage. In these scenarios, it is advised to measure the infliximab concentration before the next drug administration (trough). *Proactive TDM* involves measuring infliximab concentrations when patients are in remission, especially at protocolised time points (e.g., post-induction and after a fixed time period on therapy). While TDM is helpful, it is not available in all countries. Dose adaptations are then aimed at achieving the target drug concentration. When the infliximab concentration is below the target range, a dose increase or shortening of the infusion interval is warranted. For infliximab, a 25% reduction of the dosing interval is generally as effective as a dose increase to 10 mg/kg.[260]

Proactive TDM provides added value in patients at risk for drug underexposure, as defined above, who would require higher drug doses. Obesity may also increase drug clearance, possibly related to greater proteolytic capacity, infliximab distribution in adipose tissue, and pro-inflammatory effects of mesenteric fat.[261,262] Therefore, obese patients may also benefit from proactive TDM.

For patients on adalimumab therapy, the TC required for endoscopic remission is at least 7.5 µg/mL and in non-responders >12 µg/mL,[263] which can be measured 4–13 days after any injection.[264,265] Figure 4 shows a treatment algorithm for tailoring infliximab therapy based on drug concentrations and can be used in both proactive and reactive TDM.

7.3 | Additional biologics and small molecules

7.3.1 | Recommendations

1. Vedolizumab could be considered in chronically active or corticosteroid-dependent patients as second-line biologic therapy in cases of anti-TNF failures [EL4, adults EL2] (Agreement 100%).
2. Anti-p40 (IL12/23; e.g., ustekinumab), anti-p19 (IL23; e.g., risankizumab, mirikizumab, guselkumab), Janus kinase (JAK) inhibitors (e.g., tofacitinib, upadacitinib, filgotinib), golimumab and sphingosine-1-phosphate (S1P) receptor agonists (e.g., Ozanimod, Etrasimod) may be also considered following failure of approved anti-TNF [EL4, adults EL2] (Agreement 100%).

7.3.2 | Practice points

1. A combination of two biologic agents or a biologic agent with small molecules as dual-targeted therapy (DTT) may be a therapeutic option in highly refractory UC. Since the safety of this strategy is not established, it should only be practiced in experienced centres after standard treatments have been exhausted. The potential efficacy should be weighed against the risk of possible serious adverse events (Agreement 96%).

7.3.3 | Vedolizumab

In the GEMINI-1 trial exploring vedolizumab in adult patients with UC,[266] 47% of the patients responded to two-dose induction (300 mg per dose) by Week 6. The 52-week remission rates among Week 6 responders were 42% (q8 weeks interval) and 45% (q4 weeks interval). Increased dosing frequency to every 4 weeks was beneficial in those losing response to 8-weekly dosing.[267] There is no evidence that adding IMMs to vedolizumab is superior to monotherapy.[268,269] In a meta-analysis,[270] bio-naïvety was associated with a higher probability of clinical remission at Week 52 in UC (RR = 1.32), with 40% and 64% bio-naïve patients achieved clinical remission at Weeks 14 and 52, respectively, but the bio-naïve patients had milder disease severity and shorter disease duration at baseline then bio-experienced. The largest paediatric cohort of vedolizumab is the VEDOKIDS study,[271,272] a multicentre, prospective study ($N = 68$ UC and $N = 9$ IBD-U, one-third biologic-naïve). The optimal drug concentration associated with corticosteroid-free clinical remission was 7 µg/mL at Week 14, corresponding to a dose of 200 mg/m^2 BSA or 10 mg/kg (Supporting Information S5: Table S6). Nonserious adverse events were reported in 23% of the patients; the most common were headache, myalgia and fever. Several retrospective paediatric cohorts in UC[269,273,274] reported a clinical remission rate of 37%–61% at Week 14 and 40% at Week 52. Anti-TNF-naïve patients present higher remission rates compared to anti-TNF-exposed patients yet again, but the baseline characterises of the bio-naïve patients were significantly different with milder disease and shorter duration.[268] In all these cohorts, adverse effects were uncommon and mild.

7.3.4 | Comparative effectiveness of anti-TNFs and vedolizumab

It remains uncertain whether vedolizumab is superior to anti-TNF in UC or vice versa. In adults, the VARSITY RCT demonstrated higher rates of clinical and endoscopic remission with vedolizumab over adalimumab

monotherapy, but not of corticosteroid-free remission.[275] Even ignoring the higher corticosteroid use in the vedolizumab arm and the fact that this study did not allow dose adjustment, which may be more important for adalimumab, the effect size of clinical remission was modest, with a number needed to treat of 11.4. Regardless, as aforementioned, infliximab may be more effective than adalimumab in UC. Indeed, *post hoc* analyses of three RCTs reported higher rates of corticosteroid-free remission and endoscopic remission in infliximab-treated patients compared with vedolizumab-treated patients.[248] Three network meta-analyses[238–240] compared the outcomes of anti-TNFs and vedolizumab in different RCTs of adult UC patients showing conflicting results. Almost all aforementioned trials did not stratify monotherapy from combo therapy. Addressing this gap, a recent nationwide study from the epi-IIRN included 15,111 adults and children with UC, of whom 2322 (15%) received biologics and reported that when prescribed as monotherapy, vedolizumab had comparable durability as infliximab and adalimumab, but the durability of infliximab was superior when prescribed with an IMM, which was not the case with adalimumab.[63] Impact of cost of these therapeutic options also needs to be considered.

7.3.5 | Ustekinumab

The UNIFI trial explored ustekinumab in adult patients with UC, achieving clinical remission in 15% and 44% (of responders at Week 8) at Weeks 8 and 44, respectively.[276] A significant symptomatic benefit of the therapy was also observed as early as Week 2.[277] The main adverse events were nasopharyngitis, UC exacerbation and upper respiratory tract infection.

In the largest paediatric cohort to date from the Porto group of ESPGHAN ($N = 58$), corticosteroids-free clinical remission was observed in 45%, 55% and 63% at 16, 26 and 52 weeks, respectively.[278] Another study of the Canadian Children IBD Network[279] reported a corticosteroid-free remission rate of 44% at Week 52 among 25 children with UC. A multicentre study from the paediatric GETAID ($N = 35$) reported improvement in the PUCAI score by 3 months of treatment.[280] The pharmacokinetic and safety profiles of ustekinumab in the paediatric population were generally consistent with those observed in adults, as was demonstrated in the UNISTAR paediatric trial of ustekinumab in CD.[281] These results suggest, however, that a higher per/kg dosing may be required for patients <40 kg.

While other antibodies directed to the p19 subunit of IL-23, such as mirikizumab, risankizumab and guselkumab, showed promising efficacy in achieving clinical and endoscopic outcomes in adults with UC,[282–284] there are currently no data regarding the efficacy and safety of these agents in paediatric patients.

7.3.6 | Golimumab

A third anti-TNF agent, golimumab, which is not approved for use in paediatrics, has been studied in paediatric UC in an open-label phase 2 pharmacokinetic study of 35 children with moderate-to-severe disease,[285,286] following two placebo-controlled studies in adults, the PURSUIT-SC for induction and PURSUIT-M for maintenance.[287] Weeks 0 and 2 doses in the paediatric trial were given subcutaneously, 90 and 45 mg/m^2, respectively, for children weighing <45 kg, and 200 mg, followed by 100 mg for those ≥45 kg. Maintenance doses of 45 mg/m^2 if weight <45 kg and 100 mg if weight ≥45 kg were given every 4 weeks. Among Week 6 responders (60%) who continued to receive q4w golimumab, 57% were in clinical remission at Week 14. Complete endoscopic healing at Week 6 was achieved in 23%. While the PK data of the entire paediatric cohort were comparable with those reported in the adult trials, drug levels in the subgroup of children weighing <45 kg were numerically lower than those ≥45 kg. This likely stems from the underdosing of the former group as the equivalent dosing of 200 mg in adults and adolescents would translate to 115 mg/m^2 in BSA (considering 200 mg/1.73 m^2) followed by 60 mg/m^2 for maintenance. In a long-term extension follow-up, 50% of initial responders continued clinical benefit through 2 years.[288]

7.3.7 | Small molecules

In the OCTAVE trials,[289] 19% and 17% of the patients in the tofacitinib group achieved remission at 8 weeks. A remission rate of 34% was observed among the patients in the 5-mg tofacitinib group and 41% in the 10-mg tofacitinib group after 52 weeks of therapy.[289] The main adverse events reported were non-melanoma skin cancer, cardiovascular events and hyperlipidaemia. The long-term data at 36 months revealed that 50% of patients were in remission, and 55% had endoscopic improvement.[290] Higher dose was associated with an increased frequency of adverse events.[291] A meta-analysis of real-world adult data ($N = 830$) showed a pooled clinical remission rate of 37% (26%–45%) at 8 weeks.[292]

In the largest paediatric cohort (retrospective, $N = 78$, all with previous biologic failure), 19% achieved corticosteroid-free clinical remission at Week 8.[293] The colectomy rate was 25% by Week 24. Adverse events included infections (such as herpes zoster, herpes simplex-2 cheilitis and septic arthritis), pancreatitis and abnormal blood test results (anaemia, elevated hepatic transaminases and hypercholesterolaemia). Therefore, administering the recombinant shingles vaccine and monitoring cholesterol are suggested. Ryan et al.[294] reported on a real-world experience of tofacitinib

therapy in 15 children with UC, 10 received combination therapy with biologic agents. A significant reduction in PUCAI by Week 16 was observed, and eight patients achieved clinical remission. One patient developed zoster and another herpangina. In another series of 21 children (18 with UC or IBD-U), 33% were in corticosteroid-free remission under tofacitinib at Week 12.[295] One patient developed an intra-abdominal abscess.

