Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition

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ABSTRACT

Background: The contemporary management of ambulatory ulcerative colitis (UC) continues to be challenging with ~20% of children needing a colectomy within childhood years. We thus aimed to standardize daily treatment of pediatric UC and inflammatory bowel diseases (IBD)-unclassified through detailed recommendations and practice points.

Methods: These guidelines are a joint effort of the European Crohn's and Colitis Organization (ECCO) and the Paediatric IBD Porto group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). An extensive literature search with subsequent evidence appraisal using robust methodology was performed before 2 face-to-face meetings. All 40 included recommendations and 86 practice points were endorsed by 43 experts in Paediatric IBD with at least an 88% consensus rate.

Results: These guidelines discuss how to optimize the use of mesalamine (including topical), systemic and locally active steroids, thiopurines and, for more severe disease, biologics. The use of other emerging therapies and the role of surgery are also covered. Algorithms are provided to aid therapeutic decision-making based on clinical assessment and the Paediatric UC Activity Index (PUCAI). Advice on contemporary therapeutic targets incorporating the use of calprotectin and the role of therapeutic drug monitoring are presented, as well as other management considerations around pouchitis, extraintestinal manifestations, nutrition, growth, psychology, and transition. A brief section on disease classification using the PIBD-classes criteria and IBD-unclassified is also part of these guidelines.

Conclusions: These guidelines provide a guide to clinicians managing children with UC and IBD-unclassified management to provide modern management strategies while maintaining vigilance around appropriate outcomes and safety issues.

Key Words: anti-TNF, calprotectin, children, guidelines, inflammatory bowel disease-unclassified, management, mesalamine, monitoring, pediatrics, Pediatric Ulcerative Colitis Activity Index, thiopurines, treatment, ulcerative colitis, vedolizumab

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What Is Known

- The previously published European Society of Paediatric Gastroenterology, Hepatology and Nutrition–European Crohn's and Colitis Organization guidelines were published in 2012 and are updated herein.

What Is New

- The diagnosis section has been replaced by the inflammatory bowel disease-classes criteria; a discussion of inflammatory bowel disease-unclassified has been added; fecal calprotectin has been given more emphasis; new drugs (eg, vedolizumab, golimumab) have been incorporated as off-label medications; recommendations for therapeutic drug monitoring have been provided; a treat to target algorithm has been added and other sections updated.

INTRODUCTION

Ulcerative colitis (UC) is a disease with a less heterogeneous phenotype than Crohn disease (CD) but it still poses many unique challenges. The incidence of pediatric onset UC, which constitutes roughly 15% to 20% of all UC, ranges at 1 to 4/100,000/year in most North American and European regions (1). It is extensive in 60% to 80% of all cases, twice as often as in adults

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(2). Since disease extent has been consistently associated with disease severity, it is not surprising that children with UC more often require hospitalization for an acute severe exacerbation (25%–30% over 3–4 years) (3,4) and more often undergo colectomy for medically refractory disease (up to 30%–40% in 10-year follow-up (2,5), although lower colectomy rates have also been reported (6–8)). Canadian population-based health administrative data showed no reduction of colectomy rate from 1994 to 2007 before the widespread use of biologics (9). In addition to more severe colitis, children also have unique age-related issues, such as growth, pubertal development, nutrition, and bone mineral density accretion, as well as differing psychosocial needs. Finally, although mortality in pediatric UC has become rare, a retrospective case collection across Europe over 6 years reported 19 deaths in children with UC mainly due to infections and cancer (1 case of colorectal cancer [CRC]), including 1 with toxic megacolon (10).

The revised Porto criteria (11) proposed explicit guidance for diagnostic workup in pediatric inflammatory bowel diseases (IBDs). Consequently, the Paediatric IBD Porto group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the ''PIBD-Classes'' criteria that standardized the differentiation of pediatric IBD into 5 categories: typical UC, atypical UC, IBD-unclassified (IBDU), Crohn colitis and CD (12); the first 3 categories will be covered in these guidelines.

The PIBD-classes system is based on 23 features that are typical of CD, grouped in 3 classes: those that are totally incompatible with UC and thus should be diagnosed as CD; those that may be present in UC but rarely (<5%; class 2); and those that may be present in UC uncommonly (5%–10%; class 3). Accumulation of the different features, weighted by the classes, standardized the diagnosis of PIBD (Fig. 1, Table 1). The sensitivity and specificity of the PIBD-classes to differentiate UC from CD and IBDU was 80% and 84%, and CD from IBDU and UC 78% and 94%, respectively (12).

The use of the Paris classification is advocated for phenotyping pediatric UC, with E1-E4, A1a-A2, and S0-S1 denoting disease extent, age of diagnosis and severity, respectively (13). Additional labels of very-early onset IBD (≤6 years of age at diagnosis) and infantile IBD (<2 years of age) may also be added (14).

We aimed to develop guidelines for managing UC in children based on a systematic review of the literature and a robust consensus process of an international working group composed of specialists in pediatric IBD from the ESPGHAN and the European Crohn's and Colitis Organization (ECCO). We focus on the principles, pitfalls, and pediatric considerations related to the diagnosis and care of children and adolescents with UC. These guidelines supplement those published for adults (15,16); similar topics are covered only in brief, referencing the extensive ECCO review. The pediatric UC guidelines are divided into 2 parts but should be read as 1 manuscript: Part 1: ambulatory UC (updating the previous 2012 ECCO-ESPGHAN guidelines (17)) and Part 2: acute severe colitis (ASC; updating the previous 2011 ECCO-ESPGHAN guidelines (18)).

In addition to providing an update of new literature, several major topics have changed from the previous guidelines. The diagnosis section has been replaced by the aforementioned IBD-Classes criteria; a discussion of IBDU has been added; fecal calprotectin has been given more emphasis; new drugs (eg, vedolizumab, golimumab, and locally active steroids) have been incorporated as off-label medications; practical recommendations for therapeutic drug monitoring have been provided; the use of thrombotic prophylaxis has been revisited based on predicting variables; sequential therapy has been newly presented; a treat to target algorithm has been added; and other sections updated and changed.

METHODS

Following an open call in ECCO and the Porto plus the Interest Paediatric IBD groups of ESPGHAN, 22 international experts in pediatric IBD were selected by the steering committee, including 2 pediatric surgeons. A list of 23 questions addressing the management of UC in children was first developed (composing the subtitles of the current manuscript and the next one on ASC). Next, a systematic review of the literature was performed centrally by 2 of the authors (E.O.M. and C.S.) with the aid of an experienced librarian searching for all combinations of UC and pediatrics (Supplemental Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B393*). Electronic searches were performed in Oct 2016 using Medline, Embase, and web of science. 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 1985 were all utilized if performed in children. Following elimination of duplicates, 10,096 abstracts were reviewed by EOM for eligibility. A total of 8,996 abstracts were excluded, mainly for the following reasons: clear irrelevance to

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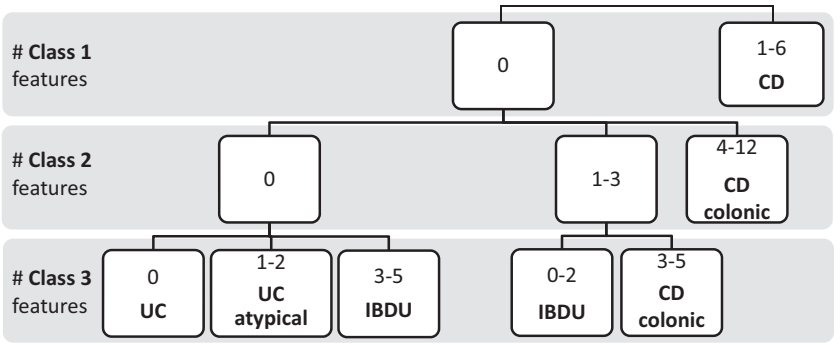

FIGURE 1. Classification algorithm into paediatric inflammatory bowel disease (IBD) subclasses based on the ''PIBD-classes'' features of Table 1 (reproduced from reference 12).

the pre-defined topics, manuscripts published before 1985, review manuscripts, manuscripts focusing on CD, or on molecular/genetic pathways. Although we aimed to base our adult literature on the recently updated ECCO UC guidelines (15,16), salient adult RCTs identified in the initial search were not excluded for perusal and reference. The decision regarding questionable eligibility was made by one of the senior authors (D.T.). Finally, 1100 full-text manuscripts were retrieved and circulated to the relevant subgroups for writing their sections. Highly relevant manuscripts published after the search date were included individually.

Each of the 23 questions was allocated to a subgroup of 2 experts for drafting of the first text. The subgroup's text and recommendations were iterated by e-mail with the steering committee until refined. The guidelines include both recommendations and practice points that reflect common practice where evidence is lacking or provide useful technical details, including grading of

TABLE 1. PIBD-classes features

	Q	Feature
Class 1	1	At least 1 well-formed granuloma anywhere in the gastrointestinal tract, remote from ruptured crypt
	2	At least one of deep ulcerations, cobblestoning or stenosis anywhere in the small bowel or upper gastrointestinal tract (excluding stomach)*
	3	Fistulizing disease (internal or perianal)
	4	Large inflamed perianal skin tags
	5	Thickened jejunal or ileal bowel loops on radiology or other evidence of significant small bowel inflammation on capsule endoscopy not compatible with backwash ileitis
	6	Any ileal inflammation in the presence of normal cecum (ie, incompatible with backwash ileitis)†
Class 2	7	Macroscopically and microscopically normal appearing skip lesions in untreated patients (excluding rectal sparing and cecal patch)
	8	Complete (macroscopic and microscopic) rectal sparing
	9	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation (ie, relative patchiness)
	10	Significant growth delay (height velocity < minus 2 SD), not explained by other causes (eg, celiac disease, prolonged steroid treatment or growth hormone deficiency)
	11	Transmural inflammation of the colon in the absence of severe colitis
	12	Small and not deep ulcers (including aphthous ulcerations), anywhere in the small bowel, duodenal and esophageal (excluding stomach and colon) not explained by other causes (eg, *Helicobacter pylori*, NSAIDS and celiac disease)‡
	13	Multiple (≥5) small and not deep ulcers (including aphthous ulcerations), in the stomach or colon (on the background of normal mucosa), not explained by other causes (eg, *H pylori* and NSAIDs)
	14	Ileitis, otherwise compatible with backwash ileitis,§ but in the presence of only mild inflammation in the cecum
	15	Positive ASCA in the presence of negative pANCA
	16	Reverse gradient of mucosal inflammation (proximal > distal (except rectal sparing))
	17	Severe scalloping of the stomach or duodenum, not explained by other causes (eg, celiac disease and *H pylori*)
	18	Deep ulcerations (at least 1) or severe cobblestoning of stomach not explained by other causes (eg, *H pylori*, NSAIDs and celiac disease)
Class 3	19	Focal chronic duodenitis on histology
	20	Focal active colitis on histology in >1 biopsy
	21	Several (<5) aphthous ulcerations in the colon or in the stomach
	22	Non-bloody diarrhoea
	23	Focal enhanced gastritis on histology

To be used in the PIBD-classes algorithm (Fig. 1). Reproduced from reference 12.

*Deep ulcerations or severe cobblestoning of stomach score as item #18; if there are ulcerations in the duodenum or oesophagus, which are small and not deep, score as item #12.

†If cecum with mild inflammation score as item #14.

‡If ulcers are deep score as item #2.

§Backwash ileitis: a short segment of non-stenotic erythema or edema in the presence of pancolitis including the ileocecal valve, without granulomata or deep ulcers.

evidence according to the Newcastle-Ottawa assessment scales for case-control and cohort studies (19) and according to the Cochrane Handbook for clinical trials (20) (Supplemental Table 2: tables of evidence with grading, Supplemental Digital Content 2, *http://links.lww.com/MPG/B394*). The group then voted on all recommendations and practice points while adding specific comments using a web-based voting platform. A second round of electronic voting and revisions was done, including all members of the Paediatric IBD Porto group of ESPGHAN. In addition, the draft was circulated for comments to ECCO (national representatives and governing board) and to members of the IBD Interest group of ESPGHAN.

The group met twice face-to-face: during UEGW annual meeting (Barcelona, October 2016) before drafting the initial topics and during ESPGHAN annual meeting (Prague, May 2017) after the 2 voting rounds were completed. The meetings were supplemented by an e-mail Delphi process with the entire group until agreement was reached. In total 43 pediatric IBD experts voted on all recommendations and practice points: 35 Porto group members (of whom 14 were authors) and 8 non-Porto group authors (Supplemental Table 3: names of the 43 voting experts, Supplemental Digital Content 1, *http://links.lww.com/MPG/B393*). All statements and practice points were supported by at least 88% of the group. Recommendations were graded according to Oxford Centre for Evidence-Based Medicine (see table at *https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf* (21)).

EVALUATION AND PREDICTION

Assessing and Predicting Disease Activity

Recommendations

1. Disease activity should be monitored at every visit utilizing the PUCAI [EL2] and treatment should be revisited when PUCAI $\geq$ 10 points [EL2]. **(93% agreement)** (Fig. 2)
2. Colonoscopic evaluation is recommended at diagnosis [EL4, adults EL4], before major therapeutic modifications [EL5, adults EL5], for cancer surveillance [EL5, adults EL3], and when it is not clear if symptoms are disease-related especially if calprotectin is elevated [EL5, adults EL5]; it is not routinely indicated during relapses that are not severe [EL5, adults EL5]. **(100% agreement)**
3. If available, fecal calprotectin should be obtained while in sustained clinical remission and endoscopic evaluation should be considered when calprotectin is high, as defined below and in Figure 2 [EL2, adults EL2]. **(88% agreement)**

Practice Points

1. Clinical remission is defined as PUCAI $<$ 10 points, mild disease as 10 to 34 points, moderate disease 35 to 64 points and severe disease $\geq$65 points (**Appendix 1**). Clinically significant response is defined by a PUCAI change of at least 20 points, or entering remission. (**95% agreement)**
2. Long-term prognosis is better in patients who achieve complete clinical remission (ie, PUCAI $<$ 10) during the first 3 months after diagnosis. (**95% agreement)**
3. There is currently no evidence whether measuring calprotectin in a child who is in a PUCAI-defined remission has an added value for predicting disease course. Given the fact that significant endoscopic disease may, however, be present in $\sim$20% of children with PUCAI $<$ 10, it is reasonable to measure calprotectin once sustained clinical remission has been achieved to verify mucosal healing and select those who require endoscopic assessment. Other fecal markers (eg, lactoferrin) may have a comparable diagnostic value, but less supportive data are available. **(93% agreement)**
4. There is no ideal cutoff value of fecal calprotectin to reflect mucosal inflammation and predict disease outcome (Tables 2 and 3). Values differ substantially in the different studies using different reference standards. Cutoff value $<$100 μg/g usually reflects remission while $>$250 μg/g more accurately predicts mucosal inflammation. The value that should trigger an endoscopic evaluation or a change in treatment should be thus individualized based on these values, especially when values increase over time. **(98% agreement)**
5. An episode of acute severe colitis (ie, PUCAI $\geq$ 65) is a risk factor for a more aggressive disease course and thus this should be incorporated in the management scheme. **(100% agreement)**
6. Blood tests (CBC, albumin, transaminases, gGT, CRP, and ESR) should be performed regularly depending on symptoms and therapy and at least every 3 months while on immunosuppressive medications and at least every 6 to 12 months otherwise. It is a common practice to include testing for renal function in patients taking mesalamine and annual urinalysis; however, there is no evidence that this prevents adverse outcomes. **(98% agreement)**
7. Before treatment modification, it is essential to consider other clinical conditions such as non-adherence, irritable bowel syndrome, celiac disease, medication-related adverse events, and infections (especially *Clostridium difficile*, which should be excluded in any acute exacerbation, but also bacterial infections and CMV). (**95% agreement)**
8. A standardized endoscopic activity index, including the Mayo endoscopic subscore or Ulcerative Colitis Endoscopic Index of Severity (UCEIS), should be used during colonoscopic examinations. (**95% agreement)**
9. CRC surveillance by a trained endoscopist is recommended following 8 to 10 years of disease duration, dictated by risk factors such as disease extent, disease severity over the course of disease and family history. Surveillance recommendations in children with primary sclerosing cholangitis (PSC) can be found in the PSC section. According to the adult guidelines, chromoendoscopy with targeted biopsies has been shown to increase dysplasia detection rate. If not available, random biopsies (quadrantic-biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed using high definition endoscopes. **(93% agreement)**

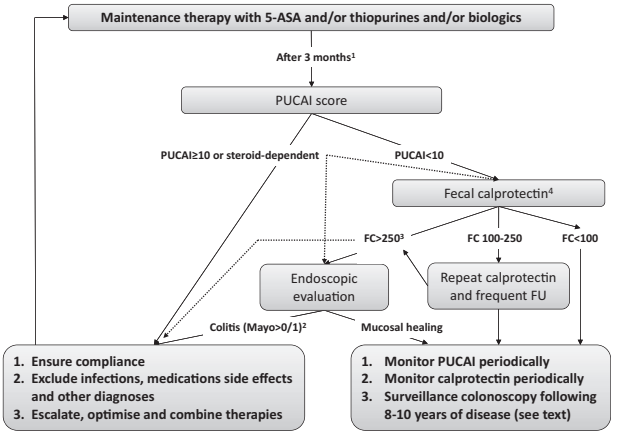

FIGURE 2. Algorithm for monitoring paediatric ulcerative colitis (UC) during the maintenance phase. (1) Assessments earlier than 3 months are usually required and in any significant disease or deterioration, early intervention is required. (2) The decision whether to escalate therapy based on a Mayo—0 or 1 endoscopic findings should be individualized such as based on the current treatment (eg, 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). (3) Proceeding to colonoscopy should preferably be based on at least 2 independent measurements of calprotectin. (4) Obtaining calprotectin may be delayed to 4 to 6 months since histological remission lags after macroscopic improvement.

In 2 pediatric inception cohorts, disease severity during the first 3 months after diagnosis and the occurrence of an episode of ASC were associated with increased risk of refractory disease (22,23). Thus, by using constructs of disease severity it is possible to characterize children who are at high risk for a more complicated disease course and to guide management and tight monitoring.

Endoscopy is the reference standard to evaluate mucosal inflammation. Mayo endoscopic score of none, mild, moderate, or severe (0–3 points) with number of involved colonic segments (rectum, sigmoid, and descending, transverse, and ascending colon) may be used in pediatric UC (24). The modified Mayo endoscopic score is an easy to use, non-validated tool, which combines disease extent with Mayo Endoscopic score (25). The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a convenient and validated index which includes vascular pattern, bleeding, and ulcers at the worst part (26,27). These indices are described in the coming ESPGHAN Porto group guidelines of endoscopy utilization in IBD (*JPGN* 2018).

Mucosal healing in UC is associated with a favorable disease outcome in adult patients (28–31). Nevertheless, clinical remission has been proven to predict long-term outcomes in UC, with no less accuracy than endoscopic evaluation, both in children using the PUCAI (23,32) and in adults (33). An adult study showed that UCEIS predicted relapse in 155 patients who were in clinical remission; however, clinical remission was not stringently defined (ie, partial Mayo score of 0–1, allowing for streaks of blood for instance) and the number needed to test was high (34). A post-hoc analysis of the adult ACT trials showed that while endoscopic inflammation predicted colectomy, this was not the case in the subgroup of patients who were in clinical remission (28). A PUCAI-

TABLE 2. The utility of different cutoff values of faecal calprotectin to predict endoscopic disease in UC (selected references)

	Study design	Cutoff	Reference standard	Sens	Spec	PPV	NPV
Paediatric							
Diamanti (60)	n = 41; retrospective	275	Histology	94	95	94	95
Adult							
D'Haens (471)	n = 39; prospective	250	Endoscopic Mayo > 0	71	100	100	47
			Endoscopic Mayo > 1	86	78	82	82
Schoepfer (472)	n = 228; prospective	57	Modified Baron ≥ 2	91	90		
		50	Modified Baron ≥ 2	92	86		
Scaioli (473)	n = 121; prospective	110	Endoscopic Mayo > 0	98	90	93	98
		270	Endoscopic Mayo > 1	88	88	88	93
Dranga (474)	n = 103; prospective	15	Endoscopic Mayo > 0	98	76	96	46
Langhorst (475)	n = 42; prospective	48	Endoscopy total score > 1	81	72		
Falvey (476)	n = 65; prospective	125	Baron score > 1	74	80	85	67
Guardiola (477)	n = 59; prospective	155	Endoscopic Mayo = 0–1 and activity on histology	89	71	54	89
Lin (478)	n = 52; prospective	191	UCEIS < 3	88	75		
Lobatón (479)	n = 123; prospective	250	Endoscopic Mayo = 0–1	73	89	86	79
		160	Endoscopic Mayo = 0	66	85		
Samant (480)	n = 32; retrospective	800	Endoscopic Mayo > 1	96	71		
Xiang (481)	n = 66; prospective	50	Sutherland criteria > 2	91	79		
Nancey (482)	n = 55; prospective	250	Rachmilewitz ≤ 2	91	87	87	91
		100		100	53	85	100
Takashima (483)	n = 92; prospective	250	Endoscopic Mayo = 0	82	62	61	83
		200		77	72	67	81
		369	Endoscopic Mayo = 0–1	86	63	79	74
		250		70	66	76	59
Sandborn (484)	n = 194; prospective	150	Mayo score ≤2, with no subscore >1	68	79	57	86
			Endoscopic Mayo = 0	79	75	39	94
			Endoscopic Mayo = 0–1	85	54		

NPV = Negative Predictive Value; PPV = Positive Predictive Value.

TABLE 3. Cutoff values of faecal calprotectin in prediction poor outcome in ulcerative colitis (selected references)

	Study design	Sampling time	Reference outcome	Cutoff	Follow-up	Sens	Spec	PPV	NPV
De Vos (486)	n = 113; pro	Clinical remission with infliximab	Relapse: change in therapy or endoscopic Mayo > 2	>300	52 weeks	93	58	—	—
Gisbert (487)	n = 74; pro	Clinical remission for 6 months	Remission	<150	12 months	31	91	—	—
				<167		69	74	—	—
Ho (488)	90; pro	Acute severe colitis	Colectomy	>1922		24	97	—	—
				>431		96	20	—	—
Lasson (489)	n = 69; pro	At diagnosis	Mayo score < 3	<169	12 months	64	70	80	51
				<262	24 months	51	81	85	45
				<262	36 months	52	85	88	45
Costa (490)	n = 41; pro	Clinical remission for 1–12 months	Remission; (UCAI < 5)	<150	12 months	89	82	81	90
D'Inca (491)	n = 97; pro	Remission	Remission; (Edwards and Truelove score < 3)	<130	12 months	70	70	—	—
Garcia-Sanchez (492)	n = 69; pro	Clinical remission for ≥3 months	Remission; (modified Truelove and Witts < 11)	<120	12 months	81	63	49	88
Yamamoto (61)	n = 80; pro	Clinical remission for ≥3 months	Relapse by the DAI	<170	12 months	76	76	—	—
Hosseini (493)	n = 157; pro	Clinical remission for ≥3 months	Seo index > 220; or need for therapy change	>341	12 months	80	89	—	—
Jauregui-Amezaga (494)	n = 70; pro	Partial; Mayo ≤ 1	Endoscopic Mayo > 0	>100	12 months	64	53	67	88
				>250	12 months	78	45	85	88
Ferreiro-Iglesias (495)	n = 20; pro	Clinical remission for ≥6 months with infliximab	Clinical relapse by the partial Mayo	>198	2 months	100	81	48	100
Tursi (496)	n = 20; pro	Before starting biologics	Active disease by the DAI	>15	12 months	66	56	18	92
			Endoscopic Mayo = 2–3	>15	12 months	47	87	90	37
Theede (497)	n = 70; pro	Clinical remission	Relapse requiring therapy change	>321	6 months	63	86	46	92
				>321	12 months	46	86	46	86
Frin (498)	n = 31; pro	2 weeks after starting infliximab	Response (by the Mayo score)	<800	14 weeks	82	69	78	85
		14 weeks after starting infliximab	Sustained remission (by the partial Mayo score) without IFX dose intensification or other treatments	<146	54 weeks	90	72	86	80

DAI = Disease Activity Index; FU = follow-up; IFX = infliximab; NPV = Negative Predictive Value; PPV = Positive Predictive Value; Pro = prospective; Retro = retrospective; UCAI = Ulcerative Colitis Activity Index.

defined remission at 3 months following diagnosis predicted 1-year sustained steroid-free remission (AUROC 0.7, 95% CI 0.6–0.8) and colectomy by 2 years (AUROC 0.75, 0.6–0.89). It was superior to both CRP and ESR (23) and predicted choice of treatment (35,36). Furthermore, in the prospective multicenter PROTECT pediatric cohort study, failure to achieve clinical remission (PUCAI < 10) 4 weeks after discharge of children who required intravenous corticosteroids at disease onset was highly associated with need for additional medical therapy by week 12 (37).

PUCAI cutoff scores of remission, mild, moderate, and severe disease have been validated in several cohorts (35,38,39) and were successfully utilized in the PROTECT study to guide the choice of initial treatment at disease onset, as outlined in Figure 3 (37). PUCAI at diagnosis was associated with steroid-free remission rates at week 12 and with long-term outcomes (at 54 weeks). Selected children with moderate disease activity were, however, treated with 5-aminoscalicylic acid (5-ASA) and not with oral steroids, and on average had similar outcomes at week 12; this supports our algorithm that 5-ASA may be considered also in the lower range of the moderate disease activity group (Fig. 3). The PUCAI correlates well with endoscopic appearance of the colonic mucosa, showing similar remission rates in multiple studies (38–43). In addition, the correlation of the PUCAI with Mayo score has been reported to be as high as 0.95 (32,38,39). While most aforementioned studies report a group *average*, on an individual basis there is a likelihood of ~20% for a significant mucosal inflammation even in the presence of a PUCAI-defined complete remission (44). Therefore, biomarkers should be used to confirm endoscopic remission in those who are in sustained clinical remission, particularly in the presence of PSC where the PUCAI does not correlate well with mucosal inflammation (45) (Fig. 2).

Routine laboratory parameters (platelets, CRP, albumin, hemoglobin) are more frequently normal in UC than in CD during mild to moderate flares (46,47). In contrast to adult UC, high sensitivity (hs)-CRP was not suitable to differentiate between remission and relapse in children with normal standard CRP (48). In

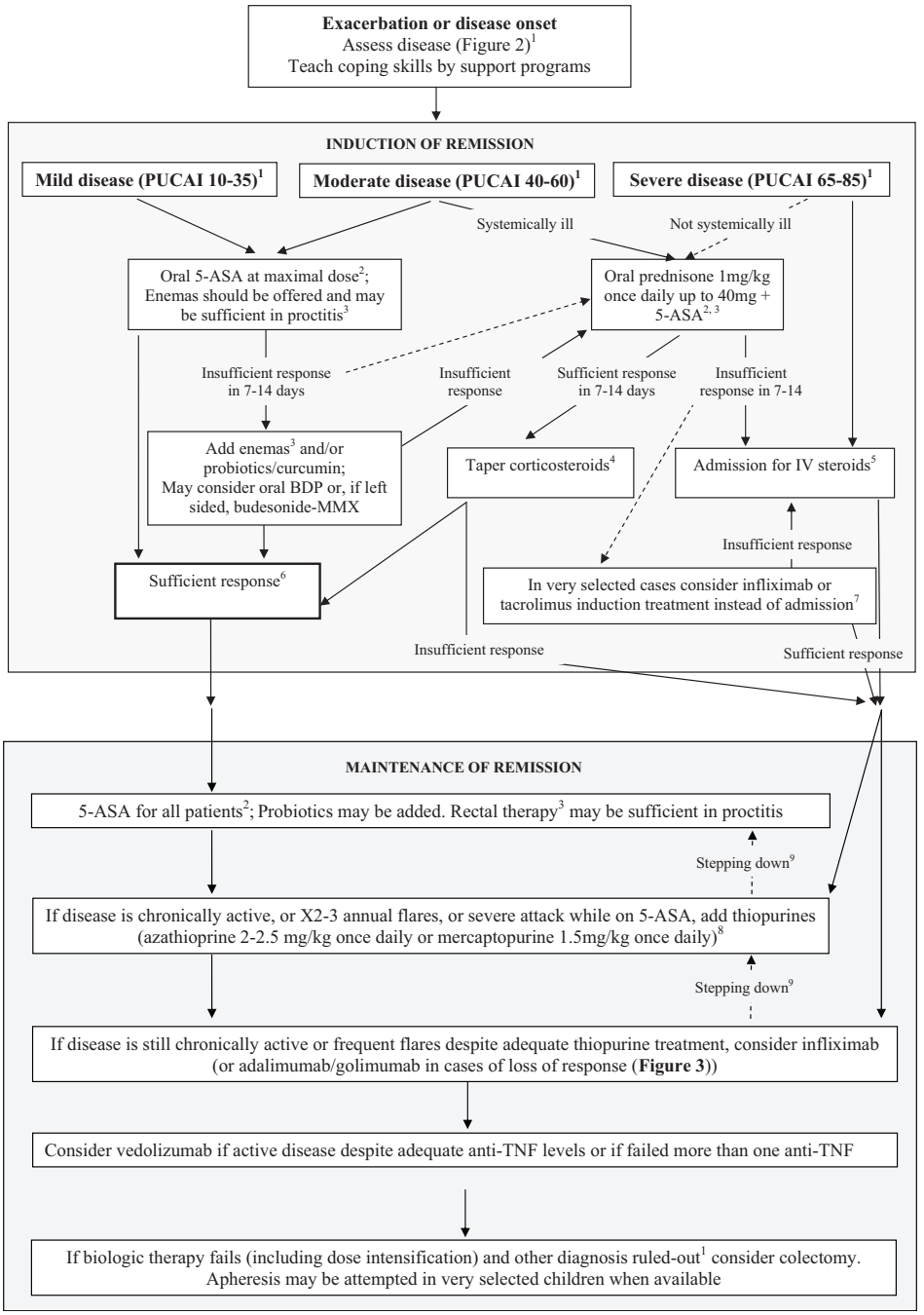

FIGURE 3. Summary flowchart of managing pediatric ulcerative colitis (UC). Comments: Medical therapies in UC should be divided into those that induce remission (5-ASA, corticosteroids, anti-tumur necrosis factor (TNF) therapy, calcineurin inhibitors and likely probiotics) and those that maintain remission (5-ASA, thiopurines, anti-TNF therapy, vedolizumab and selected probiotics). 1. The following should be considered in active disease: infectious colitis (including CMV and *C. difficile)*, 5-ASA related colitis, lactose intolerance, irritable bowel syndrome, celiac disease. In case of discrepancy between PUCAI and endoscopic grading of colitis, endoscopy should prevail. 2. 5-ASA is dosed 60-80 mg/kg/day up to 4.8 grams daily. Once daily dosing may be as effective as twice daily dosing. 3. 5-ASA enemas (1g daily is as effective as higher doses) are more effective than steroid enemas. Enemas should be administered in the left decubitus position. Liquid enemas are more difficult to tolerate than foams and suppositories but are more suitable for extensive colitis. 4. If lack of improvement (i.e. PUCAI decrease of $<$20 points) after 7–10 days, or increase in PUCAI $\geq$20 points at any time, consider treatment escalation. Steroid dependency must be avoided. 5. See Part 2 of these guidelines. 6. Response is defined as a drop in PUCAI of at least 20 points. However, the goal of induction therapy is eventually complete remission (Figure 2). 7. e.g. previous intolerance or resistance to steroids, or when infliximab is indicated anyway for maintenance treatment after failing thiopurines. 8. Measuring TPMT (genotyping or enzymatic activity) at baseline, and 6-TG and 6-MMP levels after 2–3 months, may aid in optimizing thiopurine dosing. 9. If infliximab has been used in thiopurine-naïve disease, thiopurines may be added and infliximab discontinued after 4–8 months if complete remission has been achieved. Stepping down to 5-ASA may be considered in selected cases, if 5-ASA did not fail previously, and after a period of sustained deep remission.

pediatric UC, ESR and CRP should be measured at least initially, since at times only 1 measure is elevated (49). Initial albumin was the only significant laboratory test that was predictive for acute severe colitis in 1 follow-up study (23). Similarly, earlier surgery was necessary in children with initially low serum albumin (HR 6.05, 99% CI 2.15–17.04) in 57 children who ultimately required colectomy (median time to surgery was 3.8 years) (50). In another study, elevated white blood cell and low hematocrit measured at diagnosis were associated with colectomy rate at 3 years (51).

Fecal biomarkers reflect especially histological activity (52–54). High correlation of calprotectin with clinical disease activity, endoscopic, and histological indices has been described in both children and adults (52,55–59) (Table 2). In a retrospective pediatric study, calprotectin value of 275 μg/g achieved sensitivity and negative predictive value of 97% and specificity and positive predictive value of 85% in evaluating histological activity (60). A few studies have indicated that calprotectin can be useful to predict relapses in UC patients (56,61,62), but its added predictive utility while in clinical remission is less clear (Table 3).

Roughly 60% of children with UC are pANCA positive at the time of diagnosis (63). pANCA positivity was not associated with disease activity in 1 pediatric study (64), or with early relapse (1-year follow-up) (65). In a recent Porto group multicenter retrospective study of 801 children with colonic IBD, pANCA predicted the need for biologics in UC ($P = 0.026$) (63). In an adult UC population, pANCA status was associated with higher risk of pouchitis after colectomy (66).

Data supporting CRC surveillance recommendations can be found in extensive adult guidelines (15,16,67). Of note, a Swedish nationwide cohort study of pediatric IBD confirmed that CRC was almost non-existent during the first 5 years of follow-up, but incidence was higher after 10 years of follow-up (68). Interestingly, the incidence of CRC in the first 20 years of follow-up was considerably lower in childhood-onset IBD than in disease with onset at other ages.