In a real-world comparison, no difference in corticosteroid-free remission between tofacitinib and vedolizumab was noted in patients with UC who have failed an anti-TNF agent.[296] Endoscopic improvement and histological healing at Week 16 were higher, however, in the tofacitinib group.

Upadacitinib is an oral JAK inhibitor with increased selectivity for JAK1.[297–299] In a case series of 20 adolescents with IBD treated with upadacitinib, corticosteroid-free remission rate at Week 12 was 75%, and 80% with CRP normalisation.[89] A multicentre paediatric study from the Porto IBD Group evaluated the effectiveness and safety of upadacitinib in 100 children and adolescents with refractory UC and IBD-U. At the end of the 8-week induction period, clinical response, clinical remission and corticosteroid-free clinical remission were observed in 84%, 62% and 56% of the children, respectively. Combined corticosteroid-free clinical remission and faecal calprotectin <150 mcg/g was reported in 18/46 (39%) children at 8 weeks. Adverse events were recorded in 37 children; the most frequent were hyperlipidaemia ($N = 13$), acne ($N = 12$) and infections ($N = 10$, 5 of whom with herpes viruses).[300]

Ozanimod, a selective S1P receptor modulator, was more effective than placebo as induction and maintenance therapy in adult patients with moderately to severely active UC.[301] There are no data regarding the use of Ozanimod in paediatric UC. Etrasimod, another S1P modulator, has been licenced by the European Medicines Agency (EMA) for use in UC in children aged 16 and over after inclusion of a small number in the initial clinical studies. The ELEVATE UC programme demonstrated superiority of Etrasimod over placebo at the end of induction (Week 12) and Week 52.[302]

7.3.8 | Dual Targeted Therapy (DTT)

A combination of biologic agents or a biologic agent with small molecules as DTT may be a possible therapeutic option for refractory IBD.[303] While DTT may exhibit high rates of clinical and biomarker remission, the rates of endoscopic remission were low. Retrospective reports offer some support for this option,[304] and a recent adult RCT, combining guselkumab and golimumab, did show benefit to initiating two biologic therapies in UC,[305] but more studies on the utility of DTT are required.

Yerushalmy-Feler et al.[306] reported on 27 children with UC, treated with DTT, the most frequent of which was anti-TNF and vedolizumab. Clinical remission was observed in 35% and 63% of the children at 3 and 12 months, respectively. Normalisation of CRP and a decrease in faecal calprotectin to <250 µg/g were achieved in most patients. Eight serious adverse events were reported, including skin abscess and deep vein thrombosis. While DTT may be effective in children with highly refractory IBD, efficacy should be weighed against the potential risk of serious adverse events and the alternative management choice of colectomy.

7.4 | Stopping biologics

Discontinuation of anti-TNF therapy in paediatric UC after reaching 'deep remission' is generally discouraged due to a high risk of relapse. On the other hand, de-escalating anti-TNF to standard dosing in patients who achieved remission after previous dose intensification (or an initial high dose), or stepping down to thiopurines or 5-ASA without anti-TNF when not previously attempted, is more frequently employed.[307,308] Approximately 30%–50% of anti-TNF de-escalated patients are likely to relapse within a year.[309] The risk of relapse is lower for patients in sustained clinical, biologic and endoscopic remission.[310] Disease monitoring following de-escalation should include regular clinical evaluation (PUCAI and TUMMY-UC) as well as objective disease assessment (i.e., CRP, haemoglobin and faecal calprotectin). Any consideration for de-escalation of anti-TNFs or other biologics must be tailored, accounting for risks and consequences of a flare and patients' preferences.

8 | OTHER THERAPIES

8.1 | Recommendations

1. Faecal microbiota transplantation (FMT) should not be routinely used in paediatric UC [EL2, adults EL1] (Agreement 100%).
2. Antibiotics should not be routinely used for induction or maintenance of remission of ambulatory paediatric UC [EL1A] (Agreement 96%).
3. In children with UC, vitamin D serum level should be monitored at least annually, and adequate supplementation is recommended to achieve a satisfactory concentration (at least >50 nmol/L) [EL3] (Agreement 100%).
4. Curcumin, indigo naturalis, saffron, myrrh, omega-3, *aloe vera* or glutamine supplementation should

not be used as a single agent for induction and maintenance of remission in children with UC. Curcumin and indigo naturalis may be considered as an adjuvant induction therapy to mesalamine in patients with mild-to-moderate UC [EL4, adults EL1] (Agreement 100%).
5. Granulocyte/monocyte apheresis (GMA) should not be routinely used in paediatric UC [EL2, adults EL2] (Agreement 100%).

8.2 | Practice points

1. FMT should only be considered in controlled research studies for children with UC who have failed conventional treatments and who can safely defer subtotal colectomy (Agreement 96%).
2. FMT may be considered in highly specialised centres in children with UC and recurrent symptoms associated with persistent (more than two episodes) toxin-positive *C. difficile* infection, despite attempts at eradication with antibiotics (Agreement 100%).
3. Intravenous immunoglobulin should not be used for induction and maintenance of remission in children with UC (Agreement 100%) (changed from recommendation to practice point).
4. The reported treatment duration of indigo naturalis (Qing Dai) is 8 weeks at a daily dosage of 0.5–2 g divided into two doses. Given a few reports of pulmonary hypertension in adults receiving long-term high doses, and the lack of long-term safety data, this treatment should be considered only as an add-on therapy and for a limited course (Agreement 96%).
5. Neither the formulation nor the dosage of curcumin is established for children but available evidence in adults suggests that it can be safely used up to 4 g/day for induction and up to 2 g/day during maintenance and as an adjuvant induction therapy to mesalamine (Agreement 96%).
6. Vitamin D treatment protocols may vary across regions and nations. Overall, recommended dosing for children with IBD and vitamin D deficiency/insufficiency (level < 50 nmol/L) is as follows: 2000–3000 IU (50–75 mcg) a day for infants and toddlers, and 3000–5000 IU (75–125 mcg) a day for children and adolescents (4–18 years), with treatment duration of 1–3 months depending on the level achieved following supplementation. An alternative is to prescribe a loading dose (50,000 IU of vitamin D3 orally once weekly for 2–3 months, or three times weekly for 1 month). A single high-dose of oral cholecalciferol (Stoss dose, 200,000–600,000 units) may also be considered. Preventative vitamin D supplementation is 600 IU (15 mcg) a day for children, adolescents and adults (Agreement 100%).

Most of the therapeutic strategies for UC currently target the immune response directly.[311–317] Nevertheless, patients are showing increasing interest in the use of complementary and alternative medicines.[315,316,318,319]

FMT:

FMT involves the transfer of faeces (or a cocktail of microorganisms or other constituents including metabolites [e.g., bile acids or bacteriophages]) to the lower gastrointestinal tract via colonoscopy or enema or the upper gastrointestinal tract via naso-jejunal tube or capsules.[315,319–321] The US Food and Drug Administration (FDA) has classified human stool as a biological agent and determined that its use in FMT therapy and research applications should be regulated to ensure patient safety.[319] Similar recommendations are also made by the EMA.[322]

FMT is currently recommended in the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines only for recurrent *C. difficile* infection treatment.[314,323] At present, the FDA recommends that only individual donors be used in RCTs,[314] while an internationally standardised faecal pool is yet to be established.[324] Choice of faecal donor and time of UC diagnosis appear to affect outcomes.[325] Donor-recipient matching is the subject of ongoing research.[326–328]

An RCT by Goyal et al.[329] included 21 children with IBD and identified clinical response post-FMT in 57% at 1 month and in 28% at 6 months. Another RCT on 25 children with UC by Pai et al.[330] showed clinical and laboratory improvement (based on PUCAI, CRP and faecal calprotectin) in 92% (11/12) in the arm treated with FMT, compared with 50% (6/12) in the placebo arm. A systematic review and meta-analysis by Hsu et al.[331] analysed 11 RCTs, identifying clinical response in 13/20 paediatric UC patients within 1 month, clinical remission in 10/20, and both clinical response and remission in 8/20. However, the low number of RCTs and the small cohorts enroled should prompt further research to increase the quality of evidence.[314,319] No studies have assessed FMT for maintenance of remission in UC,[319] but the study by Kedia et al.[332] did show a superior outcome when FMT was followed by dietary intervention.

An increase in colon microbiota diversity has been demonstrated In IBD patients undergoing successful FMT, with a tendency to a shift towards the donor profile, and variable durability depending on the FMT-regimen.[313,315,329,332] Emerging evidence supporting the role of FMT in

inducing remission in patients with active UC is promising,[325] but to date, FMT is still considered an experimental procedure and has not been approved by the FDA for the treatment of IBD.

Dietary interventions:

Dietary factors present in Western diets may reshape the microbiota.[318,333] A large, placebo-controlled study has shown no benefit of fish oil supplementation in patients with UC, while association studies have found that consumption of vegetables, fruits, fish and dietary fibre decreases the risk of CD, but not UC.[333] Exclusive enteral nutrition (EEN) is the first option to induce remission in children with mild-to-moderate luminal CD, and evidence is emerging for the benefit of solid food diets.[319,332–334]

There is evidence that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols reduces gut symptoms in quiescent IBD in adults,[335] but corresponding studies in children are lacking.