MEDICAL MANAGEMENT

5-ASA and Enemas

Recommendations

1. Oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-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]. **(98% agreement)**
3. Rectal monotherapy should be reserved for mild-to-moderate ulcerative proctitis, an uncommon pediatric phenotype [EL2, adults EL1]. **(100% agreement)**
4. When rectal therapy is used, 5-ASA is preferred over steroids [EL5, adults EL1]. **(100% agreement)**

Practice Points

1. No mesalamine delivery system has proven clearly superior for induction or maintenance of remission. Sulfasalazine may be somewhat superior to mesalamine for maintenance of remission in adult studies. Only sulfasalazine is available in liquid formulation and may be also effective for arthritis, but it is associated with more adverse events. **(100% agreement)**
2. Suggested dosing: *oral mesalamine* 60 to 80 mg · $kg^{-1} \cdot day^{-1}$ to 4.8 g daily; *rectal mesalamine* 25 mg/kg up to 1 g daily; *sulfasalazine* 40 to 70 mg · $kg^{-1} \cdot day^{-1}$ up to 4 g daily. Higher rectal doses up to 4 g are being used but evidence suggest that it is no more effective than 1 g. **(98% agreement)**
3. Suppositories are useful for limited proctitis, while foam and liquid mesalamine enemas are also suitable in more extensive colitis. **(95% agreement)**
4. Dosing 5-ASA once-daily can be considered for induction of remission and for maintenance. **(95% agreement)**
5. Gradual sulfasalazine dose augmentation over 7 to 14 days may mitigate against dose-dependent side-effects (see text). **(93% agreement)**
6. The effective induction dose should be continued also as the maintenance dose. Dose reduction, within the suggested dose range, may be considered after several months of sustained remission. Maintenance therapy should be continued in pediatric patients. **(93% agreement)**
7. Most children with mild-moderate UC will not achieve remission with oral mesalamine monotherapy alone. Treatment modification should be considered in those who do not show initial meaningful response within 2 to 3 weeks of therapy. **(95% agreement)**
8. 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 re-challenge is diagnostic and precludes its future use. Symptoms usually recur also following rectal administration. **(100% agreement)**
9. Rectal tacrolimus may be considered in patients with ulcerative proctitis who are either refractory or intolerant to mesalamine and steroids topical therapies (suggested dose 0.07 mg · $kg^{-1} \cdot day^{-1}$; maximum dose in adult trials 3 mg/day). **(88% agreement)**

Strong evidence, mostly from adult trials, supports the use of 5-ASA for induction and maintenance of remission in mild-moderate UC (41,69–72). In that context, mesalamine induces remission in 35% to 55% of children, as defined by the PUCAI (73,74).

The MUPPIT trial randomized children with mild-moderate UC into once versus twice daily oral mesalamine (Pentasa), with comparable outcomes (74). Once daily dosing achieved clinical response in 25/43 (60%) and remission in 13/43 (30%), compared with 25/40 (63%) and 16/40 (40%), respectively, for the twice daily group. Most responders did so by week 2 and no further response was seen after week 3. While the groups were statistically comparable, more patients in the once-daily study arm had pancolitis and were already on immunomodulators. Endoscopic remission was not assessed and the study was not powered for non-inferiority. Long-term studies of 5-ASA of once daily maintenance in pediatrics are currently ongoing. In another pediatric RCT, low versus higher dose balsalazide induced remission in 3/35 (9%) versus 4/33 (12%) of children, respectively (72). Clinical improvement in

mild-moderate UC was seen in nearly twice as many children randomized to sulfasalazine (22/28, 79%) compared to olsalazine (11/28, 39%) (71).

There are no pediatric maintenance comparative trials of 5-ASA, but only ~ 40% (86/213) of children treated with 5-ASA within 1 month of diagnosis were in steroid-free remission by 1 year in the North American registry (75). Similar data were reported from the prospective Italian pediatric IBD registry, with 45% of patients in remission at 1 year on 5-ASA therapy alone (76). EPIMAD data reported that 32% (36/113) of children with UC remained on 5-ASA therapy without steroids, by maximum follow-up (5). In a recent Cochrane analysis of adult trials, the relative risk of successful induction of clinical and endoscopic remission with 5-ASA was 1.16 (95% CI 1.12–1.21) and 1.29 (95% CI 1.16–1.69), respectively (69). No specific 5-ASA compound was superior for inducing remission, although sulfasalazine was statistically superior to other 5-ASA compounds for maintenance of remission (69,70,77,78).

The pharmacokinetics of 5-ASA are comparable between children and adults (79–81). 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 (82–84). In a multicenter RCT, 81 children with mild-moderate UC were, however, randomized to high dose (53–118 $mg \cdot kg^{-1} \cdot day^{-1}$) or lower dose (27–71 $mg \cdot kg^{-1} \cdot day^{-1}$) delayed release mesalamine with similar PUCAI-defined remission rates after induction (55% and 56% respectively) (73). While greater reductions in fecal biomarkers were seen in the higher dose group, this did not reach significance. This trial enrolled on average children with milder disease which may explain the higher remission rates compared to other aforementioned pediatric trials.

Oral mesalamine may be better tolerated than sulfasalazine (relative risk of adverse effects 0.48, 95% CI 0.36–0.63), but the latter is cheaper and remains the only 5-ASA available in liquid formulation (70,71). Moreover, except for the uncommon allergic reaction (<0.1%), the vast majority of events are mild (eg, headache and gastrointestinal symptoms) (85,86). Serious adverse events with 5-ASA treatment are rare and include renal, pancreatic, pulmonary, and cardiac complications (87–93). Withdrawal due to intolerance in adult studies is in the range of 2% to 5% (69,70). Intolerance to 5-ASA medications may mimic a colitis flare, and when clinically proven by re-challenge, it precludes further use of 5-ASA compounds (94). Regular laboratory monitoring of full blood count, renal function, and urinalysis, though not supported by evidence, remains the practice of many clinicians.

Rectal therapy (as suppositories) is indicated for ulcerative proctitis, an infrequent phenotype in pediatrics (95). In order to allay concerns and ensure optimal compliance, children and their caregivers require support and reassurance when topical rectal therapies are proposed.

In a pediatric ulcerative proctitis trial, mesalamine suppositories (0.5 g daily) were associated with improved disease activity at 3 and 6 weeks in children with mild-moderate proctitis (95). Combining oral and rectal 5-ASA therapy improves clinical outcomes (96–98). Remission was reported in 16/38 children (42%) in a prospective uncontrolled trial of 3 weeks' rectal mesalamine in patients unresponsive to oral high dose mesalamine (99). Adult studies with larger numbers and a higher evidence level have shown that rectal mesalamine foam, gel or liquid enema formulations have comparable tolerance, safety and outcomes (100–103). Once daily rectal therapy is as effective as divided daily dosing (104). In adults, daily doses in excess of 1 g of rectal mesalamine do not enhance outcomes including clinical, endoscopic and histological remission (100,101). Rectal steroid preparations are useful for patients who are 5-ASA intolerant. They are superior to placebo in children and adults for inducing remission of proctitis, but meta-analysis data consistently support the superiority of rectal mesalamine over rectal steroids (symptomatic remission OR 1.65 [95% CI 1.1–2.45]) (100,101).

Rectal tacrolimus has been reported in children and adults as a successful third-line treatment of ulcerative proctitis (105,106). In a recent double-blind placebo-controlled trial, 8/11 adult patients receiving rectal tacrolimus ointment (1.5 mg twice daily) achieved mucosal healing by week 8, compared with 1/10 receiving placebo (107). Although usually well tolerated, rare toxicity episodes have been reported (106).

TABLE 4. Steroids tapering schedule (doses are in mg/day prednisone equivalent): the goal is to discontinue steroids by week 10

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
60	50	40	35	30	25	20	15	10	5
50	45	40	35	30	25	20	15	10	5
45	40	40	35	30	25	20	15	10	5
40	40	40	35	30	25	20	15	10	5
35	35	35	30	25	20	15	15	10	5
30	30	30	25	20	15	15	10	10	5
25	25	25	20	20	15	15	10	5	5
20	20	20	15	15	12.5	10	7.5	5	2.5
15	15	15	12.5	10	10	7.5	7.5	5	2.5

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 since many factors come into play when weaning off steroids. Consider the possibility of adrenal insufficiency, even many months after tapering off steroids.

First 2 to 3 weeks: start prednisone at 1 mg/kg up to 40 mg once daily (after discharge from acute severe colitis admission, the dose may be as high as 60 mg/day; see part 2 of these guidelines). If there is no significant improvement (ie, PUCAI decrease of <20 points) after 7 to 14 days, or an increase in PUCAI ≥ 20 points at any time, then escalate treatment after excluding other causes for steroid-refractory disease (see text and Figs. 2 and 3).

After the first 2 to 3 weeks: PUCAI 15 to 30: consider keeping the dose stable (while prolonging the total course by 1 week); PUCAI > 35, increase steroids to the dose of the previous 1 to 2 steps for 1 week and then re-start weaning more slowly; PUCAI > 60 or increase in PUCAI by ≥20 points at any time, escalate treatment.

Oral Steroids

Recommendations

1. Oral steroids should be used as second-line treatment for mild-moderate UC not responding to 5-ASA (oral ± rectal) and may be considered as first line in the higher end of the moderate disease range [EL3, adults EL1]. **(100% agreement)**
2. Severe UC should normally be treated with intravenous steroids [EL2, adults EL1]. **(98% agreement)**
3. Second-generation oral steroids with lower systemic effect such as beclomethasone dipropionate (BDP) [EL2, adults EL1] and budesonide-MMX [EL5, adults EL2; the evidence for budesonide-MMX is supportive only for left-sided colitis] may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone. **(93% agreement)**
4. Steroids are not recommended for maintaining remission; steroid sparing strategies should be applied [EL5, adults EL4]. **(100% agreement)**

Practice Points

1. Regarding recommendation #2, a short trial of oral steroids could be considered in selected children with severe colitis (ie, PUCAI $\geq$ 65) who appear well with normal or near-normal lab values. **(93% agreement)**
2. The recommended daily dose for oral prednisolone/prednisone is 1 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} (max 40 mg) once daily for 2 to 3 weeks followed by a tapering period of up to 8 to 10 weeks (Table 4). **(98% agreement)**
3. Once daily administration of steroids in the morning is as effective as the same dose given in multiple divided doses. **(100% agreement)**
4. 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 and no liquid formulation is available. There is no evidence to support tapering of either drug. While abrupt discontinuation has been practiced in the RCTs, alternate day tapering over 2 to 4 weeks has been proposed by some. **(93% agreement)**
5. The term ''steroid-dependency'' applies to patients who are unable to stop steroids within 3 months without recurrent active disease, or who have a relapse requiring steroids within 3 months of stopping steroids. **(95% agreement)**
6. High glucocorticoid dose and long duration of the therapy (>3 months) has been associated with adrenal suppression (ie, present after gradual weaning off) in 20% of children with IBD. **(98% agreement)**
7. If symptoms of adrenal suppression (eg, weakness/fatigue, malaise, nausea, vomiting, diarrhea, headache, arthralgia, and abdominal pain) are present while weaning steroids, adrenal insufficiency should be excluded by first testing cortisol level at 08:00 AM before drug intake, and, if abnormal, consult with a pediatric endocrinologist. **(93% agreement)**

Studies of oral steroids for treating children with active UC report short-term (1-3 months) remission rates of 50% to 64% (108–110); at 1 year 49% to 61% had prolonged response, 14% to 49% were steroid-dependent, and 5% to 29% required surgery (5,7,108,110). Mucosal healing lags behind clinical improvement; in a non-randomized study after 8 weeks of steroids or 5-ASA, 87% had clinical remission, 40% endoscopic remission and 15% histological remission with no significant difference in outcomes between the 2 therapies (111).

Steroid dependency has been reported to be higher in children than in adults (45% vs 8%, respectively) (7). Strategies to avoid steroid dependency include optimization of 5-ASA, adjuvant therapy with enemas, and escalation to thiopurines or biologics.

Second-generation topical steroids have a more favorable safety profile and may be considered before systemic steroids in selected patients (112). BDP uses gastro-resistant film coatings to target delivery to the distal small intestine and the colon. Studies in adults demonstrate the effectiveness of BDP compared with both prednisolone and mesalamine (15,113). An RCT of 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 (41).

A Cochrane systematic review of older selective release budesonide in adults showed that it was less likely to induce remission than mesalamine (relative risk [RR] 0.72, 95% confidence interval [CI] 0.57–0.91) with no benefit over placebo (RR 1.41, 95% CI 0.59–3.39) (114). Budesonide-MMX is a novel oral formulation designed to extend release of the drug to the colon. Two adult trials showed significant benefit in the intention to treat (ITT) population (combined left sided and extensive), but subanalysis based upon disease extent was only significant for left-sided disease (115,116). Indeed, in a recent case series of 16 children, 15 of whom with pancolitis, budesonide-MMX showed minimal clinical effectiveness (117). Another recent RCT in adult UC refractory to 5-ASA showed superiority over placebo but with a disappointing 6% effect size difference; no subgroup analysis of disease extent was performed (118).

Children with UC may have more steroid-related complications, including osteopenia, acne, glaucoma, and cataracts, than adults even when adjusted for weight (119). Even low steroid doses (0.1–0.4 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) can suppress growth (120). The ECCO statement in adults suggests supplementation with vitamin D while on steroid therapy (121), but we could not find clear evidence to support supplementing vitamin D in those who are not deficient.

AS may present with non-specific symptoms (including abdominal pain, malaise, weakness/fatigue, nausea, diarrhea, headache, fever, arthralgia) or rarely adrenal crisis (hypotension, lethargy, decreased consciousness/coma, hyponatraemia, hypoglycemia, seizures) (122). There are no published consensus guidelines that advise who should be screened for AS. In 1 recent review, it was recommended to screen patients who received steroids for >3 weeks and after gradual weaning have persistent symptoms that may be attributable to AS (123). The range of 8 AM morning cortisol value at which AS is confirmed varies between studies. In 1 recent review a value of <100 nmol/L was used while >500 nmol/L virtually excluded AS (124). Another manuscript suggested that <85 nmol/L should be used to diagnose AS (123). In a study of consecutive children with IBD about to stop steroids (ie, on

physiological doses of oral steroids meaning 5 to 10 mg daily prednisolone) 20% had biochemical AS using a value <69 nmol/L and of these half had an undetectable cortisol (125). Higher glucocorticoid dose and longer duration of the therapy were associated with increased risk (125). In the only study of children with IBD, all children treated with steroids for <3 months did not have biochemically confirmed AS (after gradually weaning to physiological doses of steroids) (125–127).

Immunomodulators

Recommendations

1. Thiopurines are recommended for maintaining remission in children who are corticosteroid-dependent or relapsing frequently (≥2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant patients [EL3, adults EL1]; thiopurines should be considered following discharge from acute severe colitis episode [EL4, adults EL3]. **(98% agreement)**
2. Thiopurines should not be used for induction of remission in pediatric UC patients [EL5, adults EL2]. **(100% agreement)**
3. Measuring thiopurine metabolites is recommended in patients with incomplete response on a stable thiopurine dosage, in patients who present with leucopenia or elevated transaminases, or if poor compliance is suspected [EL2, adults EL2]. **(95% agreement)**

Practice Points

1. Thiopurines may be somewhat more effective than 5-ASA for maintaining remission in UC, but considering their safety profile, they should generally be reserved as second-line therapy after 5-ASA has failed. **(93% agreement)**
2. Determination of TPMT genotype or phenotype (ie, TPMT activity) is encouraged to identify patients at greater risk of profound myelosuppression. Dose should be reduced in heterozygous patients or in those with low activity. Thiopurines should not be used in children homozygous mutants for TPMT or those with very low TPMT activity as defined at each laboratory. **(93% agreement)**
3. Regular monitoring of blood counts and liver enzymes is recommended in all cases every 1 to 2 weeks during the first month then every month up to 3 months followed by every 3 months thereafter. **(100% agreement)**
4. Families should be instructed to use sun protection with the use of thiopurines and other immunosuppressive drugs. **(100% agreement)**
5. Given its excellent safety profile, it is reasonable to continue 5-ASA with thiopurines, at least initially, despite lack of evidence. 5-ASA inhibits the enzyme TPMT thus increasing the active metabolite 6-thioguanine (6-TGN). **(88% agreement)**
6. The maximal therapeutic effect of thiopurines may not be evident until 10 to 12 weeks of treatment. **(98% agreement)**
7. Thiopurine dose should be approximately 2 to 2.5 mg/kg of azathioprine and 1 to 1.5 mg/kg of mercaptopurine, in a single daily dose in patients with a normal TPMT. Measuring thiopurine metabolites may assist in further dose adjustments and reduce adverse events while considering 6-TGN level of 235 to 450 pmol/8×10^8 RBCs and 6-methylmercaptopurine ribonucleotides (6-MMP) < 6700 pmol/8×10^8 RBCs as optimal (note that cutoff values may vary between methods (128)). **(95% agreement)**
8. Patients who show gastrointestinal intolerance or flu-like reaction to 1 thiopurine compound may tolerate lower doses or a ''switch'' to another thiopurine (azathioprine to 6-mercaptopurine and vice versa). Limited data suggest that splitting the daily dose into 2, may alleviate gastrointestinal and hepatic toxicity in patients who have hyperactive TPMT activity. **(95% agreement)**
9. Thiopurines should be discontinued in clinically significant myelosuppression or pancreatitis. Reintroduction of thiopurines after leucopenia (but not usually pancreatitis) can be considered at a lower dose after carefully assessing the risks and benefits and after measuring thiopurine metabolites and/or TPMT. **(95% agreement)**
10. Change in treatment should be considered in patients with active disease despite adequate 6-TGN level after at least 12 weeks of thiopurine treatment. **(98% agreement)**
11. Concomitant use of allopurinol) 50 mg once daily in patients <30 kg and 100 mg once daily is patients ≥30 kg, maximum 5 mg/kg) with reduced dose of azathioprine (to approximately 25% to 30% of initial dose), may provide a valid therapeutic option in cases of hyperactive TPMT resulting in high 6-MMP (often associated with elevated transaminases) and low 6-TGN, in suitably experienced units. Children must be closely monitored given the increased risk of toxicity. **(95% agreement)**
12. Benefits of withdrawal should be carefully weighed against an increased risk of 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 also histological remission. In the case of thiopurine withdrawal, 5-ASA treatment may assist in maintaining remission (particularly in patients naïve to 5-ASA). **(91% agreement)**
13. Methotrexate may rarely be considered in UC patients who fail to respond or are intolerant to thiopurines, when other alternatives are not possible or available. **(91% agreement)**
14. Oral tacrolimus (FK-506) may be considered in selected outpatient UC children as another option to steroids for bridging to thiopurines or vedolizumab (given the longer time to onset of action). At initiation, high target serum trough level (10–15 ng/mL) should be achieved with a gradual titration to lower trough levels (5–10

and eventually 2–5 ng/mL) in order to avoid serious adverse events. Selected patients may benefit from a long-term, low-dose treatment (ie, drug level target of 2 ng/mL), but the potential toxicity should be carefully considered, as well as noting the limited supportive evidence. **(93% agreement)**

The efficacy of thiopurines (azathioprine and 6-mercaptopurine) was evaluated systematically for both induction and maintenance of remission in adult UC patients. Meta-analyses of adult data concluded that azathioprine is not more effective than placebo for induction of remission but is superior to placebo in preventing relapse (129–131). In a recent prospective cohort study, sustained clinical benefit was achieved in 60% of 255 adult UC patients receiving azathioprine following 5-ASA failure, at a median follow-up of 30 months (132).