Strisciuglio et al.[336] investigated the role of Mediterranean diet (MD) in children with IBD in remission through a single-centre study that showed an inverse correlation between MD and faecal calprotectin. MD was found to be well-tolerated and to improve markers associated with a healthy microbiome in a recent RCT in quiescent adult UC.[337]

Sarbagili-Shabat et al.[333] undertook a prospective, multicentre, open-label pilot trial to evaluate the potential efficacy and feasibility of a novel UC exclusion diet (UCED) for clinical remission. The UCED diet consists of decreased protein, sulphated amino acids and saturated fatty acids while providing fibre as a substrate for short-chain fatty acids, to protect the mucus layer. The findings of this study support UCED as an effective and feasible option for the induction of remission in children with mild-to-moderate UC.[333] A blinded, randomised, controlled trial from 2022, also by Sarbagili-Shabat et al., evaluated whether adult patients with refractory UC undergoing FMT would benefit from integration of novel diets for donors and patients. While the study was stopped due to futility, the data available showed that UCED alone achieved non-significantly higher rates of clinical remission and significantly higher rates of mucosal healing than single donor FMT.[338] Surprisingly, the arm of the UCED plus FMT was similar to FMT alone. More data are needed to understand the effectiveness of UCED in UC.

In summary, diets appear to have the potential to affect disease course and may be used as treatment in UC in the future, however the evidence available at present is insufficient to make any firm recommendations. Nevertheless, a healthy diet avoiding potentially harmful foods and individual triggers should be encouraged.[339]

Antibiotics and prebiotics:

While evidence from high-quality RCTs supports antibiotic therapy as an effective and safe option for UC, no evidence-based recommendations exist regarding the antibiotic of choice, dose or duration of treatment.[340] Current adult guidelines recommend the use of antibiotics only if a risk of translocation or infection is considered, or immediately before surgery, in patients refractory to conventional therapies,[9] as also discussed in the ASC paper.[15] The use of broad-spectrum antibiotics may aggravate dysbiosis, and increase the risk of *C. difficile* infection and the risk of bacterial resistance to antibiotics in society.[340] Use of vancomycin in PSC-UC is discussed below.

Prebiotics studied in IBD include mostly classes of oligosaccharides and inulin. The use of psyllium husk has been shown to alleviate gastrointestinal symptoms in patients with UC in remission. Moreover, the use of oligofructose-enriched inulin combined with 5-ASA was well tolerated, and resulted in a significantly earlier decrease in faecal calprotectin.

Studies on the use of germinated barley food products, which are mainly composed of dietary fibre and glutamine-rich protein, have shown their effectiveness in reducing clinical activity in patients with mild-to-moderate UC and maintaining remission.[341,342] Recently, Armstrong et al.[343] demonstrated that some dietary fibres have detrimental effects in select patients with active IBD who lack fermentative microbe activities.

Probiotics/synbiotics are not discussed in these guidelines due to limited and conflicting evidence and have been reviewed elsewhere.[344]

Natural and herbal products:

Studies have shown that vitamin D level is negatively correlated with the risk of UC.[345] While the evidence on a correlation between an optimised vitamin D level and IBD-related outcomes is limited, a satisfactory vitamin D level of >50 ng/L should be aimed for in each child to maximise bone health, general health and growth potential.

Curcumin, a natural phenol found in the large-leafed Indian herb turmeric (*Curcuma longa*), is a lipophilic substance with anti-inflammatory properties and low and variable absorption in the gastrointestinal tract.[346] Its

mechanism of action involves the modulation of various cell signalling pathways, producing anti-inflammatory, antitumour, antioxidant and immunomodulatory effects.[317] Studies on its potential benefits in treating patients with UC are limited. Nevertheless, early findings from RCTs are promising and prompt further research.[347–350] While no recommendations on the use of curcumin in mild-to-moderate UC have been made by the AGA to date,[346] the FDA states that curcumin is 'generally recognized as safe' and has limited toxic effects, with a daily intake of curcumin of up to 3 mg/kg/day recommended.[317] Neither the formulation nor the dosage of curcumin is established for children, but based on adult RCTs, curcumin may be considered for induction of remission, in patients with incomplete or loss-of-response to mesalamine.[348]

Indigo naturalis is another traditional herbal remedy that has been shown in recent years to be effective in inducing remission in patients with active UC, either given alone or in combination with curcumin.[350–353] A recent systematic review by Kakdiya et al.,[354] on indigo naturalis in IBD showed a pooled clinical response rate of 0.796 (95% CI: 0.747–0.838, $I^2 = 0$), and a clinical remission rate in UC of 0.668 (0.488–0.809, $I^2 = 85.2\%$), suggesting its effectiveness. Except for one reversible pulmonary arterial hypertension case, most reported adverse effects were mild.[354] Moreover, an adult RCT found 8 weeks of indigo naturalis (0.5–2 g per day) to be effective in inducing a clinical response in patients with UC, with no serious adverse events observed, only 10 patients with mild liver dysfunction.[352]

GMA:

Apheresis aims to reduce the activated cells and the associated circulating cytokines implicated in chronic colonic inflammation. The ADAPT study prospectively investigated the efficacy of weekly GMA in 25 paediatric patients with moderately active UC. Significant improvement (based on a decrease in PUCAI score at Week 12) was recorded in 9 out of 20 patients (45%) and moderate improvement in 5 (25%).[355] Rolandsdotter et al.[356] investigated the effect of GMA as induction treatment for new-onset IBD colitis, in combination with 5-ASA. Clinical remission at 12–16 weeks was observed in 8/12 and endoscopic healing in 9/12, while 2 patients achieved histological healing.

The only randomised, double-blind, sham-controlled trial evaluating the efficacy of GMA was performed by Sands et al.[357] on 168 adults with CD and concomitant immunosuppressive treatment, with negative findings. GMA has a good safety profile, especially in difficult-to-treat and paediatric settings.[358] GMA also requires central venous access but may still be considered in children with UC who do not respond or lose response to conventional treatments, but more studies are needed before formal recommendations can be made.

9 | IBD-U

9.1 | Recommendations

1. Treatment of IBD-U patients should broadly follow that of UC patients of a similar disease severity [EL4, adult EL4] (Agreement 100%).

9.2 | Practice points

1. A diagnosis of IBD-U should only be made after a complete assessment, including ileocolonoscopy, gastroscopy and small bowel imaging (Agreement 100%).
2. A lower threshold for disease reassessment should be adopted in patients with IBD-U before treatment change (Agreement 100%).
3. Although not validated for this indication, it is reasonable to use the PUCAI score to assess disease activity also in IBD-U, given the similarity of IBD-U, clinically, to UC (Agreement 100%).
4. A multi-item algorithm should be used to standardise the diagnosis of IBD-U (Supporting Information S3: Figure S2; Supporting Information S5: Table S7) (Agreement 100%).
5. While ASCA+/ANCA− profile is more suggestive of CD, and ASCA−/ANCA+ of UC, their diagnostic accuracy is too low to be used in isolation in the setup of IBD-U (Agreement 100%).

The rate of IBD-U diagnosis at presentation remained relatively unchanged over time and ranges between 5% and 10% in paediatric patients with IBD. The rate is higher in children compared with adults[359] and even higher in VEO-IBD.[134,360] The proportion of patients with IBD-U is reduced if a full diagnostic workup is performed.[361] In most cases, IBD-U is not a misclassification but rather a true overlap diagnosis within the spectrum of phenotypes between UC and Crohn's colitis.[16] Indeed, in adult studies, more than half of patients with IBD-U diagnosis at presentation remain with the diagnosis after 5 years of follow-up, whereas only one in four patients is re-classified, mainly to UC.[362] Paediatric data vary: in a sub-analysis of the North American RISK cohort,[363] among 136 children initially diagnosed as IBD-U, 26% were reclassified as UC and 14% as CD within 2 years of diagnosis. The molecular and serological features of IBD-U at the end of follow-up were very similar to UC and very different from CD. In a recent large paediatric cohort based on the

ImproveCareNow multi-centre international registry, 44% of patients with IBD-U changed their classification within the first four visits, with a similar rate of CD and UC reclassification.[364] However, longer follow-up impacts rates of reclassification as shown in a Scottish cohort of 102 prospectively followed children diagnosed with IBD-U, where 60% reclassifies when followed for up to 20 years (equally to CD and UC). Interestingly, those who remained IBD-U had a more benign course (77% 1–5-year remission rate vs. 28% with reclassification), likely also reflecting a need for more investigation, leading to reclassification, with active symptoms.[365]

The PIBD-Classes criteria that were validated on a large data set of 749 patients with colonic IBD utilise a diagnostic algorithm of 23 features to differentiate between patients with UC, atypical UC, IBDU, Crohn's colitis and ileal/ileocolonic CD (Supporting Information S5: Table S7).[16] While this classification was somewhat challenged by another study, showing 81% concordance between pre-colectomy PIBD-classes-based diagnosis and post-colectomy pathology-based diagnosis (Fleiss kappa 0.48),[366] defining IBD-U is more complex. Conceptually, IBD-U is not a misclassification between CD and UC but a true overlap syndrome on the range between the two diseases. Therefore, the diagnosis of IBD-U, just like the diagnosis of CD or UC, cannot be based solely on colonic pathology; IBD-U is established based on a combination of clinical, laboratory, serological, radiographic and endoscopic (upper and lower tract) features.

In most investigator-initiated paediatric studies, patients with IBD-U are cropped together with patients with UC, preventing accurate evaluation of long-term IBD-U outcomes; they are usually assigned as an exclusion criterion in most industry-designed PIBD studies. In a cohort of 537 children with colonic IBD, including 260 IBD-U,[367] therapeutic regimens for IBD-U and UC were broadly similar, with the exception of lower usage of corticosteroids in IBD-U. IBD-U was more likely to be mild at follow-up, with lower rates of surgery than in patients with UC and CD. Dietary therapy as typically used in CD (EEN or Crohn's Exclusion Diet with Partial Enteral Nutrition) may have adjuvant benefit in a subgroup of patients (IBD-U favouring CD), given that some of this group of IBD-U may later be reclassified to CD.[367]

The natural history of IBD-U following colectomy is controversial. In adult patients with IBD-U who underwent colectomy with ileal pouch anal-anastomosis (IPAA), 22% were diagnosed with CD at a median of 37 months, whereas the sole clinical predictor for the development of CD after IPAA was younger age at disease onset.[368] Nevertheless, another study demonstrated similar postoperative reclassification to CD between patients with a preoperative diagnosis of either UC or IBD-U.[369]

10 | PREVENTION AND TREATMENT OF ANAEMIA

10.1 | Recommendations

1. Regular monitoring for iron deficiency anaemia (IDA) and iron deficiency (ID) is recommended every 6–12 months and following a treatment course in all UC patients (Figure 5) [EL3, adults EL3] (Agreement 100%).
2. Oral iron (OI) is recommended for treatment of IDA except if anaemia is moderate-to-severe, there is significant disease activity, or there is intolerance to two or more OI supplements; intravenous iron (IVI) is preferred in these situations (Figure 6) [EL2, adults EL1] (Agreement 100%).

10.2 | Practice points

1. Given the complexity in distinguishing IDA from anaemia of chronic disease, in patients with micro- or normocytic anaemia without involvement of other blood cell lines, an iron trial (usually given intravenously) should be considered in parallel with UC treatment/re-evaluation in cases of ongoing inflammation. Non-anaemic ID should be supplemented in the same way as IDA (Agreement 100%).
2. OI failure is defined as a limited increase in haemoglobin with iron therapy (<1 g/dL within 2 weeks or 2 g/dL within 4 weeks). OI intolerance is defined as the inability to tolerate at least two different OI formulations. A switch to IVI should be considered in both situations (Agreement 100%).
3. OI should be administered as a single daily dose or on alternate/days (to reduce adverse events and improve absorption), usually for at least 12 weeks. Preparation choice should be guided by patients' preference, gastrointestinal tolerability and local availability (Agreement 100%).
4. IVI preparations should be chosen according to local availability/licence and cognisant of the side effect profile, including the risk of allergic reactions and hypophosphatemia (Agreement 96%).
5. In severe anaemia, IVI should be considered as first-line treatment, with RBC transfusion reserved for acute cases with a rapid drop in haemoglobin values (<7–8 gr/dL) and/or in clinically unstable patients (Agreement 100%).

Anaemia is the most common systemic complication in paediatric IBD, with a prevalence at diagnosis between 45% and 81% in paediatric UC.[370–376] Although anaemia is associated with disease course, underlying disease activity,[371,373,377–379] and patients' QoL,[380–382] it is still frequently under-recognised and under-treated.[383,384]

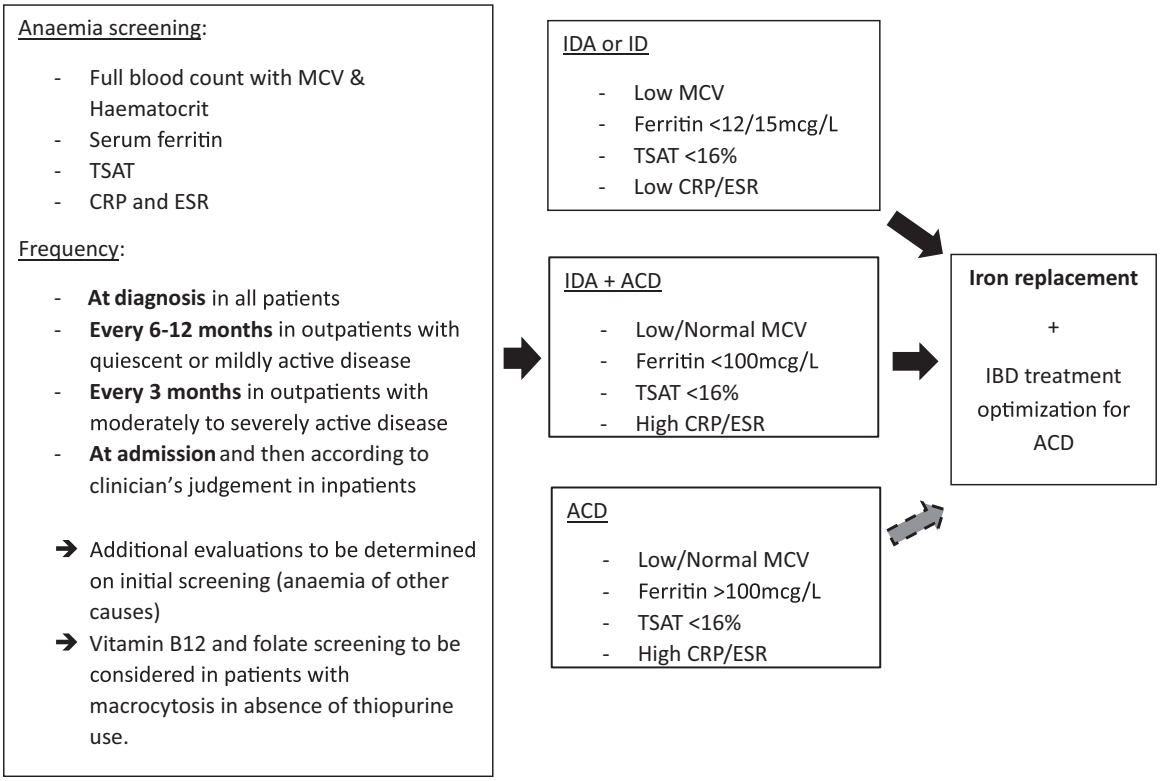

FIGURE 5 Iron deficiency and anaemia screening in paediatric UC. Anaemia screening tools mainly evaluate iron stores and inflammation, although inflammation impact on routine iron deficiency (ID) markers poses significant challenges in distinguishing IDA from ACD in clinical practice. Other blood markers of ID, serum soluble transferrin receptor (sTfR) and sTfR/log ferritin ratio, have been recently demonstrated to outperform routine markers, but a lack of standardisation, costs and availability limit their clinical use currently. ACD, anaemia of chronic diseases; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IDA, iron deficiency anaemia; MCV, mean corpuscular volume; TSAT, transferrin saturation;

Anaemia is defined as a reduced blood haemoglobin concentration with established World Health Organization (WHO) reference ranges that vary according to age, sex and ethnicity.[385,386] Its etiopathogenesis is multifactorial, with IDA as the leading cause.[370,387–389] Together with impaired iron absorption and increased blood loss, inflammation plays a major role in ID.[390] Hepcidin (an acute phase peptide) regulates iron homoeostasis via ferroportin-1 and, when increased, drives iron accumulation and impaired absorption.[391,392] Hepcidin is directly associated with disease activity in IBD and inversely related to iron absorption/availability.[377,379]

Iron treatment aims to normalise haemoglobin, replenish iron stores and improve patients' QoL. Multiple meta-analyses, including a Cochrane review, demonstrate superiority of IVI over OI in treating IDA in adult IBD with faster response, improved tolerance and lower treatment discontinuation.[393–396] Multiple studies (adult and paediatric) demonstrate that CRP and serum hepcidin are inversely related to haemoglobin response to OI.[377,379] A systematic review of adult IBD studies has concluded that IVI could be of advantage compared to OI in patients with severe anaemia or with active IBD.[388] Studies comparing and/or associating IVI and OI in paediatric IBD, have shown encouraging but limited data on OI in IDA treatment even in patients with active disease (Figure 6).[397,398] Therefore, iron treatment choice depends on anaemia severity, disease activity, patient's preferences and drug availability.

OI use has well-documented gastrointestinal side effects with high discontinuation rates.[395,399,400] Although shifts in faecal metabolome and gut microbiota have been demonstrated with OI, no significant changes in faecal calprotectin have been identified.[377,401] OI supplementations historically contain the ferrous form (Fe^{2+}), with newer ferric formulations (Fe^{3+}) potentially improving gastrointestinal tolerance.[402–405] The optimal dose and administration scheme for OI are still unclear. A higher single-dose alternate or every 3-day regimen optimised OI absorption, lowering serum hepcidin levels in iron-depleted women.[406–409] A systematic review of alternate-day dosing was equally effective on haemoglobin than daily OI with less adverse events.[410] In a general paediatric OI meta-analysis, intermittent iron supplementation (1–2 days/week) was similarly effective in reducing anaemia compared to frequent supplementation (3–7 days/week).[411]