Prospective pediatric studies reported steroid-free remission rates of 49% at 1 year (133) and 72% at 2 years (134) in thiopurine treated children with no difference in either clinical or endoscopic end-points between early or late initiation of treatment. A few retrospective studies (135–138) in children supported the benefit of thiopurines in maintaining remission and steroid sparing with a median time to achieve steady state of thiopurine levels of 55 days (139). Cox proportional hazard modeling of retrospective data from 1175 incident children and young adults, did not demonstrate a benefit to early thiopurine use in reducing the risk of colectomy (140).

Despite 1 negative small adult study (141), it is not unreasonable to combine 5-ASA with thiopurines given the excellent safety profile of the former and its possible additive effect, including chemoprotection. 5-ASA may partially inhibit TMPT activity and therefore may increase 6-TGN levels (142,143).

Most adult studies used doses of 2.5 mg/kg for azathioprine and 1.5 mg/kg for 6-MP. There was, however, no clear dose-response effect for azathioprine, implying that low-dose azathioprine (1.5 mg/kg) may not be inferior to standard dose (144). Children younger than 6 years may require higher doses of azathioprine per body weight with doses of up to $3\,mg \cdot kg^{-1} \cdot day^{-1}$ (145,146).

The relative risk of serious adverse events with thiopurines was found to be 2.82 in a Cochrane meta-analysis of adult data (130). Thiopurine withdrawal rate due to adverse events in large pediatric cohorts was 18% (147) and 30% (148). Dose-independent adverse reactions include fever, pancreatitis, rash, arthralgias, nausea, vomiting, and diarrhea, while dose-dependent toxicities included leucopenia (up to 5%), thrombocytopenia, infections, and hepatitis (149,150). A meta-analysis of studies of 6-MP found that it was tolerated in 68% of 455 adult patients who were azathioprine-intolerant, lending support to switching between these drugs in cases of specific dose-independent adverse events (151). Switching in the case of pancreatitis has traditionally not been recommended but some recent case series have challenged this notion (151).

A meta-analysis (25,728 IBD patient-years) demonstrated that patients younger than 30 years have a high relative risk for non-Hodgkin lymphoma (SIR = 6.99) with younger men being at the highest risk. However, the absolute risk is much higher in the elderly. In patients younger than 30 years, the absolute risk is estimated at only 1 in 4000 to 5000 (152). Hepatosplenic T-cell lymphoma (HSTCL) is a very rare but fatal complication of thiopurine therapy. Of over 40 reported cases of IBD-related HSTCL, almost all received thiopurines, with or without anti-TNF and almost all were males; there are only extremely rare and anecdotal case reports of children with HSTCL who were treated solely with anti-TNF (153,154).

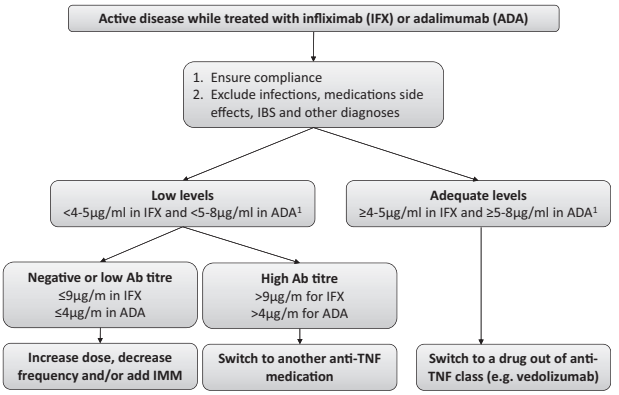

FIGURE 4. Practical interpretation of drug levels and antibodies for infliximab and adalimumab. Different countries use different measuring kits with different cutoff values; absolute drug and antibodies levels should be adapted accordingly. (1) Some studies (and the AGA recommendation in adults (210)) suggest that higher levels for infliximab (>5 μg/mL) and adalimumab (>8 μg/mL) should be the goal (see text).

TPMT assay (either phenotype or genotype) can be used before initiation of thiopurines to identify some of the patients who are at risk for dose-dependent myelosuppression, and in whom this drug should either not be used (if homozygous for variant alleles or have very low TPMT activity) or administered at lower dosage (if heterozygous for variant alleles or having low TPMT activity). TPMT testing does not, however, replace the need for mandatory monitoring of complete blood cell count especially during initiation of treatment. In an adult study (155), a significantly smaller proportion of carriers of a TPMT variant with adjusted dose developed hematologic adverse events (RR = 0.11). In a pediatric study, 7 of 46 (15%) carriers of at least 1 variant allele or low/intermediate TPMT activity developed myelosuppression compared to 0/62 in the wild type/high activity group (156). In contrast, a study of 72 children showed no association between TPMT polymorphisms and the occurrence of thiopurine-related adverse events (157).

In the case of hyperactive TPMT resulting in high 6-MMP and low 6-TGN, concomitant use of allopurinol with reduced dose of azathioprine may provide a valid therapeutic option (158,159) but needs to be used with caution. Adequate dose reduction and repeated monitoring of CBC and 6-TGN/6-MMP is essential to avoid myelosuppression related side effects. In adult trials, allopurinol was used at 100 mg once daily (158,160) whereas in the few pediatric case series lower doses (50 or 75 mg once daily) were utlized in younger children (159,161).

Therapeutic drug monitoring, namely measurement of thiopurine metabolites, specifically 6-TGN and 6-MMP levels, has been implemented as a means of optimizing efficacy and avoiding myelosuppression. In a meta-analysis which included 1026 IBD children (162), higher 6-TGN concentrations were not consistently associated with leucopenia, while marginally associated with greater likelihood of clinical remission. High 6-MMP levels correlated with hepatotoxicity, and low thiopurine metabolite levels with non-compliance. In a retrospective study including 86 IBD children, 6-TGN levels of >250 pmol per 8×10^8 red blood cells correlated with a higher response rate (OR = 4.14) (163). The association between both bone marrow toxicity and clinical response with 6-TGN levels was demonstrated in prospective adult studies

(164,165) as well as several retrospective pediatric cohort studies (163,166,167). Dose adjustment following measurement of metabolites was reported to increase disease remission rate (168). Children with IBD were shown to experience fewer exacerbations when thiopurine metabolites were measured (169). In a study of 78 IBD children, 6-TGN level above 405 pmol/8×10^8 RBCs was the only predictor for azathioprine resistance (OR 10.8) implying that patients with active disease and adequate 6-TGN level should receive alternative therapies (170).

Thiopurine withdrawal after attaining sustained remission is controversial. In a retrospective study of 127 UC patients in remission, approximately one-third relapsed within 12 months following withdrawal, and two-thirds within 5 years (171). Moderate/severe relapse rate of 26% at 2 years was observed in 108 UC patients who withdrew treatment following prolonged thiopurine treatment (172).

Cochrane meta-analyses of methotrexate (MTX) for induction (2 RCTs, 101 patients) (173) or maintenance (3 RCTs, 165 patients) (174) of remission in adult UC concluded that there is no evidence supporting the use of MTX for either induction or maintenance of remission in UC. Nevertheless, this conclusion relies on low-quality evidence. In the METEOR double-blind, placebo-controlled trial of 111 steroid-dependent UC adults, steroid-free remission at week 16 was not statistically different than placebo (32% vs 20%, respectively; $P > 0.05$) though clinical remission did differ (42% vs 24%, respectively; $P = 0.04$) (175). In a retrospective study of 32 UC children unresponsive or intolerant to thiopurines, response/remission was achieved in 72%, 63% and 50% of patients treated with parenteral MTX at 3, 6, and 12 months, respectively (176).

Tacrolimus has been studied in ambulatory UC patients (177). An RCT comparing high target trough level of tacrolimus (10–15 ng/mL) versus low trough level (5–10 ng/mL) versus placebo in adult moderate-to-severe UC patients who were hospitalized for the study, reported a significantly higher response rate in the high trough group (68% vs 38% vs 10%, respectively) (178). A retrospective cohort study of 25 ambulatory moderate-to-severe adult UC patients reported 52% clinical improvement and 44% clinical remission at 6 months (179). Three small retrospective pediatric studies, including 18 steroid refractory/dependent UC patients (180), 10 (181), and 8 (182) steroid-resistant patients treated with tacrolimus, reported 50% to 95% response rate; however, colectomy was eventually performed in most patients during the follow-up period. In a subgroup analysis, steroid-dependent patients had a significantly higher long-term colectomy free rate when compared with steroid refractory patients (78% vs 0%) (180).

Biologics

Recommendations

1. Infliximab (IFX) should be considered in chronically active or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission [EL2, adults EL1]. **(100% agreement)**
2. Adalimumab [EL4, adults EL4] or golimumab [EL4, adults EL3] could be considered in those who initially respond but then lose response or are intolerant to IFX, based on serum levels and antibodies (Fig. 4). **(95% agreement)**
3. Adalimumab and golimumab have no role in patients with primary non-response to IFX [EL4, adults EL4]. **(93% agreement)**
4. Vedolizumab should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure [EL4, adults EL2]. **(95% agreement)**

Practice Points

1. Screening for latent tuberculosis with 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 BCG immunized patients. Screening for hepatitis B and C viruses, varicella zoster virus, and HIV when appropriate, is also recommended if not done recently. **(95% agreement)**
2. In ambulatory patients with UC, IFX should be administered initially at 5 mg/kg per dose (at weeks 0, 2, and 6 followed by 5 mg/kg every 8 weeks for maintenance). Higher initial dosing should be considered in children with low body weight (<30 kg) or high BMI, and in the presence of higher inflammatory burden and hypoalbuminemia. Target trough levels post induction (week 14) and subsequent doses are reported in different studies as >4 to 5 μg/mL. Rapid infusion (over 1 hour) seems as safe and effective as traditional slower infusions, if the induction doses were well tolerated and dose is stable. **(98% agreement)**
3. IFX is recommended to be used preferably in combination with an immunomodulator (IMM) (with the most evidence in UC being thiopurines) in order to reduce the likelihood of developing antibodies to IFX (ATI) and in thiopurine-naïve patients to enhance effectiveness. Discontinuation of the IMM may be considered after 6 months, especially in boys, preferably after ensuring trough IFX level >5 μg/mL, since levels may decrease after stopping IMM. **(98% agreement)**
4. The utility of combination adalimumab, golimumab, and vedolizumab with thiopurines is more controversial and they are most commonly prescribed as monotherapy in children. **(100% agreement)**
5. Golimumab recommended doses for induction are 200 mg at week 0 followed by 100 mg at week 2 for those weighing ≥45 kg. Children with lower weight should be dosed based on body surface area (115 and 60 mg/m^2 at weeks 0 and 2). Maintenance doses q4w are 60 mg/m^2 if weight <45 kg and 100 mg if weight ≥45 kg. Target trough levels during maintenance are >2 μg/mL. **(100% agreement)**
6. Extrapolating from pediatric Crohn disease, 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. Optimal dosing in younger children has not been well defined, but BSA-based dosing could be considered

taking as a base an adult BSA of 1.73m^2 (ie, induction with 92 mg/m^2 followed by 46 mg/m^2 followed by 23 mg/m^2 every other week for maintenance). Adalimumab target levels during maintenance are reported in different studies as >5 to 8 μg/mL. **(100% agreement)**

7. Measurement of drug levels and anti-drug antibody levels following induction (ie, at the week 14 infusion for IFX and at 8–10 week for adalimumab) can assist in optimizing treatment. Measuring drug levels is also useful in the assessment of unsatisfactory response to anti-TNF to guide dose escalation or a switch to another biologic (see text). **(98% agreement)**
8. Standard vedolizumab dosing in adults has been adapted in pediatric studies (5 mg/kg up to 300 mg per dose at weeks 0, 2, 6 followed by every 8 weeks thereafter). For those weighing <30 kg, higher dose per kg is required, but BSA-based calculation may be preferred (ie, 177 mg/m^2). The effect of vedolizumab in UC has been described to occur by week 6 of treatment, but complete response may not be apparent until week 14. Shortening of interval between infusions to 4 weekly may be required during maintenance in partial responders. **(93% agreement)**
9. In patients with persistent symptomatic distal inflammation despite adequate optimal anti-TNF treatment, addition of rectal therapies (preferably 5-ASA) could be beneficial. **(98% agreement)**

A Cochrane systematic review of 7 adult UC trials concluded that IFX is effective in inducing clinical remission, promoting mucosal healing, and reducing the need for colectomy in patients with active UC (183). Combination therapy with IFX and azathioprine was shown to be superior in the SUCCESS trial in adult UC to monotherapy with azathioprine or IFX alone, while there was no superiority of IFX monotherapy over azathioprine (184).

In the pediatric UC regulatory RCT (ie, the T-72 study), 45 of 60 (75%) ambulatory children with moderate-severe UC responded to a standard induction protocol of IFX (40). Both clinical remission (PUCAI < 10 points) and complete mucosal healing (Mayo endoscopic subscore = 0) were achieved in 33% at week 8. Dose escalation to 10 mg/kg was required in 44% of the patients in the maintenance phase.

Different studies in children have shown a pooled long-term success rate of IFX in UC of 64% (185), and a corticosteroid-free remission of 38% and 21% at 12 and 24 months, respectively, with a likelihood of avoiding colectomy at 2 years of 61% (186). A relationship between the increased use of anti-TNF agents and the reduction of surgery risk for UC children has also been suggested (187).

Adalimumab has shown efficacy and safety for induction and maintenance in the adult moderate-to-severe active UC. In the adult ULTRA-1 trial, clinical remission was obtained in 18.5% of patients in the 160/80 mg group, 10% in the 80/40 mg group and 9.2% in the placebo group (188). In the ULTRA-2 trial, overall rates of clinical remission for active drug at week 52 were 17.3%, with better results among anti-TNF-naïve patients (22%) as compared to those anti-TNF experienced (10.2%) (189). A network meta-analysis of 5 RCTs in moderate-to-severe adult UC suggested that while IFX is more effective than adalimumab in the induction of remission, response and mucosal healing, both are comparable in efficacy at 52 weeks of maintenance treatment (190). Another meta-analysis showed superiority of IFX over adalimumab in inducing and maintaining endoscopic healing in UC (191). In a propensity score adjusted analysis, a study of 419 adults with UC found no difference in the effectiveness of these agents, but the adalimumab group was relatively small (192).

In a retrospective cohort study of 188 children, Vahabnezhad et al showed that 60% of UC children who discontinued IFX were commenced on adalimumab, with 83% of these remaining on adalimumab at last follow-up (193). In another retrospective study, 55% of UC children switched to adalimumab after IFX failure, achieved and maintained clinical remission at a median of 25 months while 36% underwent colectomy (194). There are no published data on adalimumab in UC children naïve to anti-TNF.

A second subcutaneously administered, fully human anti-TNF agent, golimumab, has been studied in placebo-controlled trials among anti-TNF-naïve adults with moderately-severely active UC in the PURSUIT-SC (195) for induction, and PURSUIT-M (196) for maintenance. Golimumab use in pediatric UC was studied in an open-label pharmacokinetic study of 35 children with moderate-severe UC (197,42). Doses given subcutaneously at weeks 0 and 2 were 90 and 45 mg/m^2 for children weighing <45 kg and 200 mg followed by 100 mg for those weighing ≥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 Mayo clinical responders (60%) who continued to receive 4 weekly golimumab maintenance, 57% were in PUCAI remission at week 14. Complete mucosal healing at week 6 was achieved in 23%, slightly higher than reported in the adult trials. While the pharmacokinetics data of the entire pediatric cohort were comparable with those previously reported in the golimumab adult trials, drug levels in the subgroup of children weighing <45 kg were numerically lower than those ≥45 kg. This likely stems from the under-dosing of the former group. 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. Given the lower drug levels in the pediatric study, these higher doses should be considered in practice.

In general, response to anti-TNF medication can occur as early as 1 to 4 weeks and peaks by week 12 to 16 of treatment (188,189,198). During induction, trough level of ≥15 μg/mL at week 6 best predicted likelihood of short-term mucosal healing (area under the ROC of 0.69) (199). Recommended optimal levels for IFX during maintenance therapy for improved clinical outcomes has been defined as >4 μg/mL (200–202), for adalimumab >5 μg/mL (203,204), and for golimumab >1.4 μg/mL (205). For mucosal healing, adult studies from both UC (206,207) and CD (207,208), however, suggested that higher adalimumab level ≥7.1 to 9.4 μg/mL may be more appropriate. Similarly, IFX trough levels >5 μg/mL were associated with mucosal healing in adult IBD (207) and with a decreased risk for loss of response when withdrawing concomitant immunomodulators (209). The American Gastroenterological Association guidelines thus recommend using higher cutoff values of ≥5 μg/mL for IFX and ≥7.5 μg/mL for adalimumab (210).