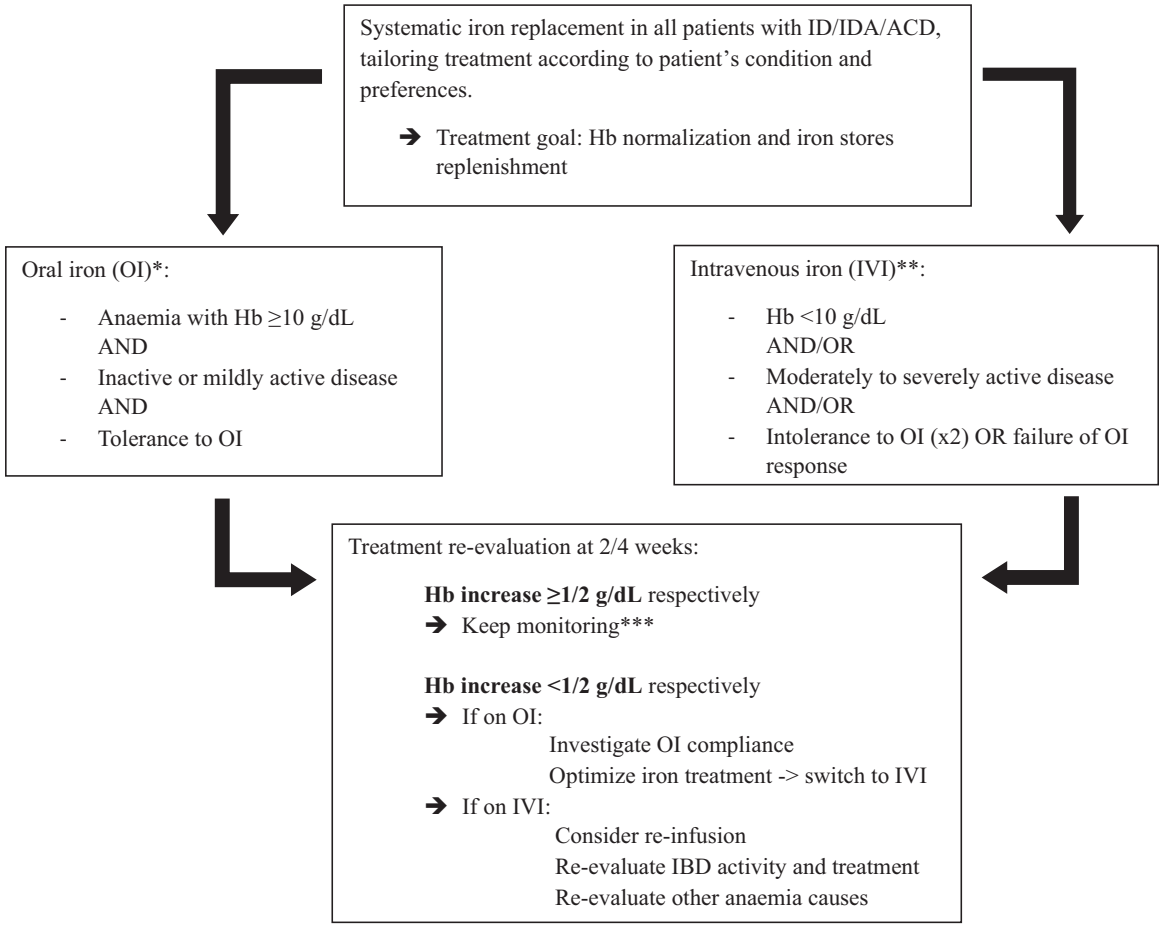

FIGURE 6 Iron deficiency and anaemia management in paediatric ulcerative colitis. *OI should be taken on an empty stomach in a mildly acidic medium, such as ascorbic acid, to increase absorption further. **Intravenous iron (IVI) should be considered as the first choice in severe anaemia. Blood transfusion (BT) should be evaluated in acute cases with rapid Hb drop and/or clinically unstable. IVI should be administered subsequently to BT to replenish iron storages. ***Treatment monitoring should include phosphate levels in patients who have received IVI formulations at risk for causing hypophosphatemia. ACD, anaemia of chronic diseases; Hb, haemoglobin; ID, iron deficiency; IDA, iron deficiency anaemia; OI, oral iron.

Several IVI preparations are available in paediatric and adult studies.[412–414] Dosing and administration scheme should follow the manufacturer's instructions, with newer third-generation IVI formulations allowing fewer and shorter infusions.[387,412] Retrospective IVI studies have shown comparable efficacy and safety, with more evidence available in paediatrics for iron sucrose and ferric carboxymaltose.[415–424] A Cochrane review in adult IBD suggested that ferric carboxymaltose was superior to iron sucrose with moderate certainty.[396,425] Hypersensitivity reactions are usually mild and manageable, with severe cases rare (0.2%–1.7%).[412,426,427] Hypophosphatemia is an increasingly recognised IVI side effect, modulated via fibroblast growth factor-23,[428–433] potentially determining long-term alterations in bone metabolism.[412,433,434] Ferric carboxymaltose has the greatest risk for both severe and persistent hypophosphatemia,[435,436] therefore clinicians should be aware of the presenting hypophosphatemia features and monitor accordingly.[437–439]

In cases of inadequate response to IVI, IBD re-evaluation and a broader anaemia assessment should be considered (e.g., vitamin B12/folate deficiency) and treated accordingly.[440,441] IVI efficacy and safety profile has allowed a progressive reduction in RBC transfusions.[384,442] Due to blood shortages and associated risks,[443,444] RBC transfusions should be reserved for hemodynamically unstable severe acute anaemias, rather than being solely haemoglobin-driven.[387]

11 | EIMS

11.1 | Recommendations

1. Treatment of peripheral arthritis should be directed at inducing remission of the luminal disease [EL4, adult EL3]; anti-TNF should be considered as first-line treatment for moderate-to-severe peripheral arthritis with UC and

sulfasalazine for mild cases, with prompt escalation to anti-TNF if sulfasalazine fails [EL4, adults EL2] (Agreement 100%).
2. Anti-TNF is the first-line therapy of axial spondyloarthropathy associated with UC (Agreement 100%).
3. Transaminases and GGT should be monitored at diagnosis and at least every 6 months in all UC patients, to screen for PSC and autoimmune hepatitis (AIH) [EL4, adults EL4] (Agreement 100%).
4. Sustained elevation of liver enzymes in the presence of cholestasis should be investigated with serologic assessment for autoimmune sclerosing cholangitis (AISC) and ultrasound followed by magnetic resonance-cholangiopancreatography (MRCP), in addition to liver biopsy when indicated (see practice point); endoscopic retrograde cholangiopancreatography is reserved for therapeutic interventions [EL3, adults EL3] (Agreement 96%).

11.2 | Practice points

1. Treating both axial and peripheral arthritis requires close collaboration with paediatric rheumatologists (Agreement 100%).
2. The diagnosis of axial spondylo-arthritis or sacroiliitis is based on typical clinical symptoms and signs such as progressive lower back, gluteal, and thigh pain, combined with radiological abnormalities (most often seen on MRI). In these cases, anti-TNF should be the first-line therapy (Agreement 100%).
3. If required for the treatment of articular inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) may be used for a short course and at low doses to minimise the risk of aggravating intestinal inflammatory activity. Although selective cyclooxygenase-2 inhibitors are known to have fewer gastrointestinal side effects, there is no evidence that their use is safer as compared with other NSAIDs at low doses (Agreement 100%).
4. No medication has been proven to reduce the time from PSC diagnosis to liver transplant or the development of cholangiocarcinoma. The benefit of ursodeoxycholic acid (UDCA) remains questionable, and if used, doses should be preferably low (15–20 mg/kg/day). Oral vancomycin may be considered (50 mg/kg/day in three divided doses <30 kg, and 500 mg three times/day ≥30 kg) for 12 weeks, but long-term data are lacking (Agreement 100%).
5. In children with IBD and PSC with features of AIH corticosteroids and azathioprine are effective in suppressing immune-mediated hepatitis (Agreement 92%).
6. Treatment of skin lesions in paediatric IBD patients (either specific, reactive, associated or treatment-related), may require the involvement of expert paediatric dermatologists. First-line early treatment with anti-TNF, particularly infliximab, is recommended in pyoderma gangrenosum (PG) (Agreement 100%).

As literature on paediatric IBD and EIMs is scarce, we refer the reader to recent comprehensive ECCO guidelines on this topic,[445] highlighting here only pertinent points common in children. Some EIMs are associated with intestinal disease activity (i.e., erythema nodosum [EN], peripheral arthritis), whereas others occur independently (i.e., PG, uveitis, ankylosing spondylitis and PSC).[446] Paediatric registries[447–449] indicate that one or more EIMs are present at diagnosis in 6%–17% of children with UC, especially those older than 5 years, with an increase to almost 50% with disease evolution,[450] and more with extensive colitis.

Joint disease in IBD may be axial (sacro-ileitis or ankylosing spondylitis) or peripheral. Two main patterns of IBD-associated peripheral arthritis have been described. The classic type 1 arthropathy (oligoarticular asymmetric arthritis affecting less than five joints, and involving preferentially large joints) is often associated with active IBD, whereas the type 2 (polyarticular symmetric involvement affecting small joints of both hands with pain, swelling or effusion and persisting for months or years) is largely independent of IBD activity. In the first case, treatment should be directed at inducing remission of luminal disease, whereas in type 2, therapy should cover both diseases. Sulfasalazine can be considered as first-line therapy when peripheral arthritis coexists with UC, and anti-TNF could be considered second-line therapy.[451] NSAIDs are associated with gastrointestinal injury, but the link between their use and IBD flare is still debated. A recent meta-analysis did not find a consistent association between its use and risk of CD or UC exacerbation.[452] Therefore, these drugs are considered safe if prescribed for a short course and at low doses for peripheral arthritis. Axial joint disease (sacro-ileitis or ankylosing spondylitis) causes lower back pain and can be very limiting. Anti-TNF remains the first-line therapy of axial IBD-associated spondyloarthropathy.[445] As etanercept can cause paradoxical gastrointestinal inflammation, its use should be avoided.[453] Vedolizumab and ustekinumab, as well as small molecules, are not recommended in IBD-associated axial spondyloarthropathy, as the results of the available studies are still conflicting. Recent adult data support a role for JAK inhibitors in peripheral and axial spondyloarthropathy.[454]

A wide spectrum of concomitant liver diseases can be present in paediatric IBD, mostly related to autoimmune features. Classical differentiation among AIH, PSC, and AISC or PSC/AIH-overlap syndrome (with biochemical, serological and histological manifestations common to both PSC and AIH) has been recently reviewed.[22] PSC is a cholestatic disease of unknown

aetiology where chronic inflammation of bile ducts leads to progressive destruction of the biliary tree. Recently, it has been proposed that AISC represents a specific inflammatory phase of PSC, frequently manifesting earlier, most notably in younger patients.[455] Moreover, disease outcomes remain similar to those of a more classical PSC phenotype in later life. Combination of PSC and IBD, in particular UC, constitutes a well-known disease constellation. It is estimated that IBD is present in 60%–80% of adults with PSC and, conversely, PSC is diagnosed in 2%–14% of IBD patients.[456–460] Studies investigating the presence of PSC in IBD patients, irrespective of elevated liver function tests or symptoms, report the highest prevalence figures (7%–14%).[461] PSC prevalence in paediatric IBD has been described to be 1.6% at 10 years after diagnosis,[448] but higher at 3% if systematic screening tests are performed.[462] As described in adults, PSC in children is also three times more likely to occur in UC compared to CD, and associated with older age.

The IBD phenotype in patients with PSC also seems different compared to classic UC or CD. Colitis in PSC-IBD is characterised by extensive inflammatory distribution, with highest signs of active inflammation in proximal colon that decrease towards the rectum, even with rectal sparing.[463] High pancolitis rates (68%–83%) but low rates of proctitis (2%–4%) have been reported.[464–466] Backwash ileitis, endoscopic and/or histologic inflammation of distal ileum in patients with pancolitis, has been described also as one of the classical IBD phenomena in PSC.[467] PSC, that may precede IBD onset by years but also occur after colectomy, may progress to liver cirrhosis, ultimately necessitating liver transplantation. UC patients with PSC have a greater risk of malignancies such as CRC and cholangiocarcinoma (8%–30% of UC patients with long-standing PSC).[468,469] However, CRC in paediatric UC before age 12 years is extremely rare. As PSC is associated with more extensive disease, the theoretical cancer risk is higher than in limited colitis, but the clinical course is usually milder. The higher colectomy rate in these patients in older ages is mainly secondary to dysplasia and CRC. Older age at PSC diagnosis increases the risk of colonic neoplasia.[470] Targeted biopsies aimed at abnormal areas identified by newer colonoscopic techniques (chromoendoscopy, confocal endomicroscopy) are recommended.[471] The optimal follow-up method is still debatable.[472] In a multicentre report of 781 children with PSC (4277 person-years of follow-up), overall event free survival was 70% at 5 years and 53% at 10 years but PSC-IBD was associated with a favourable prognosis; cholangiocarcinoma occurred in 1%.[473] In another registry, median time to complications was similar in both paediatric and adult cohorts.[474] A recent study evaluating 82 paediatric IBD patients with sclerosing cholangitis (31% female; mean age at diagnosis 11.9 ± 2.8 years), followed up for a mean of 6.8 ± 3.3 years, suggested that children have better clinical outcomes than previously reported, particularly if diagnosed early. The authors recommend prompt assessment for PSC, including liver biopsy and biliary imaging, when liver function abnormalities are detected.[475] MRCP remains the most appropriate imaging modality for diagnosing PSC in children. A pattern of irregular bile ducts, with zones of narrowing and dilatation, is characteristic of PSC.[476]

In adults with PSC, UDCA has been largely used based on studies showing improvement of serum markers of cholestasis.[477,478] However, no significant improvement of transplant-free survival rates has been found with low (13–15 mg/kg), moderate (17–23 mg/kg) or very high (28–30 mg/kg) daily doses, when compared to placebo.[479,480] Its use at 10–15 mg/kg/day may exert protective effects in the hepatobiliary tract, but its effectiveness as monotherapy is probably not sufficient to prevent PSC progression. Conversely, very high doses (28–30 mg/kg) are potentially harmful and are generally not recommended.[481,482] Oral vancomycin also reduces and even normalises liver enzymes and GGT in different adult and paediatric studies.[483–491] The recommended dose is 50 mg/kg/day in three divided doses if weight <30 kg, and 500 mg three times/day if weight ≥30 kg and for a minimum of 12 weeks. Metronidazole has also shown some efficacy, although the higher rate of side effects makes vancomycin a preferred option.[488,491–495] However, although the aforementioned therapies improve liver enzymes, no therapy has been shown in larger prospective studies to reduce time to liver transplantation, cholangiocarcinoma or death.

IBD-associated skin diseases are among the most common EIMs, with paediatric rates ranging from 10% to 15%,[496] and their relationship with underlying intestinal disease may be either specific (metastatic CD), reactive (PG, Sweet syndrome, EN, oral lesions), associated (hidradenitis suppurativa, psoriasis) or treatment-related (TNF-α antagonist-induced skin lesions, other drug hypersensitivities, skin cancer). When these manifestations appear, consultation with a paediatric dermatology expert would be appropriate. EN is usually associated with underlying intestinal activity, although other causes should be excluded. In EN associated with IBD activity, the primary aim is control of the underlying intestinal activity. In very painful cases, a short course of oral corticosteroids can induce rapid resolution, as well as advanced therapies (TNF-α antagonists, ustekinumab or vedolizumab), whose efficacy is probably related to effective control of inflammation.[497] PG, characterised by the appearance of pustules or erythematous papules and plaques, often at a site of trauma, is the second most common reactive cutaneous EIM and is the most debilitating. PG may parallel IBD activity or run an independent course,

and even appear before IBD onset. Rapid ulceration with dermal necrosis leads to painful, deep ulcers with undermined, irregular violaceous borders and a purulent but sterile base. PG is more common in females, Black Africans, and those with a positive family history of UC. First-line early treatment with TNF-α antagonists, particularly infliximab, is recommended in the adult ECCO guidelines,[445] particularly in severe cases. Other treatments include systemic corticosteroids, ciclosporin, ustekinumab, dapsone, metronidazole and tetracyclines, although there are very scarce data in the literature in paediatric cases. Systemic corticosteroids are the first-line treatment for Sweet syndrome, with TNF-α antagonists indicated in corticosteroid-dependent or refractory cases. Regarding hidradenitis suppurativa, topical treatment or systemic treatment (antibiotics and dapsone) may be used in mild-to-moderate cases, adalimumab being recommended as first-line treatment for severe disease, with early dose intensification frequently required. Other management options include infliximab, ustekinumab or surgery.[445,498]

12 | SUPPORTIVE CARE IN UC

12.1 | Nutrition, growth and bone health

12.1.1 | Practice point

1. Bone density assessment using dual x-ray absorptiometry (DEXA) (corrected for height and age to produce age and sex-matched *z*-scores) should be considered at diagnosis, and later in the disease course in high-risk patients such as those with severe disease, prolonged malnutrition, amenorrhoea, delayed puberty and/or corticosteroid dependency (Agreement 100%).

Peak bone mass attained during adolescence is the most important determinant of lifelong skeletal health. DEXA is commonly performed in paediatric IBD patients to assess bone health and identify osteoporosis and osteopenia (bone mineral density [BMD] *Z*-score for age ≤−2 SD or between −2 and −1 SD, respectively). However, the relationship between BMD and the risk of fractures in children is not firmly established. Screening recommendations for DEXA in children with IBD do not differ from the general population and should be limited to those patients at higher risk, such as long-term use of corticosteroids.[499] A DEXA scan should also be considered in patients with malnutrition, nutritional deficiencies, growth delay, and in those with unexplained fractures. Reduced bone density is identified in up to 50% of paediatric IBD patients,[500,501] and is significantly more common in CD than in UC.[502] Severe osteopenia is only present in 3%–6% in UC.[503–505] Nutritional status seems to have a greater impact on bone mineral density than corticosteroid therapy.[506]

12.2 | Psychosocial support, adherence to therapy and transitional care

12.2.1 | Recommendations

1. Adolescents should be included in a structured transition to adult care programme, which can be adapted to the local organisation of the paediatric and adult facilities [EL4, adults EL4] (Agreement 100%).

12.2.2 | Practice points

1. Paediatric IBD centres should offer psychosocial support to screen for and address anxiety, depression and low resiliency, to improve daily functioning and self-efficacy, based on available resources (Agreement 100%).
2. Treatment adherence should be regularly evaluated by patient interviews, but also assisted by serum medication level monitoring and prescription refill rates when available (Agreement 100%).
3. Treatment adherence may be improved by a multicomponent approach, providing medication information to both patients and caregivers, using a single daily dosage when possible, and utilising electronic self-management tools (Agreement 100%).

Readiness to transition from paediatric to adult IBD care may be hampered, especially in younger patients, males and those with active IBD.[507–509] Higher resiliency and self-efficacy have been identified as predictors of transition readiness, which is also linked to improved IBD QoL.[509–511] Improving disease and medication knowledge, as well as practicing independence at appointments, can improve transition readiness.[508,512] Age of transition to adult care may be flexible and should ideally be within a multi-disciplinary structured programme, starting a minimum of 1 year before full transfer.[513,514] Providers should complete a structured medical transition template.[514] Inclusion of a transition coordinator (typically an IBD nurse), paediatric gastroenterologist and adult gastroenterologist is ideal.[513,515–517] Both in-person and electronic transition programmes have shown success.[511,518–520] The ECCO topical review on transition care in IBD discusses steps to be followed during the transition process.[513]

Several systematic reviews and large population-based studies have found higher rates (as high as 25%) of anxiety and depression, as well as lower QoL, in those with IBD compared to without, and in those

with active versus inactive IBD.[521–526] Psychosocial support should screen and address this and include supportive strategies to improve resiliency. Physical activity, specifically yoga, has been found to reduce stress levels and improve IBD symptom management in adolescents.[527]

Symptoms of anxiety, depression and poor QoL have also been associated with worse treatment adherence, as high as 90% in adolescents with IBD, and consequently increased health care burden.[528,529] Non-adherence is highest in adolescence, as well as in those taking medication more than once a day.[530] First morning void urine 5-ASA tests and serum 5-ASA metabolites can be used to assess adherence.[183,531] Combining education and behaviour modification, or utilising digital self-management tools, has shown success in improving adherence.[532,533] Adherence is associated with reduced health care costs, less treatment escalation, clinical remission and improved QoL.[105,534–536]

12.3 | Cancer surveillance in UC

12.3.1 | Recommendations

1. Children with UC aged 12 years and over with a disease duration of greater than 8 years should be considered for surveillance for CRC and dysplasia [EL4, Adults EL1] (Agreement 96%).
2. Children with UC and PSC should be considered for surveillance for CRC and dysplasia starting at age 12, regardless of disease duration [EL4, Adults EL3] (Agreement 100%).
3. When possible, surveillance for CRC and dysplasia should entail a colonoscopy using dye-based chromoendoscopy, virtual electronic chromoendoscopy or high-definition white light endoscopy completed by an experienced endoscopist, with targeted biopsies. In PSC, additional random biopsies are recommended [EL4, Adults EL4] (Agreement 100%).