Drug and antibody levels should dictate the course of action in patients with secondary loss of response (211) (Fig. 4). Ongoing symptoms despite adequate drug levels, mandates switching therapy ''out of class.'' High antibodies titer predicts failure of dose intensification (211) (Fig. 4).

Factors predicting lower drug levels (and thus possibly dictating higher dosing) include higher body mass index (212), low body weight <30 kg (213–215), male gender (216), high inflammatory burden (extent and severity of disease) (217),

TABLE 5. Paediatric VSL#3 dosing (by Miele et al (279))

Age, y	Weight, kg	Daily/dose, bacteria/day
4–6	17–23	1 sachet (450 billion)
7–9	24–33	2 sachets (900 billion)
11–14	34–53	3 sachets (1350 billion)
15–17	54–66	4 sachets (1800 billion)

hypoalbuminemia (218), the presence of anti-drug antibodies, and the absence of a concomitant immunomodulator (184,219–221).

Safety issues of anti-TNF include acute infusion reactions (within 4 hours of infusion), delayed hypersensitivity reactions (beyond 4 hours in both lines of infusion and up to 14 days), serious and opportunistic infections (222), and a potential risk of skin cancer; evidence to date does not indicate that anti-TNF is associated with lymphoma if prescribed as mono-therapy, but a recent study challenges this concept (223). Psoriasis has been well documented as an adverse class effect of anti-TNF, but it is usually mild and controllable in the majority of patients with topical therapy (224). Other very rare adverse events, such as demyelination events and optic neuritis, have been reported (225).

There is no clear evidence that pre-medication with any drug prevents the development of acute infusion reaction (226,227). A self-reporting system in the United States with >5000 documented patients calculated a rate of infusion reactions of 3% (1.1% immediate and 1.7% delayed) in IBD-treated patients (228).

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 (229). The risk of reactivation of other viruses (eg, CMV, EBV) is not clear. A recent systematic review and meta-analysis including 49 RCT comprising >14,000 patients treated with biologics (anti-TNF, natalizumab, and vedolizumab) concluded that their use has a moderate risk of any infection (OR 1.19 (95% CI 1.1–1.29)) and a significant risk of opportunistic infections in IBD (OR 1.90 (1.21–3.01)) (230). In another study, the estimated risk of severe infections in IBD patients treated with anti-TNF has been reported as 2.2% (231). Concomitant immunosuppressant treatment, particularly steroids, is an additional risk for opportunistic and other infections. Surprisingly, the meta-analysis 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 outcome the data were insufficient in terms of exposure and follow-up period (230). Studies report conflicting results regarding the risk of anti-TNF and the risk for melanoma and non-melanoma skin cancer (232,233).

DEVELOP is a prospective post-marketing industry-initiated safety registry for pediatric IBD, which includes both patients exposed and never exposed to IFX (234). 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 IFX; 3 thiopurine only); 1 only to IFX; 1 to neither biologics nor thiopurines). Comparison with rates from the SEER database of healthy controls indicated a standardized incidence rate (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 IFX exposure in the absence of thiopurine exposure (SIR 1.49, 95% CI 0.04–8.28). Five children in total experienced hemophagocytic lymphocytic histiocytosis (HLH), 4 with primary EBV infection, one with CMV infection, and all during thiopurine monotherapy.

Vedolizumab is a humanized anti-$\alpha 4\beta 7$ integrin that down-regulates intestinal inflammation by specifically inhibiting intestinal T-lymphocyte migration into the tissue. In the adult GEMINI-1 study in UC, 47% of patients responded to 2-dose induction (300 mg per dose) by week 6 and were re-randomized to continued vedolizumab 300 mg intravenously (4 weekly vs 8 weekly vs placebo). The 52-week remission rates among initial week 6 responders were 42% (q8w) and 45% (q4w) (235), regardless of the prior anti-TNF exposure status (236,237). This is supported by pharmacokinetic data demonstrating significant correlation between higher vedolizumab drug levels and clinical response in IBD patients (238–240).

Experience with vedolizumab in pediatric UC is currently limited to small retrospective cohorts, almost all with prior anti-TNF failure. The 14-week remission rates were 37% (n = 41 definition of remission included steroid-free and utilized ITT rates) (241), 40% (n = 5; (242)), and 76% (n = 22 (243)). The 22-week corresponding remission rates in the 3 studies were 34%, 40%, and 71%, respectively. There is no evidence that combination therapy with IMM is superior over sole vedolizumab treatment based on very limited data from adults (244) and children (241).

Limited safety data are reported for vedolizumab in children. Conrad et al reported 29 adverse events in children including upper respiratory tract infections, nausea, fatigue, headaches, nasopharyngitis, skin infections, and sinusitis (242). Pruritus, infusion reaction, and nasopharyngitis (1 each) was also reported by the Paediatric IBD Porto group of ESPGHAN (241).

In a recent network meta-analysis in adults, IFX, adalimumab, golimumab and vedolizumab were all superior to placebo for maintenance of remission and response; however, superiority of 1 agent over another could not be clearly established (245).

Other Interventions

Recommendations

1. Granulocyte/monocyte apheresis should not be routinely used in pediatric UC [EL4, adult EL2]. **(100% agreement)**
2. Fecal microbiota transplantation (FMT) should not be routinely used in pediatric UC [EL4, adult EL1]. **(100% agreement)**
3. Antibiotics should not be routinely used for induction or maintenance of remission of pediatric UC [EL5, adult EL2]. **(100% agreement)**
4. Probiotic agents (eg, VSL#3 [Table 5], *Escherichia coli* Nissle 917) may be considered in mild UC as an adjuvant therapy or in those intolerant to 5-ASA [EL2, adult EL2]. **(100% agreement)**
5. Curcumin may be considered as an add-on therapy for inducing and maintaining clinical remission of mild-to-moderate UC [EL4, adult EL1]. **(91% agreement)**
6. Germinated barley foodstuff, omega-3, aloe vera, herbal medicine, and intravenous immunoglobulin, are not recommended as primary treatment [EL5, adult EL2]. **(98% agreement)**

Practice Points

1. If apheresis is considered, then the most commonly utilized scheme involves 1 session per week of granulocyte/monocyte apheresis for 5 to 10 consecutive weeks. **(93% agreement)**

2. VSL#3 dosing may be seen in Table 5. *E coli* Nissle 1917 strain is prescribed as 200 mg/day in adults and adolescents. No dosing recommendation is available for young children. **(98% agreement)**
3. Neither the formulation nor dosage of curcumin (the active ingredient of tumeric/curcum) are established for children but evidence suggests that it can be safely used up to 4 g/day for induction and up to 2 g/day during maintenance. The induction dosing of an ongoing pediatric trial is as follows: (all doses are daily, prescribed as 2 divided doses): 4 g for children over 30 kg, 3 g for 20 to 30 kg and 2 g for those under 20 kg (safety has not been established in infants). Doses may be halved for maintenance treatment. **(98% agreement)**

Apheresis acts by an extracorporeal removal of leukocytes and other cells of the immune system (granulocytes, granulocyte/monocyte) through an adsorptive system of cellulose acetate beads (Adacolumn, Otsuka Pharmaceuticals, UK), or a polyester fiber filter (Cellsorba, Asahi Medical Company). Overall, pediatric data suggest a possible clinical efficacy of apheresis in children with both steroid-dependent and resistant UC, with reported response rates ranging between 60% and 85%, although they are mainly small case series or cohort studies (246–251). Data in adults are conflicting, with some observational and randomized clinical trials suggesting benefit (252–257), others, among them a large randomized, double-blind clinical trial evaluating active versus sham apheresis, showing no efficacy (258). A systematic review published in 2010 reported that, although there may be some efficacy in specific settings, concerns about methodological quality of identified studies prevent a rigorous meta-analysis and definitive conclusions (259).

FMT is based on the transfer of stool from a healthy donor, with a presumed healthy diverse microbiome, to a patient. Related or unrelated donors can be used, and they must undergo an accurate clinical and laboratory screening before the procedure. Some studies have used specifically prepared fresh stools, although frozen stools seem to have the same efficacy and safety (260), with delivery both to the upper gastrointestinal tract through nasogastric tube or to the lower gastrointestinal tract through colonoscopy or serial enemas. A few case series on the efficacy of FMT in pediatric UC have been published, reporting inconclusive results (261–263). The largest pediatric series (9 children with UC) showed a 33% clinical remission (PUCAI < 10) with serial enemas (261). One small pediatric study reported no clinical improvement after FMT delivered via nasogastric tube (262). Overall, the safety profile appears acceptable, although mild-to-moderate side effects were common, and a case of transitory systemic reaction (profuse sweating, vomiting, paleness, tachycardia, and fever) has been reported (264). There may be a theoretical risk pertaining the transfer of an adult microbiome to a child, particularly very young with a developing microbiome, to quickening of immune aging and developing immune-related consequences (265). Rapid weight gain and the development of autoimmune disease have been reported after FMT in adults and in animal models (266–268).

Two small RCTs in adults with active UC reported different results: one showed clinical and endoscopic benefit of FMT administered via enema compared to sham (269); the other reported no difference between FMT using healthy donors or autologous feces administered via naso-duodenal tube, although the limited number of patients and the route of administration may have impacted on these results (270). Interestingly, patients who responded to FMT from a healthy donor restored their altered microbiota toward the healthy donor composition, while non-responders had no changes. Recently, the results of a third large, randomized, placebo-controlled trial in active UC resistant to conventional treatment have been reported (271). Eighty-one adults with UC were randomized to receive a single FMT or placebo colonoscopic infusion on day 1, followed by FMT or placebo enemas 5 days per week for 8 weeks. Each active enema was derived from 3 to 7 unrelated donors. Steroid-free clinical remission with endoscopic response was achieved in 11/41 (27%) patients receiving FMT compared to 3/40 (8%) patients receiving placebo ($P = 0.02$). Microbial diversity increased and persisted after FMT while *Fusobacterium* spp was associated with lack of remission. Although FMT is gaining increased enthusiasm, the ideal donor and method of administration should be first determined before this can be incorporated outside the research setting.

Probiotics have been evaluated for induction and maintenance of remission in UC. One pediatric and 3 adult trials found *E coli* Nissle 1917 to be as successful as mesalamine in maintaining remission (272–275). The dosage used in all these studies, including the pediatric one, is 200 mg/day (100 mg contains 25×109 viable *E coli* bacteria), administered as capsules. A recent systematic review and meta-analysis suggests that *E coli* Nissle is equivalent to mesalamine to prevent relapse, while its efficacy is comparable to placebo in the induction of remission (276). A previous Cochrane systematic review, however, highlighted several methodological limitations in the maintenance studies, preventing any conclusion (277).

A small randomized, placebo-controlled trial of 29 children treated with 5-ASA reported that the combination of VSL#3 in conjunction with concomitant steroid induction and mesalamine maintenance treatment was superior to placebo in inducing and maintaining 1-year remission (278). A small open-label study in 18 children with mild-moderate UC evaluated the efficacy of VSL#3 added to standard treatment with 56% remission rate (279). Overall, adult data suggest a therapeutic benefit of VSL#3 in the maintenance of remission, supported by a systematic review (280). Studies on VSL#3 in IBD patients were performed on the original formulation containing 8 bacterial strains (*Lactobacillus paracasei* DSM 24733, *Lactobacillus plantarum* DSM 24730, *Lactobacillus acidophilus* DSM 24735, *Lactobacillus delbrueckii* subspecies bulgaricus DSM 24734, *Bifidobacterium longum* DSM 24736, *Bifidobacterium infantis* DSM 24737, *Bifidobacterium breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731). Changing the manufacturing processes by different manufacturers may not have the same clinical efficacy and safety. Scarce published data report varying content of live/dead bacteria in various VSL#3 products and differences in effect on intestinal epithelial cell status (281,282). More studies are, however, needed to confirm these data and no changes in the recommendations are warranted at this stage. One randomized pediatric trial showed that rectal enemas of *Lactobacillus reuteri* ATCC 55730, added to oral mesalamine, were superior to placebo for inducing remission in left-sided UC (283).

Antibiotics have been evaluated as a therapy for UC both in the induction of remission and to prevent disease relapses as shown in 2 systematic reviews and meta-analyses (284,285). Both included 9 RCTs and concluded that antibiotics may improve outcomes in UC, but further studies are required to confirm this benefit since the included trials were very heterogeneous in their methodology and the type of drug intervention. The use of antibiotics in treating pediatric UC outside the research setting awaits further trials.

Recently, a small case series on the tolerability of curcumin added to standard therapy in pediatric IBD has been published, reporting an acceptable tolerability and a possible signal of benefit

(286). Two placebo-controlled trials conducted in adults suggested the possible efficacy of curcumin in achieving and maintaining sustained clinical remission (287,288). Moreover, endoscopic remission was observed in 38% (8/22) patients treated with curcumin, compared with 0% (0/16) in the placebo group (288). A recent randomized, placebo-controlled, pilot study reported efficacy of topical curcumin as enema, added to oral mesalamine, compared to placebo, in 45 adults with mild-moderate proctitis/proctosigmoiditis (289).

Systematic review of complementary and alternative medicine treatments in IBD, including aloe-vera, andrographis paniculata, artemisia absinthium, barley foodstuff, boswellia serrata, cannabis, evening primrose oil, Myrrhinil intest, plantago ovata, silymarin, sophora, tormentil, wheatgrass-juice, and wormwood reported a possible benefit of some interventions, although, given the small number of trials and their heterogeneous methodological quality, no definite conclusions could be drawn (290,291). Of note, oral aloe vera has been evaluated in a double-blind, randomized, placebo-controlled trial as an adjuvant therapy in 44 adults with mild-to-moderate UC (292). Higher remission and response rates with improvement of the histological score were reported in the aloe vera group. These encouraging but preliminary findings await confirmation before aloe vera can be recommended for clinical practice.

Other complementary therapies, including germinated barley foodstuff and herbal medicine have been studied in adult case series or prospective cohorts. Because of sample size, study design, concomitant therapies and methodological limitations, these agents cannot currently be recommended for treating pediatric UC (290,291,293).

A systematic review and a meta-analysis reported no efficacy of omega-3 supplement for maintaining remission in UC (293–295). Recently, a retrospective individual cohort study of 24 adults with IBD suggested efficacy and safety of intravenous immunoglobulin in the short-term management, when standard therapies are contraindicated (296). There are, however, no RCTs on its role both in adults and children.

Inflammatory Bowel Disease-unclassified

Recommendation

1. Treatment of IBDU patients should broadly follow that of UC patients of a similar disease severity [EL4, adult EL5]. **(98% agreement)**

Practice Points

1. A diagnosis of IBDU should only be made after a complete assessment including ileocolonoscopy, gastroscopy, and small bowel imaging. **(100% agreement)**
2. A lower threshold for disease reassessment should be adopted in patients with IBDU before treatment change. **(95% agreement)**
3. Although not validated for this indication, it is reasonable to use the PUCAI score to assess disease activity also in IBDU given the similarity of IBDU, clinically, to UC. **(98% agreement)**
4. A multi-item algorithm should be used to standardize the diagnosis of IBDU (Fig. 1; Table 1). **(98% agreement)**
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 IBDU. **(98% agreement)**

Patients with IBDU represent approximately 5% to 10% of pediatric IBD without a decline in incidence over time despite improved diagnostic measures. The rate is even higher in very early onset IBD. Complete examination is important, however, and the proportion of patients with IBDU is reduced if a full diagnostic work up is performed (297). IBDU is not a misclassification but rather a true overlap diagnosis within the spectrum of phenotypes between UC and Crohn colitis (12). Historically, patients with IBDU have often been poorly classified with no specific guidance available for detailed diagnostic criteria. The PIBD-Classes criteria were validated on a large multicenter dataset of 749 patients with colonic IBD from the Paediatric IBD Porto group of ESPGHAN (12). A diagnostic algorithm combining 23 features of different weightings (grouped in class 1, 2, and 3 features) (Table 1) may differentiate between patients with UC, atypical UC, IBDU, Crohn colitis and ileal/ileocolonic Crohn disease (Fig. 1) (12).

Given the rarity of IBDU and the hitherto lack of standardized diagnosis, there are very few studies which have been able to collect treatment information on significant numbers of patients. The aforementioned retrospective study from the Porto group of ESPGHAN utilized the data of 537 children with colonic IBD, including 260 IBDU, to explore common treatment schemes and to compare the treatment outcomes (298). This study demonstrated that treatment for IBDU and UC were broadly similar with the most common treatment used initially being 5-ASA. The use of steroids was lower than in UC; thiopurines and IFX use was broadly similar to patients with UC and lower than for patients with Crohn disease. Rates of surgery were lower than in Crohn disease and UC and the disease was more likely to be mild at follow-up compared to the other IBD subtypes, despite the similar use of medications as in UC. This suggests that treatment can follow that of UC initially with a 5-ASA regimen.