12.3.2 | Practice points

1. Paediatric-onset UC is a risk factor for CRC, especially UC pancolitis. However, the absolute risk of CRC in children under the age of 18 years is low; CRC is exceptionally rare before puberty (Agreement 100%).
2. Risk factors for dysplasia or CRC in children with UC include long disease duration, VEO disease, PSC and family history (first-degree relative) of CRC (Agreement 100%).
3. In patients with PSC and UC, colonoscopy should be considered annually or every 2 years from the time of PSC diagnosis. However, surveillance could be deferred in pre-pubertal children while individualising based on risk factors (disease duration, family history, severity of the disease over time, and disease extent), since CRC is extremely rare under the age of 12 years, even in the presence of PSC (Agreement 100%).
4. Children who start CRC surveillance before the age of 18 should have surveillance intervals thereafter determined as per adult CRC surveillance guidelines (Agreement 100%).
5. Characterisation, therapeutic management and follow-up of colonic dysplasia in children with IBD should largely follow guidance outlined for the adult IBD population. However, as dysplasia is such a rare occurrence in children, cases with dysplasia should be discussed between a paediatric gastroenterologist, an expert endoscopist and a histopathologist to determine optimal management (Agreement 100%).
6. Patients with UC and PSC have a high lifetime risk of hepatobiliary malignancy, with MRCP-based surveillance shown to reduce mortality in the adult population. However, the risk of hepatobiliary cancer onset in childhood is low, with the pre-puberty risk extremely low. Currently, there is insufficient evidence to recommend routine MRCP surveillance in paediatric patients with IBD-PSC (Agreement 92%).

A recent survey of Dutch paediatric gastroenterologists demonstrated profound variability in paediatric dysplasia surveillance practice, including perceived indication, surveillance interval and endoscopic approach,[537] with 70% expressing need for clearer guidance. There is no doubt that paediatric-onset IBD is an established lifetime risk factor for CRC.[73,538,539] Meta-analysis data, from five population-based studies comprising 283,540 patient years, showed a 2.4-fold increased risk of all cancers with paediatric IBD (pRR: 2.46, 95% CI: 2.06–2.93), with particularly high risk of CRC (pRR: 20.29, 95% CI: 15.90–25.90). A Scandinavian cohort study also yielded high estimates of CRC for UC pancolitis [36.3 (95% CI: 22.8–57.8)].[73]

However, cancer associated with paediatric-onset IBD usually presents in early adulthood. A recent analysis of Danish and Finnish population registry data showed a median age of CRC diagnosis to be 26.2 years (23.1–31.1) with a median time from IBD to cancer diagnosis of 11.1 years (9.4–16.4).[538] Similarly, a Korean data set demonstrated that all but one CRC associated with IBD occurred at least 8 years after diagnosis.[540]

Disease duration, PSC and VEO-IBD may confer risk for the onset of dysplasia within childhood. A Swedish nationwide cohort study (1964–2014, $N = 346$) described 5 IBD-associated CRCs diagnosed before the age of 18,[72] with higher incidence after 10 years of follow-up, and all cases occurring after 5 years of

follow-up. A cohort of 509 patients with PSC-IBD diagnosed in childhood, with a median age of diagnosis of 13.2 years (9.3–15.6), showed a risk of dysplasia or cancer of 2.8 cases per 1000 patient years, with 5 and 10 years probability of CRC of 0.8% (95% CI: 0.3%–2.7%) and 4.8% (95% CI: 2.0%–11.1%), respectively.[541] Of the eight cases of dysplasia or CRC, four were in patients with very early-onset IBD.[541]

A summary of surveillance guidelines, adapted for the paediatric IBD population with UC or colonic CD, is outlined in Figure 7. Practical guidance on how to carry out surveillance colonoscopy in IBD is provided in the ECCO IBD and malignancies guideline, including details of the approach to characterisation and therapeutic management of dysplastic lesions.[70] However, as this is such a rare occurrence in children, we recommend that the management of all dysplasia cases be determined individually with a multidisciplinary approach.

Patients with IBD-PSC also have an increased risk of hepatobiliary malignancy from the time of PSC diagnosis,[70,542] although absolute risk is low in children.[543] In the absence of change in symptoms or biochemistry, there are no data to demonstrate that routine surveillance improves outcomes. Nevertheless, cholangiocarcinoma should be considered in PSC-UC cases with new jaundice and a cholestatic biochemical profile; this should prompt MCRP and hepatology referral. In retrospective data in adults with IBD-PSC, there is a correlation between surveillance by cross-sectional imaging and survival.[544,545] Nevertheless, there are sources of bias within this literature, including a lack of comparative data between imaging modality and surveillance interval, and in a study by Ali et al.,[544] the potential for different insurance coverage in those who underwent surveillance.

13 | MAIN MESSAGES AND DISCUSSION

Management of UC has advanced considerably with the optimisation of current treatments, some emerging therapies, and the availability of useful monitoring tools. However, these developments have somewhat added to the complexity of care, and many challenges still remain. The most acute challenge is the paucity of high-quality evidence-based data to inform these guidelines, which is why some of our statements heavily rely on adult data. There are many reasons for the lack of paediatric data, but above all is the difficult state of extreme delay in regulatory approval of medications for paediatric use (e.g., vedolizumab, not yet approved for use in children with UC, was approved for use in adults in May 2014).[546] This unacceptable reality is the driver for advocacy for regulatory change by paediatric gastroenterologists, where we endorse extrapolation of results from adult studies and a focus on paediatric-specific pharmacokinetics, dose optimisation and safety,[10–12] and eliminating the need for placebo

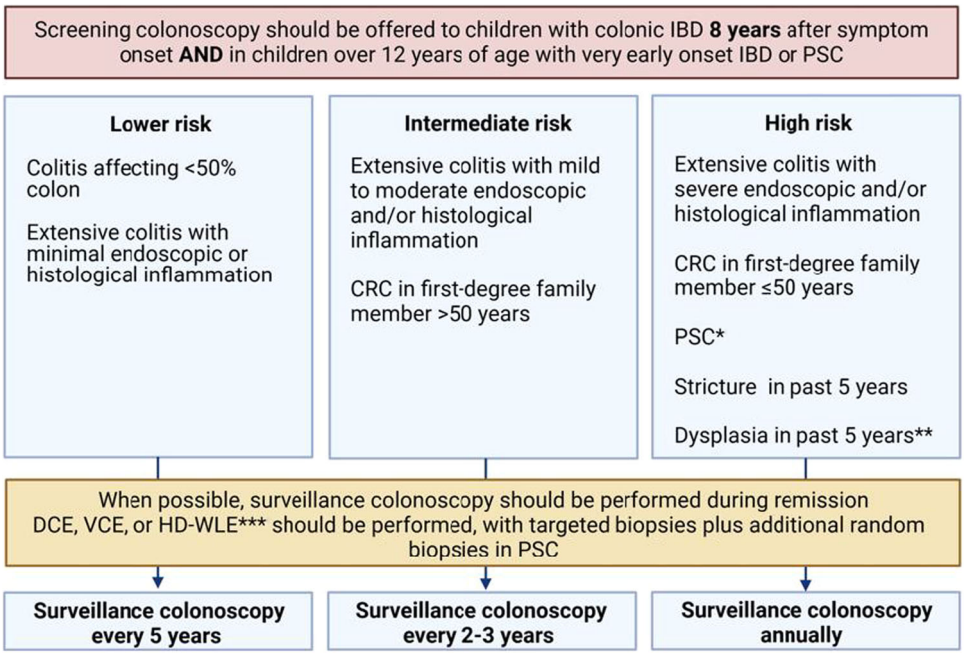

FIGURE 7 Endoscopic screening and surveillance for colorectal cancer (CRC) in children with colonic IBD. In patients who have no colonic involvement or disease limited to the rectum, no further IBD-specific surveillance is indicated. *Including post-liver transplant. **In patients who have not undergone surgery. ***Dye-based chromoendoscopy (DCE), virtual electronic chromoendoscopy (VCE), high definition white light endoscopy (HD-WLE).

arms in paediatric studies (as also suggested in the adult literature).[547,548] As a result of this disparity, together with a robust review of the available literature (as expressed in most of the recommendations), we took a more pragmatic approach and also offered *practice points* as a resource for those caring for children with UC.