SURGICAL CONSIDERATIONS (RELATED TO BOTH PART 1 AND 2 OF THESE GUIDELINES)

The Surgeon's Perspective

Recommendations

1. Elective colectomy should be considered in children with active, or steroid-dependent, UC despite optimized medical therapy, and in those with colonic dysplasia [EL4, adult EL3]. **(98% agreement)**
2. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA; J pouch) and a covering loop-ileostomy is the recommended elective surgery for pediatric UC [EL3, adult EL3]. **(93% agreement)**
3. Three-stage procedure (subtotal colectomy with ileostomy first) is recommended for patients with acute severe colitis, treated with high-dose steroids, or recent anti-TNF therapy, severe malnutrition, or IBDU; however, the final choice of the surgical approach should be individualized [EL4, adult EL3]. **(98% agreement)**

4. A minimally invasive laparoscopic approach is recommended in children as there are equivalent outcomes to open surgery both for urgent and elective cases and possibly superior outcomes regarding fertility in girls [EL4, adult EL3]. **(100% agreement)**
5. Pouch surgery for children with UC should be performed by experienced pediatric or adult surgeons in high volume centers preferably performing at least 10 pouches per year. **(100% agreement)**

Practice Points

1. Crohn disease must be excluded before the time of surgery, through a diagnostic workup including ileocolonoscopy, gastroscopy, and small bowel imaging, before colectomy, as clinical status allows. **(100% agreement)**
2. Functional outcomes and surgical complications are comparable after hand-sewn and stapled IPAA. The length of remaining anorectal mucosa between the dentate line and the anastomosis should not exceed 2 cm, regardless of anastomotic technique. **(100% agreement)**
3. IPAA without a covering loop ileostomy (ie, 1-stage procedure) may be considered in selected children with mild disease and good nutritional status without anti-TNF or steroid treatment, provided that no technical difficulties or anastomotic tension occur during surgery; however, the final choice of the surgical approach should be individualized. **(98% agreement)**
4. There is no published evidence on whether postponing pouch surgery after subtotal colectomy, for example, until after puberty, influences long-term outcomes after IPAA. If pouch surgery is delayed, a strategy to maintain the rectal stump free of inflammation should be discussed, based on topical treatment. **(100% agreement)**
5. The role of ileorectal anastomosis (IRA) remains controversial. It may be offered to selected female patients, who are particularly concerned about the risk of reduced fertility associated with IPAA. Information on higher failure rate and the need for lifelong cancer surveillance should be provided. **(98% agreement)**
6. Treatment with steroids (prednisolone $>0.25\,mg \cdot kg^{-1} \cdot day^{-1}$ or $>20\,mg/day$) is associated with an increased risk of surgical complications, whereas thiopurines and calcineurin inhibitors are not. There are insufficient data regarding vedolizumab. Anti-TNF increases the surgical risk in Crohn disease and according to the precautionary principle, colectomy should be preferably performed 4 to 6 weeks after the last IFX infusion if it can be safely postponed. **(93% agreement)**

Surgery for pediatric UC may require up to 3-staged procedures—first stage, subtotal colectomy with end-ileostomy; second stage, restorative procto-colectomy with ileal pouch-anal anastomosis or ileo-rectal anastomosis (with or without covering ileostomy); third stage, closure of the covering ileostomy. The decision concerning the best combination of procedures is dictated by the clinical status of the patient. Restorative procto-colectomy and IPAA/IRA with covering ileostomy can be performed as a combined first stage for most ''ambulatory'' elective UC cases. The covering ileostomy is reversed several months later after confirmed healing of the pouch (299–303). Three-stage surgery (subtotal colectomy and ileostomy first) is recommended for ASC, for example, where the pre-operative PUCAI is >45, or in those on high-dose pre-operative steroids (prednisolone $>0.20\,mg \cdot kg^{-1} \cdot day^{-1}$) (36,301). Although single-stage restorative procto-colectomy IPAA without a covering ileostomy was not associated with increased anastomotic complications in some retrospective pediatric series (300,304–306), this cannot be recommended before more studies are available given the retrospective design of the studies and the inherent confounding by indication bias.

Emergency surgery for ASC is an initial subtotal colectomy (leaving a rectal stump) with end-ileostomy formation only. Creation of IPAA/IRA should be deferred until the clinical status of the patient has normalized, followed by stoma closure as the third stage. Laparoscopic colectomy/ileostomy for both ASC and ambulatory UC is safe and feasible in experienced hands also in children (36,307). The PUCAI has been reported in a retrospective analysis to be a useful tool when considering 1- versus 2- versus 3-stage procedures for pediatric UC (36).

As significant complication rates are reported after colectomy for both ASC and ambulatory UC in children, in particular infectious and thromboembolic events (8,308), peri-operative antibiotic and thromboembolism prophylaxis should be routine. The rectal stump can be fashioned as a mucous fistula (open or within the subcutaneous tissue) if there is significant proctitis. A more commonly used alternative is to close the rectal stump within the abdomen and place a temporary trans-anal drain (309). Length of hospital stay, short-term surgical complications and functional outcomes seem similar after open and laparoscopic procedures (300,310–312).

Steroid treatment, hypoalbuminemia and malnutrition are also associated with increased surgical complication rates (313). In ASC, children are likely to have been on recent steroid therapy and may be in a relatively poor nutritional state, but surgery when needed should not be delayed to correct this. Thiopurine and calcineurin inhibitors were not associated with postoperative surgical complications (313–315), while current retrospective pediatric data on anti-TNF regimens are controversial (313,314,316). Meta-analysis of adult data shows an increased risk of surgical complications in patients who had been on pre-operative anti-TNF therapy in CD but not in UC (317,318).

According to a meta-analysis of 5 pediatric studies (306 patients), straight ileo-anal anastomosis (SIAA) was associated with a higher failure rate (15% vs 8%) and perianal sepsis (20% vs 10%), as well as a higher stooling frequency as compared with a J pouch ileo-anal anastomosis (JPAA) (319). A more recent multicenter study, including 112 children with SIAA, and 91 with JPAA, reported comparable postoperative complication rates (320). Both day-time and night-time stooling frequency were higher after SIAA, although the difference became less apparent by 2 years (mean 24 hours stooling frequency 8.4 vs 6.2 at 2 years). This difference may still be clinically important, because quality of life in children after restorative proctocolectomy is inversely associated with stooling frequency (302).

JPAA, on the other hand, carries a risk of pouchitis, which clearly exceeds the incidence of enteritis following SIAA (49% vs 24%, OR 4.5; see henceforth detailed chapter on the pouch) (320). Surgical complications and functional outcomes are comparable

after hand-sewn or stapled J-pouch anastomosis. For example, in 1 series, stool frequency was 4 per day after both techniques (299,321,322). A common complication of stapled IAA is, however, an undesirably long rectal stump with excessive remaining anorectal mucosa above the dentate line (>2 cm). Chronic inflammation of the rectal mucosal remnant is called ''cuffitis'' and discussed further below. One study reported a lower rate of small bowel obstruction during 4 post-operative years after laparoscopic IPAA compared to open procedures (310), while no difference was found in another (300).

In those undergoing IPAA, the diagnosis of UC may change to CD; ~15% in adult series (299,302,303,323) and 11 of 128 children (9%) in a recent multicenter pediatric study from the Paediatric IBD Porto group of ESPGHAN (324,325). Three-stage IPAA has been used to reduce these complications in children with IBDU. Histology of a colectomy specimen or pre-operative diagnosis of IBDU, however, poorly predicts the long-term outcomes of IPAA in adults with UC (326,327). In most studies, the incidence of pouchitis and post-operative diagnosis of CD is similar after IPAA in patients with UC and IBDU (321). There is no published evidence on whether postponing pouch surgery after subtotal colectomy for an extended period influences the rate of complications or long-term outcome after IPAA. Overall, results from pediatric series of IPAA in terms of later pouch abandonment (<15% at median 10–20 years follow-up) are similar to adult reports, albeit with shorter length of follow-up in most series (300,302,328). A multicenter, retrospective study from the Paediatric IBD Porto Group of ESPGHAN included 129 children who underwent IPAA, showed an increased rate of surgical complications in children undergoing colectomy under the age of 10 years but there was no difference in complications rate whether the pouch surgery was delayed or not (324).

While IPAA has been shown to reduce female fecundity and fertility in adult studies (e.g. reduction of fertility rate by 52% among women aged 15 to 44 years (323)), most used the non-stringent definition of inability to become pregnant within 1-year of intent (322,323). This should be discussed with female patients and their family before any surgical procedures. Laparoscopic IPAA, as is increasingly performed, may ameliorate the risk of subfertility due to reduced adhesion formation, pelvic scarring and Fallopian tube obstruction (329–331). In 1 adult series, spontaneous pregnancy rate was higher after laparoscopic IPAA (70%) compared to open IPAA (39%, $P = 0.023$) among 50 women who attempted to conceive (326). Fertility is also much better preserved after IRA (300). Fecundity remained similar to the general population after IRA, but dropped to 54% after IPAA among women with familial adenomatous polyposis (327). In a recent follow-up study of 343 adults with UC, 10- and 20-year IRA failure rate was 27% and 40%, respectively (328). Secondary proctectomy was required for refractory proctitis (66%), dysplasia (11%) and for cancer (10%) (332). At the end of the follow-up, 18% had undergone secondary IPAA and 13% had permanent ileostomy. Although fecal continence and stooling frequency is better preserved after IRA compared to IPAA, most patients require anti-inflammatory medication and urgency rate is higher, while quality of life similar to that after IPAA (328).

Data from the Porto group of ESPGHAN suggest that the experience of the surgeon is associated with the likelihood of development of chronic pouchitis; (15%) in surgeons with ≥10 surgeries/year versus (41%) in surgeons with <10 per year, $P = 0.013$ (325). This is in line with a large study from the UK showing the pouch outcome was superior if done in centers performing at least 9 to 10 procedures annually (333).

Pouchitis and Cuffitis

Recommendations

1. Pouchoscopy with mucosal biopsies should be performed at the first suspected episode of pouchitis [EL3, adult EL3]. **(95% agreement)**
2. A 14-day course of ciprofloxacin and/or metronidazole is recommended as first-line therapy for pouchitis while the former may be more effective [EL5, adult EL1]. **(100% agreement)**
3. Combined metronidazole and ciprofloxacin or oral/topical budesonide can be used in persistent cases [EL5, adult EL2]. **(98% agreement)**
4. In recurrent and/or chronic pouchitis, VSL#3 is recommended for maintaining remission [EL5, adult EL1]. **(98% agreement)**
5. Topical mesalamine is recommended for treating cuffitis [EL 5, adult EL4]. **(100% agreement)**

Practice Points

1. A clinically useful categorization of pouchitis is ''antibiotic-responsive'' (ie, infrequent episodes (<4 per year) each with a rapid response to a 2-week course of a single antibiotic, ''antibiotic-dependent'' (ie, frequent episodes (≥4 per year) or persistent symptoms which require long-term antibiotic therapy to maintain remission) and ''antibiotic-refractory'' (ie, failure to respond to a 4-week course of antibiotics, necessitating an alternative therapy of 4 weeks or longer). Duration of pouchitis can be categorized as acute (<4 weeks) or chronic (≥4 weeks) and frequency may be described as infrequent, relapsing, or continuous. **(100% agreement)**
2. In chronic, recurrent or refractory pouchitis-like symptoms, other diagnoses, such as cuffitis, missed Crohn disease, anastomotic ulcer, irritable pouch syndrome, infectious pouchitis, and anastomotic stenosis, should be excluded. **(100% agreement)**
3. Fecal calprotectin may be used to assess pouch inflammation to minimize repeated pouchoscopies in recurrent pouchitis and to monitor response to treatment. Calprotectin >300 μg/g is suggestive of pouchitis while lower levels do not preclude pouchitis (57% sensitivity, 92% specificity). **(95% agreement)**
4. The common antibiotic dosing strategies for pouchitis are ciprofloxacin ($30\,mg \cdot kg^{-1} \cdot day^{-1}$ up to 1 g/day in 2 divided doses) and/or metronidazole ($20–30\,mg \cdot kg^{-1} \cdot day^{-1}$ in 3 divided doses up to 1.5 g/day) for 14 days. **(98% agreement)**
5. VSL#3 can be used once daily at an age- or weight-dependent dose (Table 5). **(95% agreement)**
6. VSL#3 may be also effective for preventing the first episode of pouchitis, but this is not justified since many children will never develop pouchitis. **(100% agreement)**
7. Thiopurines may be considered in refractory pouchitis, not responding to antibiotic therapy or in the presence of budesonide dependence, despite the

lack of good evidence. The effectiveness of IFX for this indication has been demonstrated only in adult case series with a response rate of ~50%. **(98% agreement)**

Pouchitis, a non-specific and idiopathic inflammation of the ileal reservoir, is the most common complication of IPAA, occurring in 24% to 67% of pediatric UC patients (299,300,302,320, 323,334–337). A recent multicenter, retrospective cohort study from the Paediatric IBD Porto Group of ESPGHAN included 129 children who underwent IPAA (93% UC and 7% IBDU) and showed that 86 children (67%) developed pouchitis during follow-up (325). In 33 (26%) the pouchitis was chronic, 10 of whom (8%) had Crohn-like disease of the pouch. Median time from pouch formation to the first episode of pouchitis was 10.5 months (IQR 6–22); in 54% of cases the first episode occurred within 1 year. In an older cohort of 399 UC children with a mean age of 18 ± 3 years at colectomy, 121 (36%) had at least 1 episode of acute pouchitis, and 29 (9%) pouch failure (300). Pouch type, age, and operative technique had no impact on whether patients developed pouchitis.

Symptoms and severity of pouchitis vary, but typically include increased stool frequency and urgency, tenesmus, incontinence, abdominal pain, and rectal bleeding (338). Cuffitis, residual rectal cuff inflammation, may cause symptoms similar to those of pouchitis, especially bleeding. The cuff is the remaining rectal mucosa between the dentate line and the anastomosis after restorative procto-colectomy. Symptoms of pouch dysfunction in patients with IPAA may be caused by conditions other than pouchitis, including CD of the pouch, anastomotic ulcer or stenosis. In children, the occurrence of terminal ileitis, or ''pre-pouch ileitis,'' has also been reported (339), and does not necessarily confirm the diagnosis of CD if it involves only mild inflammation in a short segment. Other differential diagnoses include ischemia and, rarely, infections such as CMV and *C difficile*. A diagnosis of irritable pouch syndrome is suspected when symptoms are present without endoscopic inflammation (340). Thus, endoscopic and histological evaluation of the pouch should be performed at the first episode of pouchitis and periodically thereafter.

Endoscopic features of pouchitis may include hyperemia, diminished vascular pattern, friability, hemorrhage, and ulcers. Abnormalities may be focal or diffuse, and unlike in UC, they may be discontinuous. Often, they are more severe in the distal compared to the proximal pouch (341–343). Mucosal biopsies typically demonstrate partial to complete villous blunting with crypt hyperplasia and increased mononuclear inflammatory cells and eosinophils in the lamina propria, crypt abscesses, and ulcerations. Mucosal biopsies should be obtained from the pouch and from the afferent ileal loop, but not from the staple line, as erosions and/or ulcers along the staple line do not necessarily indicate pouchitis (344).

Two main scoring systems exist for the diagnosis of pouchitis but their utility in clinical practice is limited as they await further validation to associate the scores with clinical outcomes (345,346). The Pouchitis Disease Activity Index (PDAI) evaluates symptoms, endoscopic findings, and histological patterns in a composite score, with a score of ≥ 7 indicating pouchitis (347). The Pouchitis Activity Score (PAS) incorporates similar elements to the PDAI and a score >13 is suggestive of pouchitis (348). A modified PDAI (mPDAI), omits the histology component (349).

Several variables may predict the risk of pouchitis. A small pediatric study reported that the only predictive factor associated with risk of pouchitis was a higher PUCAI score at the time of diagnosis (337). As discussed above, data suggest that the surgeon's experience is associated with risk for pouchitis (325). Chronic pouchitis was also associated with Ashkenazi Jewish ethnicity, while any-pouchitis was associated with age at diagnosis and longer disease duration. Several adult studies have reported an increased incidence of pouchitis in patients with a younger age at onset, backwash ileitis, PSC, extensive colonic disease, positive pANCA, preoperative steroid use, being a non-smoker, and carriage of genetic polymorphisms in NOD2/CARD15, which is more prevalent in Ashkenazi Jews (66,350–358).

The probiotic mixture VSL#3 was effective in maintaining remission in adult patients with chronic pouchitis as shown in 2 double-blind placebo-controlled trials from Italy (359,360). Results regarding the effectiveness of VSL#3 in preventing the first episode of pouchitis are more controversial (361,362).

Antibiotic treatment is considered first-line treatment for pouchitis. Only small placebo-controlled trials have, however, been conducted to support this practice and none in children (363,364). Ciprofloxacin may be slightly more effective than metronidazole, with fewer adverse events. Shen et al have shown the superiority of ciprofloxacin over metronidazole in inducing remission (365). In antibiotic-refractory pouchitis, Gionchetti et al used oral budesonide for 8 weeks and achieved remission in 75% of 20 patients (366,367). A case series of 28 patients with refractory pouchitis were treated with IFX of whom 88% responded after 10 weeks, and 56% after a median follow-up of 20 months (368); other case series also support the use of IFX in refractory pouchitis (369,370) as well as adalimumab (371) and alicaforsen (an inhibitor of intercellular adhesion molecule-1) enemas (372).

In an open study, topical treatment with metronidazole induced clinical improvement within a few days without systemic side effects and with a decrease in concentrations of anaerobic bacteria (373). Furthermore, uncontrolled studies have suggested that 5-ASA either as suppositories or enemas may help in the treatment of pouchitis (374).

OTHER MANAGEMENT CONSIDERATIONS

Extraintestinal Manifestations

Recommendations

1. Treatment of peripheral arthritis should be directed at inducing remission of the luminal disease [EL4, adult EL3]; sulfasalazine should be considered as first-line treatment for peripheral arthritis, followed by anti-TNF [EL4, adult EL2]. **(93% agreement)**
2. Transaminases and γGT should be monitored at least annually in all UC patients, to screen for PSC and autoimmune hepatitis [EL4, adult EL4]. **(100% agreement)**
3. Chronic elevation of liver enzymes in the presence of cholestasis, should be investigated with ultrasound followed by MR-cholangiopancreatography (MRCP), in addition to liver biopsy when indicated (see practice point); endoscopic retrograde cholangiopancreatography (ERCP) is recommended for therapeutic interventions [EL3, adult EL3]. **(95% agreement)**
4. Patients with PSC and IBD are at increased risk for colorectal carcinoma (CRC) and thus annual or bi-annual surveillance colonoscopy should be initiated from the time of PSC diagnosis. However, surveillance could be deferred in pre-pubertal

children while individualizing 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. **(95% agreement)**

Practice Points

1. Acute peripheral arthritis affecting the large joints is usually associated with active IBD and thus treatment should be directed to the gut. **(98% agreement)**
2. The diagnosis of axial spondylo-arthritis or sacro-ileitis is based on typical clinical signs such as progressive low back pain, gluteal and thigh pain combined with radiological abnormalities (most often MRI). Treating sacro-ileitis requires close collaboration with a rheumatologist. **(100% agreement)**
3. If required for the treatment of articular inflammation, non-steroidal anti-inflammatory drugs may be used for a short course and at low doses to minimize the risk of aggravating IBD. **(98% agreement)**
4. Since some degree of autoimmune hepatits/overlap syndrome is not uncommon in children with PSC, a low threshold should be practiced when considering a liver biopsy in this setup. **(95% agreement)**
5. 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 remains questionable, and if used, doses should be preferably low (10–15 $mg \cdot kg^{-1} \cdot day^{-1}$). Alternatively, oral vancomycin may be considered (usual total daily dose 35 mg/kg (maximum 1500 mg) divided into 3 times daily), for 12 weeks but long-term data are lacking. **(95% agreement)**
6. PSC is a significant risk factor for cholangiocarcinoma also during childhood. Serial CA19.9 and liver ultrasound/MRCP testing may thus be considered every 1 to 2 years to screen for cholangiocarcinoma but there is no pediatric evidence to support this practice. **(95% agreement)**

We would like to refer the reader to comprehensive ECCO guidelines on extraintestinal manifestations (EIM) and highlight here only pertinent points common in children (375). Some EIM are associated with intestinal disease activity (ie, erythema nodosum, peripheral arthritis), whereas others occur independently (ie, pyoderma gangrenosum, uveitis, ankylosing spondylitis, and PSC) (376). Data from 2 pediatric registries in the USA (377,378) and 1 in Europe (376) indicate that 1 or more EIMs are present at diagnosis in 6% to 17% % of children with UC, especially those older than 5 years, with an increase to almost 50% with disease evolution (379–382), and more so with extensive colitis (378).

Joint disease in IBD may be axial (sacro-ileitis or ankylosing spondylitis), causing lower back pain or peripheral arthritis, which is usually acute and self-limiting, seronegative and not deforming. In children, the prevalence of arthritis seems to be twice as high as in adults, (377) with a clear female predominance. There are some concerns about aggravating the bowel disease by using NSAIDs; however, the risk seems to be low if prescribed for a short course and at low doses (383). The sulfapyridine component of sulfasalazine has an anti-inflammatory effect on both the colonic mucosa and the joints (384). MTX is the cornerstone disease-modifying anti-rheumatic drug in juvenile arthritis (385) but anti-TNF regimes have emerged in the last 2 decades (386).

TABLE 6. Diagnostic workup of very early onset IBD to be adapted according to the clinical presentation (see text)

Basic immune workup	Examples
Complete blood count	Neutropenia, lymphocytopenia, thrombocytopenia
Lymphocyte subset	T-/B-cell defects, regulatory T cell defects (FOXP3, CD25)
IgG-A-M-E	SCID, CVID, B-cell defects, agammaglobulinaemia, hyper-IgM/ hyper-IgE syndrome
Oxidative burst	CGD
Functional tests	IL10-axis (LPS-IL10 stimulation); XIAP-nod-axis (MDP stimulation); apoptosis tests (XIAP)
Genetic testing	
Candidate gene approach	Suspected defect or confirmation of identified defect
Gene panel	Unclear diagnosis
Whole exome or genome sequencing	Research protocol for search of new mutations

CGD = chronic granulomatous disease; CVID = common variable immunodeficiency; IL = interleukin; SCID = severe combined immunodeficiency; XIAP = X-linked inhibitor of apoptosis protein.

PSC is 3 times more likely to occur in UC compared to CD (378), and is associated with older age in children (378). PSC may precede the onset of IBD by years but may occur even after colectomy. The prevalence of PSC in pediatric IBD is 1.6% at 10 years after diagnosis (377), but higher at 3% (387) if systematic screening tests are performed. In a recent multicenter 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 favorable prognosis; cholangiocarcinoma occurred in 1% (388).

Being non-invasive, MRCP is 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 (389). PSC may progress to liver cirrhosis, ultimately necessitating liver transplantation. Patients with PSC and UC have a greater risk of malignancies such as CRC and cholangiocarcinoma (8%–30% of UC patients with long standing PSC) (390,391). A recent study on the cancer and mortality in children in Europe has demonstrated several cases associated with PSC (10), but CRC in UC children younger than 12 years is extremely rare. PSC is associated with more extensive disease and thus has a greater cancer risk (391) but also with milder disease course. The higher colectomy rate in these patients is secondary to dysplasia and CRC. In adults with PSC, ursodeoxycholic acid is reported to improve abnormal liver tests (392) and to reduce the risk of CRC (393), although this has not been shown by all (394,395). No therapy has been shown to reduce time to liver transplantation, cholangiocarcinoma or death (394,396,397). Recent recommendations for adult patients suggest ursodeoxycholic acid at a dose of 10 to 15 $mg \cdot kg^{-1} \cdot day^{-1}$ and warn against high dose treatment (>20 $mg \cdot kg^{-1} \cdot day^{-1}$), which may increase mortality (394,395,398).

Oral vancomycin may be considered for 12 weeks as it has been shown to reduce and even normalize serum liver enzymes and gGT (399–405). Both vancomycin and metronidazole have been efficacious in recent small studies; however, only patients in the

vancomycin groups reached the primary endpoint, and with fewer adverse effects (403). Oral vancomycin re-treatment when needed has been associated with a rise in T regulatory cells (Treg) and normalization of liver function tests (406).

Older age at PSC diagnosis increases the risk of colonic neoplasia (407). Targeted biopsies aimed at abnormal areas identified by newer colonoscopic techniques (chromoendoscopy, confocal microendoscopy) should be preferred (408). The optimal follow-up method is still debatable (409).

Nutrition, Growth, and Bone Health

Practice Points

1. High intake of red or processed meat, protein, alcoholic beverages, sulfur, and sulfates have been associated with disease exacerbations. Due to the lack of solid evidence, exclusion diets, however, should not be used to induce or maintain remission in pediatric UC, and could lead to nutritional deficiencies. **(100% agreement)**
2. DEXA (corrected for height and age to produce age- and sex-matched z scores (410)) should be considered in high-risk patients such as those with severe disease, prolonged malnutrition, amenorrhea, delayed puberty, and/or steroid dependency. **(98% agreement)**
3. Promoting mucosal healing, adequate nutrition, weight-bearing exercise, avoiding smoking, and steroid-sparing strategies should be employed to facilitate bone health. The rare use of bisphosphonates should be reserved to those with pathological fractures, in consultation with a pediatric bone specialist. **(100% agreement)**
4. Growth impairment is rare in children with UC who are not steroid-dependent. Therefore, Crohn colitis or primary growth hormone deficiency should be considered when significant growth impairment is present. **(100% agreement)**
5. Vitamin D should be supplemented if 25-OH vitamin D is <50 nmol/L, regardless of steroid use. **(93% agreement)**
6. There are different strategies in treating vitamin D deficiency in addition to daily treatment (>2000 IU/day). A commonly applied strategy is to prescribe a ''loading dose'' (50,000 IU of vitamin D3 orally once weekly for 2 to 3 months, or 3 times weekly for 1 month). Single high-dose oral vitamin D3 300,000 to 500,000 IU (ie, stoss dosing) has been reported (411) to be effective and safe. **(98% agreement)**

While nutritional deficiencies can develop quickly during periods of active UC (412), normal growth is maintained in $>95\%$ of children with UC who are not steroid dependent (413–415). A more detailed review of all nutritional issues in children with IBD can be found in the recently published guideline from the Paediatric IBD Porto group of ESPGHAN (416). Patients with active UC often reduce fiber in their diets without supportive evidence. Corn and corn products, nuts, milk, and bran were avoided by $>20\%$ of UC patients (417). Soluble fiber is, however, the best way to generate short-chain fatty acids such as butyrate, which has anti-inflammatory effects (418). In addition, many UC patients avoided tomato, dairy products, chocolate, wheat, tomato sauces, and fruit juice (417), but there is no nutritional intervention clearly supported in UC and the reader is referred to an excellent recent summary on the topic (418).

Peak bone mass attained during adolescence is the most important determinant of lifelong skeletal health. Some osteopenia is present in up to 22% of UC children (419), but severe osteopenia is only present in 3% to 6% in UC, as compared with 12% to 18% in CD (420–422). Nutritional status seems to have a greater impact on bone status than corticosteroid therapy (423). Children with IBD are at particularly risk for vitamin D deficiency, but this was not found to be directly associated with osteopenia (424). Nonetheless, vitamin D deficiency should be treated especially in children with decreased bone mineral density. A recent meta-analysis showed that low vitamin D is associated with a more active disease (425). Age-appropriate nutrition support, weight-bearing exercise, and adequate disease control using steroid-sparing strategies (410,421,426) have been suggested as means to improve bone formation but without supportive evidence. Indeed, a prospective study that followed 58 children with CD for 2 years did not show significant improvement in bone mineral density despite increased height z score and reduced disease activity (421).

The most important determinant of treating osteopenia, besides avoiding steroids, is efficient treatment aiming at mucosal healing since osteopenia may typically be a consequence of pro-inflammatory cytokines (427). Indeed, interventions that lead to mucosal healing such as anti-TNF therapy and exclusive enteral nutrition showed rapid improvement of serum bone markers in children with CD (428–432). Bisphosphonates are effective to improve bone mineral density in IBD but pediatric use should be reserved for extreme circumstances, typically when pathological fractures are present, an uncommon situation in UC.

Psychosocial Support, Adherence to Therapy, and Transitional Care

Recommendations

1. Adolescents should be included in transition to adult care programs, which can be adapted according to the local organization of the pediatric and adult facilities [EL4]. **(100% agreement)**

Practice Points

1. Paediatric IBD centers should offer psychological support according to local resources. **(100% agreement)**
2. Adherence should be regularly evaluated by patient interviews, drug monitoring (eg, serum drug level), and prescription refill rates. **(100% agreement)**
3. Adherence may be improved by providing comprehensive information regarding the prescribed medication, keeping the pill burden as low as possible, using single daily dosage when possible, utilizing electronic reminders and providing pill boxes. **(100% agreement)**

Several systematic reviews concluded that adolescents with IBD, especially boys, have reduced health-related quality of life, including anxiety, depression, social problems, and low self-esteem

(433–436). The altered quality of life of children with IBD can affect the entire family, who often lack the appropriate strategies to deal with this complicated reality (437). The rate of depression may be as high as 25% and it is often under-recognized both by parents and health care professionals. Anxiety and depression appear to be risk factors for early recurrence of the disease and adversely affect the disease course but may also commonly be a reactive response to active disease (438). Cognitive behavioral therapy has been shown to be especially effective in improving depressive symptoms and functioning in children with IBD (439).

Non-adherence in IBD is reported in 50% to 66% of children (433,440), especially during adolescence. Pediatric-specific barriers include fear of adverse events of medication, feeling that the disease is inactive, belief that the medication is not working, >1 daily medication, forgetting, interfering with other activities, difficulty in swallowing pills (441), lack of motivation, and parent-child conflict (442).

Transition is defined as the planned move of adolescents and young adults with long-term physical conditions from child-centered to adult-orientated healthcare. The optimal timing of transition from pediatric to adult management of UC has to be decided on an individual basis by a joint team of pediatric and adult gastroenterologists (443). Several suggestions for transition programs have been published, but none has been formally evaluated (444). The transition period usually starts from the age of 14 to 18 years depending on the development of the patient and availability of qualified pediatric and adult gastroenterologists. The time of transition should be individually adapted according to the psychosocial readiness. Whenever feasible, at least 1 joint clinic with both the pediatric and the adult gastroenterologist is recommended during the transition process. The adolescent should be encouraged to assume increasing responsibility for treatment and to visit the clinic room at least once without being accompanied by the parents. The ECCO topical review on transition to adult care addresses in detail all aspects related to the steps to be followed during transition (445).

Very Early-Onset Inflammatory Bowel Disease Presenting As Colitis

Practice Points

1. In infants younger than 2 years, allergic colitis, immunological disorders and monogenic forms of colitis should be excluded. **(100% agreement)**
2. Unusual disease evolution, history of recurrent infections, HLH, and non-response to multiple IBD medications may indicate an underlying genetic defect which should prompt genetic and/or immunological analyses at any age during childhood (Table 6). **(100% agreement)**

The colitis phenotype is the most common in the VEOIBD group (6 years of age and younger) (446), and even Crohn disease frequently resembles UC. Therefore, the term IBDU rather than UC may be more appropriate in this earlier age group, reported in 34% and even 71% of very young children (447,448). The differential diagnostic spectrum for this age group is challenging (448,449) since the colitis may be caused by various immunological disorders: classical immune defects (such as combined immune-deficiencies), subtle immune defects or defects of the regulation of immune responses due to a monogenetic disorder including defects in interleukin (IL)10-signaling, X-linked inhibitor of apoptosis protein (XIAP) deficiency, defective neutrophil function and many others (Table 6) (449). Since no specific biological test confirms allergic colitis, only a successful trial of elimination diet is useful diagnostically (450) and may be proposed according to the clinical context especially in those younger than 1 year.

A large percentage of children with IBD developing before age 6 years present with relatively typical colitis, including mild disease which can be easily managed with 5-ASA (451). Many monogenic forms of VEOIBD may, however, initially appear as typical polygenic IBD but then prove resistant to standard therapy (448,449). Over 50 different monogenetic defects causing an IBD-like disorder have been described. A complete review of the genetic workup of VEOIBD and treatments is beyond the scope of these guidelines and the reader is referred to a previous comprehensive review (449). Briefly, appearance of perianal disease with skin folliculitis during the first few months of life is a strong indicator of a defect in the IL10 axis (452–454). Repeated bacterial and fungal infections orientate toward defective neutrophil functions, (eg, chronic granulomatous disease (455,456)). Recurrent skin infections, and EBV or CMV-induced HLH may indicate the presence of XIAP-defect (457). This X-linked defect can affect boys and in rare cases also girls (458). The presence of multiple intestinal atresia, or evidence of increased rate of epithelial cell apoptosis on small bowel biopsy may hint toward TTC7A, especially when observed in the presence of low IgG levels, T- and B-cell lymphopenia and mild reduction in NK cells (459–461). Woollen, fragile hair, and facial abnormalities (small chin, broad flat nasal bridge, and prominent forehead), immune defects, liver disease, and colitis (referred to as trichohepatoenteric syndrome or phenotypic diarrhea) may be due to mutation in SCIVL2 (462) or TTC37 (463). If signs of autoimmunity are associated with intestinal inflammation with high rates of epithelial cell apoptosis, IPEX-syndrome or IPEX-like disorders should be considered (464–467).

If the molecular defect is caused by a mutation affecting predominantly immunological cells (eg, IL10 signaling defects, XIAP and chronic granulomatous disease), hematopoietic stem cell transplantation may be curative (452,453,458,468). Inhibition with IL1-antagonists may be a way to stabilize patients with IL10 signaling defects while awaiting hematopoietic stem cell transplantation (HSCT), but more confirmation is required before this can be utilized in clinical practice (469). Early HSCT improves life expectancy of IL10-deficient patients since they are at risk for developing lymphoma (470). HSCT is not always the ultimate treatment option, as shown in patients with *TTC7A* mutations, which involve the epithelial gut barrier rather than immunological cells. This highlights the importance of a rapid and precise molecular diagnosis in children with colitis starting early in life.

SYNTHESIS AND SUMMARY

This Part 1 of the pediatric UC guidlines yielded **40** formal recommendations and **86** practice points along with practical tables and figures, based on systematic review of the literature. Guidance for the management of pediatric UC is summarized in algorithms to be used in conjunction with reading this document (Figs. 2 and 3). The goal of treatment in active UC should be complete clinical remission (PUCAI < 10 points), and usually this can be assessed without the need for endoscopic verification. Nonetheless, ~20% of children in clinical remission can still have endoscopic inflammation, and thus calprotectin may aid in selecting those who require endoscopic evaluation to ensure mucosal healing has been achieved. The choice of treatment in adults is a factor of both the disease severity and disease extent (15,16), but since limited distal disease is uncommon in children, pediatric treatment strategy

mainly depends on disease severity. Mesalamine regimes are considered first line for inducing and maintaining remission of mild-to-moderate UC. Non-response to oral mesalamine may be treated with the addition of mesalamine enemas and/or switching to locally active steroids, with budesonide-MMX only in left-sided colitis. In ambulatory children with moderate-to-severe UC, or in those with mild to moderate disease, who have failed optimized mesalamine therapy, oral steroids should be used, but only as induction agents. If the patient does not clearly respond to oral steroids within 1 to 2 weeks, consider admission for intravenous corticosteroids (see Part 2 of these guidelines). In refractory non-severe cases, an alternative to admission may include outpatient treatment with IFX (especially in those who failed thiopurines and mesalamine); in selected patients, oral tacrolimus may be considered.