It is important to reiterate some of the main messages included in these guidelines, especially those that have evolved since the previous guidelines in 2018.[13] While most patients with UC will require corticosteroids, sparing corticosteroids is an important priority, which we have attempted to address through limiting the duration of therapy and enhanced tapering. Early recognition of corticosteroid-refractory and dependent cases and advancing to another treatment are critical and offer opportunities for quick cessation of corticosteroids. Monitoring for negative impacts of corticosteroids on the HPA axis and bone health is important. Another treatment-related message is the common need for higher doses of infliximab than those recommended by adult studies.[549] We have therefore suggested starting 10 mg/kg of infliximab in most cases of UC, but also encourage dose reduction when possible. Other biologics and small molecules (not yet approved for use in children) that have emerged as options in the adult setting[550] have little support through paediatric data, but are discussed in detail.

Active and close monitoring of disease, using clinical and laboratory-based parameters, and endoscopy when needed, is essential for optimal care, as summarised in Figures 1 and 3, and very clearly articulated in the STRIDE II initiative.[26] Briefly, it is imperative to adjust the tools, intensity, and frequency of monitoring to the disease stage and status, but this treat-to-target approach demonstrates the evolution of this field and the need for guidelines to direct proactive optimisation of outcomes. Proactive management provides benefit to disease monitoring and specifically, the use of TDM is shown to optimise anti-TNF therapy and outcomes in UC.[551] The role of bowel ultrasound as an emerging, noninvasive tool (especially important in children) for assessing UC activity and response to therapy is also noteworthy.[552] Finally, for assessment, we discuss the importance of cancer surveillance for children with UC, given the devastating impacts of cancer diagnosis at a young age, despite the very low yield of these efforts. It is important to remember that disease control (including subclinical) during childhood is critical for the risk of developing cancer as a young adult.[73] This is especially true for children with PSC, where the risk for both colon cancer and cholangiocarcinoma is dramatically increased.[76]

These comprehensive guidelines attempt to cover most aspects of managing UC in children, but should not be seen as a complete, single authority, but rather a resource with analysis of the relevant literature (which does evolve over time) and a general guide for practitioners. Especially in areas where the evidence is weak, one should research the topic and consult with relevant colleagues. Local factors and resource availability could further impact the ability to apply these guidelines globally, which are written through a lens of relatively 'developed' countries. Regions that are not as well-resourced may find it difficult to implement some of the recommendations, but we hope that these guidelines could serve as a resource for advocacy aimed at advancing the well-being of children with UC by promoting health authorities to accept high standards of care. At the same time, recognising diversity in care and resources, the legal relevance of these guidelines would need to be judged based on local criteria and circumstances.

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AFFILIATIONS

[1]Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada

[2]University of Toronto, Toronto, Ontario, Canada

[3]Department of Pediatrics, Division of Pediatric Gastroenterology, University of Alberta, Edmonton, Alberta, Canada

[4]Pediatric Gastroenterology, Hepatology and Cystic Fibrosis Unit, Department of Pathophysiology and Transplantation, University of Milan – Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico di Milano, Milan, Italy

[5]Pediatric Gastroenterology, Ghent University hospital, Ghent, Belgium

[6]Department of Paediatrics, University Hospital Motol, Prague, Czech Republic

[7]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Hospital Sant Joan de Déu, Barcelona, Spain

[8]Department of Paediatric Gastroenterology, Jenny Lind Children's Hospital, Norfolk and Norwich University Hospitals, Faculty of Medicine and Health Science, University of East Anglia (UEA), Norwich, UK

[9]Department of Paediatrics, Vittore Buzzi Children's Hospital, University of Milan, Milan, Italy

[10]Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK

[11]Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb Medical School, Referral Center for Pediatric Gastroenterology and Nutrition, Zagreb, Croatia

[12]DOCHAS Group, Children's Health Ireland, University College Dublin, Dublin, Ireland

[13]Division of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands

[14]Section of Paediatrics, Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

[15]Department of Medicine Solna, Division of Clinical Epidemiology, Karolinska Institutet, Stockholm, Sweden

[16]Colorectal Surgery, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona UAB, Barcelona, Spain

[17]Department of Advanced Medical and Surgical Sciences, Universitá degli Studi della Campania "Luigi Vanvitelli", Naples, Italy

[18]Department of Paediatric Gastroenterology Hepatology and Nutrition, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[19]Department of Paediatric Gastroenterology, Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands

[20]Department of Paediatric Gastroenterology, Royal Hospital for Children and Young People, Edinburgh, Scotland, UK

[21]Schneider Children's Medical Center of Israel, Institute of Gastroenterology, Nutrition and Liver Diseases, Petah Tikva, Israel

[22]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[23]Pediatric Gastroenterology and Nutrition Unit, Centro Hospitalar Universitário São João, Porto, Portugal

[24]Shaare Zedek Medical Centre, The Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Eisenberg R&D Authority, The Hebrew University, Jerusalem, Israel

[25]Child Life and Health, Centre for Inflammation Research, University of Edinburgh, Scotland, UK

[26]Pediatric Gastroenterology Institute, "Dana-Dwek" Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[27]Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

CONFLICT OF INTEREST STATEMENT

Over the last 3 years, Eytan Wine has received consultation fees or honoraria from Janssen, AbbVie, Nestle Health Sciences, Pfizer and BioJamp. Marina Aloi, for the last 3 years, has received speaker's fees, travel support or has performed consultancy work with AbbVie, Takeda, Pfizer and Nestle. Jiri Bronsky has received honoraria/consultation fees/congress financial support from AbbVie, MSD, Nutricia, Nestlé, Sanofi, Pfizer and Vitabalans. Javier Martín di Carpi has received honoraria/consultation/congress financial support from AbbVie, Abbott, Adacyte, FAES, Ferring, Jansen, Kern Pharma, Nutricia and Nestlé. Marco Gasparetto is a member of the CICRA (Crohn's In Childhood Research Association) Advisory Board and is currently involved in pharmaceutical clinical trials sponsored by AbbVie. Hannah Gordon has received speaker fees from Janssen, Ferring, AbbVie, IBDscope, Takeda and consultancy fees from Galapagos, AbbVie, JanssenSH, and, for the last 3 years, received research funding from Janssen. Iva Hojsak received honoraria for lectures and consultation from Sandoz, Abbott, Takeda and BioGaia, and fees for lectures from Ewopharma, Hipp, Biocodex, Nestle and GM Pharma. Séamus Hussey, for the last 3 years, received research funding from Janssen. Johan Van Limbergen, for the last 3 years, received consultation fees and honoraria from Pfizer, Nestlé Health Sciences, and was involved in research studies sponsored by AbbVie, Nestlé Health Sciences, Takeda and Eli Lilly. For the last 3 years, Erasmo Miele has received grants/research support from Danone, Nesté Health, and payment/honorarium for lectures from Bioprojet and Dicofarm. For the last 3 years, Lorenzo Norsa has received consultation fees and honoraria from Nestlè, Danone, Takeda, Sanofi and Alfasigma. Ola Olén has been and is PI for several academic projects as well as national regulatory safety programmes with funding to Karolinska Institutet from Janssen, Pfizer, AbbVie, Takeda, Galapagos/Alfasigma, Bristol Myers Squibb and Ferring. Patrick van Rheenen received financial support from BÜHLMANN Laboratories AG (Schönenbuch, Switzerland) for an ongoing trial. For the last 3 years, Lissy de Ridder has received speaker's fees, consultation fees or research grants from Medtronic, Janssen, Alvotech and Pfizer. Richard K. Russell, for the last 3 years, has received speaker's fees, travel support or has performed consultancy work with: Nestle Health Sciences, AbbVie, Pharmacosmos, Lilly, Celltrion Healthcare, Ferring, Janssen and Pfizer. Dror S. Shouval received lecturing fees from Takeda and consultation fees for Tracells. For the last 3 years, Dan Turner has received consultation fees, research grants, royalties or honoraria from Janssen, Pfizer, Shaare Zedek Medical Centre, Hospital for Sick Children, Ferring, AbbVie, Takeda, Prometheus Biosciences, Lilly, SorrisoPharma, Boehringer Ingelheim, Galapagos, BMS and AlfaSigma. The remaining authors declare no conflicts of interest.

ORCID

Eytan Wine https://orcid.org/0000-0002-3458-4142
Marina Aloi https://orcid.org/0000-0001-7404-4004
Stephanie Van Biervliet https://orcid.org/0000-0001-5609-3726
Jiri Bronsky https://orcid.org/0000-0002-2641-7280
Javier Martín di Carpi https://orcid.org/0000-0002-3631-9625
Marco Gasparetto https://orcid.org/0000-0002-3882-3606
Laura Gianolio https://orcid.org/0009-0003-1189-9373
Hannah Gordon https://orcid.org/0000-0001-7510-0071
Iva Hojsak https://orcid.org/0000-0003-3262-5964
Alexandra S. Hudson https://orcid.org/0000-0001-9016-6917
Séamus Hussey https://orcid.org/0000-0002-9362-0465
Johan van Limbergen https://orcid.org/0000-0001-5822-4371
Erasmo Miele https://orcid.org/0000-0003-4498-7305
Lorenzo Norsa https://orcid.org/0000-0003-3322-2921
Ola Olén https://orcid.org/0000-0002-5478-7019
Gianluca Pellino https://orcid.org/0000-0002-8322-6421
Patrick van Rheenen https://orcid.org/0000-0003-3867-2665
Lissy de Ridder https://orcid.org/0000-0002-6035-1182

Richard K. Russell https://orcid.org/0000-0001-7398-4926
Dror S. Shouval https://orcid.org/0000-0001-5980-2954
Eunice Trindade https://orcid.org/0000-0001-7034-3541
Dan Turner https://orcid.org/0000-0001-5160-868X
David C. Wilson https://orcid.org/0000-0003-0879-1129
Anat Yerushalmy Feler https://orcid.org/0000-0003-0200-6425
Amit Assa https://orcid.org/0000-0002-2787-4096

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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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