Patients who received intravenous corticosteroids should be usually weaned to thiopurines. Almost all children with UC must be treated with a maintenance therapy indefinitely. Anti-TNF is indicated for non-response to corticosteroids, and in loss of response or intolerance to mesalamine and thiopurines. Patients needing anti-TNF induction should continue this therapy and if thiopurine-naïve, may be subsequently stepped down to thiopurines after a period of 6 to 12 months of deep remission. Golimumab or adalimumab should be considered in secondary loss of response to IFX due to antibody formation. Vedolizumab is a valid option in primary non-response to anti-TNF, in secondary loss of response in the presence of adequate drug level, and in anti-TNF related adverse events, such as refractory psoriasis. Endoscopic evaluation is recommended before any significant treatment change. Finally, colectomy is always a viable option, which must be discussed whenever treatment escalation is considered.

These clinical management guidelines were developed to assist practitioners at all levels of health care, while recognizing that each patient is unique. The recommendations may, thus, be subject to local practice patterns, and serve merely as a general framework for the management of UC in children. The development of the guidelines should now be followed by dissemination of the information to clinical practice.

DISCLAIMER

ESPGHAN and ECCO are not responsible for the practices of physicians and provide guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

QUALIFYING STATEMENT AND ACKNOWLEDGMENT

Please refer to the end of Part 2 of these guidelines

REFERENCES

1. Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423–39.
2. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114–22.
3. Turner D, Walsh CM, Benchimol EI, et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. *Gut* 2008;57:331–8.
4. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010;4:431–7.
5. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009;104:2080–8.
6. Langholz E, Munkholm P, Krasilnikoff PA, et al. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. *Scand J Gastroenterol* 1997;32:139–47.
7. Jakobsen C, Bartek J, Wewer V, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease—a population-based study. *Aliment Pharmacol Ther* 2011;34:1217–24.
8. Ashton JJ, Versteegh HP, Batra A, et al. Colectomy in pediatric ulcerative colitis: a single center experience of indications, outcomes, and complications. *J Pediatr Surg* 2016;51:277–81.
9. Benchimol EI, Guttmann A, To T, et al. Changes to surgical and hospitalization rates of pediatric inflammatory bowel disease in Ontario, Canada (1994–2007). *Inflamm Bowel Dis* 2011;17:2153–61.
10. de Ridder L, Turner D, Wilson DC, et al. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the porto pediatric IBD group. *Inflamm Bowel Dis* 2014;20:291–300.
11. Levine A, Koletzko S, Turner D, et al. The ESPGHAN Revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;58:795–806.
12. Birimberg-Schwartz L, Zucker DM, Akriv A, et al. Development and validation of diagnostic criteria for IBD subtypes with an emphasis on IBD-Unclassified in children: a multicenter study from the Pediatric IBD Porto group of ESPGHAN. *J Crohns Colitis* 2017;11:1078–84.
13. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314–21.
14. Turner D, Muise AM. Very early onset ibd: how very different 'on average'? *J Crohns Colitis* 2017;11:517–8.
15. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769–84.
16. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017;11:649–70.
17. Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340–61.
18. Turner D, Travis SP, Griffiths AM, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. *Am J Gastroenterol* 2011;106:574–88.
19. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.2013. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
20. Higgins JPT,Green S (Eds): *Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Library.* Chichester, UK: John Wiley & Sons, Ltd.; 2011. Available at: www.cochrane-handbook.org.
21. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine. Available at: http://www.cebm.net/index.aspx?o=5653.
22. Aloi M, D'Arcangelo G, Pofi F, et al. Presenting features and disease course of pediatric ulcerative colitis. *J Crohns Colitis* 2013;7:e509–15.
23. Schechter A, Griffiths C, Gana JC, et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut* 2015;64:580–8.
24. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–9.
25. Lobaton T, Bessissow T, De Hertogh G, et al. The Modified Mayo Endoscopic Score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. *J Crohns Colitis* 2015;9:846–52.
26. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012;61:535–42.
27. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013;145:987–95.
28. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011;141:1194–201.

29. Gustavsson A, Järnerot G, Hertervig E, et al. Clinical trial: colectomy after rescue therapy in ulcerative colitis—3-year follow-up of the Swedish-Danish controlled infliximab study. *Aliment Pharmacol Ther* 2010;32:984–9.
30. Froslie KF, Jahnsen J, Moum BA, et al. Mucosal Healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007;133:412–22.
31. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009;44:431–40.
32. Turner D, Griffiths AM, Veerman G, et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013;11: 1460–5.
33. Reinish W. Association between week eight Mayo subscores and hospitalization rates in adalimumab-treated patients with ulcerative colitis from ULTRA 1 and ULTRA 2. *Am J Gastroenterol* 2013; 108(suppl 1s):S506.
34. Arai M, Naganuma M, Sugimoto S, et al. The ulcerative colitis endoscopic index of severity is useful to predict medium- to long-term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis* 2016;10:1303–9.
35. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis* 2009;15:1218–23.
36. Gray FL, Turner CG, Zurakowski D, et al. Predictive value of the Pediatric Ulcerative Colitis Activity Index in the surgical management of ulcerative colitis. *J Pediatr Surg* 2013;48:1540–5.
37. Hyams JS, Davis S, Mack DR, et al. Factors associated with early outcomes following standardised therapy in children with ulcerative colitis (PROTECT): a multicentre inception cohort study. *Lancet Gastroenterol Hepatol* 2017;2:855–68.
38. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:1081–8.
39. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
40. Hyams J, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012;10:391–9e1.
41. Romano C, Famiani A, Comito D, et al. Oral beclomethasone dipropionate in pediatric active ulcerative colitis: a comparison trial with mesalazine. *J Pediatr Gastroenterol Nutr* 2010;50:385–9.
42. Hyams JS, Chan D, Adedokun OJ, et al. Subcutaneous golimumab in pediatric ulcerative colitis: pharmacokinetics and clinical benefit. *Inflamm Bowel Dis* 2017;23:2227–37.
43. Wiernicka A, Szymanska S, Cielecka-Kuszyk J, et al. Histological healing after infliximab induction therapy in children with ulcerative colitis. *World J Gastroenterol* 2015;21:10654–61.
44. Kerur B, Litman HJ, Stern JB, et al. Correlation of endoscopic disease severity with pediatric ulcerative colitis activity index score in children and young adults with ulcerative colitis. *World J Gastroenterol* 2017;23:3322–9.
45. Ricciuto A, Carman N, Fish J, et al. Symptoms underestimate endoscopic activity in PSC-IBD. *J Ped Gastroenterol Nutr* 2017;65(suppl 2):S104.
46. Mack DR, Langton C, Markowitz J, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. *Pediatrics* 2007;119:1113–9.
47. Weinstein TA, Levine M, Pettei MJ, et al. Age and family history at presentation of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2003;37:609–13.
48. Sidoroff M, Karikoski R, Raivio T, et al. High-sensitivity C-reactive protein in paediatric inflammatory bowel disease. *World J Gastroenterol* 2010;16:2901–6.
49. Turner D, Mack DR, Hyams J, et al. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. *J Crohns Colitis* 2011;5:423–9.
50. Kelley-Quon LI, Jen HC, Ziring DA, et al. Predictors of proctocolectomy in children with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2012;55:534–40.
51. Moore JC, Thompson K, Lafleur B, et al. Clinical variables as prognostic tools in pediatric-onset ulcerative colitis: a retrospective cohort study. *Inflamm Bowel Dis* 2011;17:15–21.
52. Canani RB, Terrin G, Rapacciuolo L, et al. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. *Dig Liver Dis* 2008;40:547–53.
53. Borkowska A, Liberek A, Luczak G, et al. Fecal lactoferrin, a marker of intestinal inflammation in children with inflammatory bowel disease. *Acta Biochim Pol* 2015;62:541–5.
54. Fagerberg UL, Loof L, Lindholm J, et al. Fecal calprotectin: a quantitative marker of colonic inflammation in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007;45:414–20.
55. Schoepfer AM, Beglinger C, Straumann A, et al. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009;15:1851–8.
56. Tibble JA, Sigthorsson G, Bridger S, et al. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000;119:15–22.
57. Roszak D, Galecka M, Cichy W, et al. Determination of faecal inflammatory marker concentration as a noninvasive method of evaluation of pathological activity in children with inflammatory bowel diseases. *Adv Med Sci* 2015;60:246–52.
58. Komraus M, Wos H, Wiecek S, et al. Usefulness of faecal calprotectin measurement in children with various types of inflammatory bowel disease. *Mediators Inflamm* 2012;2012:608249.
59. Ashorn S, Honkanen T, Kolho KL, et al. Fecal calprotectin levels and serological responses to microbial antigens among children and adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2009;15:199–205.
60. Diamanti A, Colistro F, Basso MS, et al. Clinical role of calprotectin assay in determining histological relapses in children affected by inflammatory bowel diseases. *Inflamm Bowel Dis* 2008;14:1229–35.
61. Yamamoto T, Shiraki M, Bamba T, et al. Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. *Int J Colorectal Dis* 2014;29:485–91.
62. Sipponen T, Kolho KL. Faecal calprotectin in children with clinically quiescent inflammatory bowel disease. *Scand J Gastroenterol* 2010; 45:872–7.
63. Birimberg-Schwartz L, Wilson DC, Kolho KL, et al. pANCA and ASCA in children with IBD-unclassified, Crohn's colitis, and ulcerative colitis—a longitudinal report from the IBD Porto Group of ESPGHAN. *Inflamm Bowel Dis* 2016;22:1908–14.
64. Zholudev A, Zurakowski D, Young W, et al. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. *Am J Gastroenterol* 2004;99:2235–41.
65. Miele E, Pascarella F, Quaglietta L, et al. Altered intestinal permeability is predictive of early relapse in children with steroid-responsive ulcerative colitis. *Aliment Pharmacol Ther* 2007;25:933–9.
66. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. *Gut* 2001;49:671–7.
67. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2015;81:489–501e26.
68. Olen O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. *BMJ* 2017;358:j3951.
69. Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (4):2016:CD000543.
70. Wang Y, Parker CE, Feagan BG, et al. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (5):2016:CD000544.
71. Ferry GD, Kirschner BS, Grand RJ, et al. Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. *J Pediatr Gastroenterol Nutr* 1993;17:32–8.

72. Quiros JA, Heyman MB, Pohl JF, et al. Safety, efficacy, and pharmacokinetics of balsalazide in pediatric patients with mild-to-moderate active ulcerative colitis: results of a randomized, double-blind study. *J Pediatr Gastroenterol Nutr* 2009;49:571–9.
73. Winter HS, Krzeski P, Heyman MB, et al. High- and low-dose oral delayed-release mesalamine in children with mild-to-moderately active ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2014;59:767–72.
74. Turner D, Yerushalmi B, Kori M, et al. Once- versus twice-daily mesalazine to induce remission in paediatric ulcerative colitis: a randomised controlled trial. *J Crohns Colitis* 2017;11:527–33.
75. Zeisler B, Lerer T, Markowitz J, et al. Outcome following aminosalicylate therapy in children newly diagnosed as having ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013;56:12–8.
76. Nuti F, Tringali G, Miele E, et al. Aminosalicylates and pediatric UC: use and efficacy at one year from diagnosis, results from the pediatric IBD Italian Registry. Digest Liver Dis 2015;47: e262.
77. Nikfar S, Rahimi R, Rezaie A, et al. A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. *Dig Dis Sci* 2009;54:1157–70.
78. Feagan BG, Chande N, MacDonald JK. Are there any differences in the efficacy and safety of different formulations of Oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? evidence from cochrane reviews. *Inflamm Bowel Dis* 2013;19: 2031–40.
79. Cuffari C, Pierce D, Korczowski B, et al. Randomized clinical trial: pharmacokinetics and safety of multimatrix mesalamine for treatment of pediatric ulcerative colitis. *Drug Des Devel Ther* 2016;10:593–607.
80. Wiersma H, Escher JC, Dilger K, et al. Pharmacokinetics of mesalazine pellets in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2004;10:626–31.
81. Christensen LA, Fallingborg J, Jacobsen BA, et al. Bioavailability of 5-aminosalicyclic acid from slow release 5-aminosalicyclic acid drug and sulfasalazine in normal children. *Dig Dis Sci* 1993;38:1831–6.
82. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2 4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007;21:827–34.
83. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009;137: 1934–43e1-3.
84. Lichtenstein GR, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2 4 g/day in endoscopic mucosal healing—ASCEND I and II combined analysis. *Aliment Pharmacol Ther* 2011;33:672–8.
85. Buurman DJ, De Monchy JG, Schellekens RC, et al. Ulcerative colitis patients with an inflammatory response upon mesalazine cannot be desensitized: a randomized study. *Scand J Gastroenterol* 2015;50: 399–405.
86. Gonzalo MA, Alcalde MM, García JM, et al. Desensitization after fever induced by mesalazine. *Allergy* 1999;54:1224–5.
87. Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. *J Crohns Colitis* 2016;10:149–58.
88. Arend LJ, Springate JE. Interstitial nephritis from mesalazine: case report and literature review. *Pediatr Nephrol* 2004;19:550–3.
89. Co ML, Gorospe EC. Pediatric case of mesalazine-induced interstitial nephritis with literature review. *Pediatr Int* 2013;55:385–7.
90. Rosenbaum J, Alex G, Roberts H, et al. Drug rash with eosinophilia and systemic symptoms secondary to sulfasalazine. *J Paediatr Child Health* 2010;46:193–6.
91. Kohli R, Melin-Aldana H, Sentongo TA. Mesalamine-induced pneumonitis during therapy for chronic inflammatory bowel disease: a pediatric case report. *J Pediatr Gastroenterol Nutr* 2005;41:479–82.
92. Sentongo TA, Piccoli DA. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of the literature. *J Pediatr Gastroenterol Nutr* 1998;27:344–7.
93. Nair AG, Cross RR. Mesalamine-induced myopericarditis in a paediatric patient with Crohn's disease. *Cardiol Young* 2015;25:783–6.
94. Iofel E, Chawla A, Daum F, et al. Mesalamine intolerance mimics symptoms of active inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;34:73–6.
95. Heyman MB, Kierkus J, Spenard J, et al. Efficacy and safety of mesalamine suppositories for treatment of ulcerative proctitis in children and adolescents. *Inflamm Bowel Dis* 2010;16:1931–9.
96. Probert CS, Dignass AU, Lindgren S, et al. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. *J Crohns Colitis* 2014;8:200–7.
97. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005;54: 960–5.
98. Connolly MP, Poole CD, Currie CJ, et al. Quality of life improvements attributed to combination therapy with oral and topical mesalazine in mild-to-moderately active ulcerative colitis. *Digestion* 2009;80: 241–6.
99. Levine A, Yerushalmi B, Kori M, et al. Mesalamine enemas for induction of remission in oral mesalamine-refractory pediatric ulcerative colitis: a prospective cohort study. *J Crohns Colitis* 2017;11: 970–4.
100. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (11):2012:CD004118.
101. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (1):2010:CD004115.
102. Cohen RD, Dalal SR. Systematic review: rectal therapies for the treatment of distal forms of ulcerative colitis. *Inflamm Bowel Dis* 2015;21:1719–36.
103. Watanabe M, Nishino H, Sameshima Y, et al. Randomised clinical trial: evaluation of the efficacy of mesalazine (mesalamine) suppositories in patients with ulcerative colitis and active rectal inflammation—a placebo-controlled study. *Aliment Pharmacol Ther* 2013;38:264–73.
104. Lamet M. A multicenter, randomized study to evaluate the efficacy and safety of mesalamine suppositories 1 g at bedtime and 500 mg Twice daily in patients with active mild-to-moderate ulcerative proctitis. *Dig Dis Sci* 2011;56:513–22.
105. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther* 2008;28: 1214–20.
106. Lee CH, Tasker N, La Hei E, et al. Raised tacrolimus level and acute renal injury associated with acute gastroenteritis in a child receiving local rectal tacrolimus. *Clin J Gastroenterol* 2014;7:238–42.
107. Lawrance IC, Baird A, Lightower D, et al. Efficacy of rectal tacrolimus for induction therapy in patients with resistant ulcerative proctitis. *Clin Gastroenterol Hepatol* 2017;15:1248–55.
108. Tung J, Loftus EV Jr, Freese DK, et al. A population-based study of the frequency of corticosteroid resistance and dependence in pediatric patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2006;12:1093–100.
109. Cakir M, Ozgenc F, Yusekkaya HA, et al. Steroid response in moderate to severe pediatric ulcerative colitis: a single center's experience. *World J Pediatr* 2011;7:50–3.
110. Hyams J, Markowitz J, Lerer T, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol* 2006;4:1118–23.
111. Beattie RM, Nicholls SW, Domizio P, et al. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 1996;22:373–9.
112. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012;6: 965–90.
113. Campieri M, Adamo S, Valpiani D, et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003;17:1471–80.

114. Sherlock ME, Seow CH, Steinhart AH, et al. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (10)2010CD007698.
115. Travis SP, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. *Gut* 2014;63:433–41.
116. Sandborn WJ, Danese S, D'Haens G, et al. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. *Aliment Pharmacol Ther* 2015;41:409–18.
117. Karolewska-Bochenek K, Dziekiewicz M, Banaszkiewicz A. Budesonide MMX in pediatric patients with ulcerative colitis. *J Crohns Colitis* 2017;11:1402.
118. Rubin DT, Cohen RD, Sandborn WJ, et al. Budesonide multi-matrix is efficacious for mesalamine-refractory, mild to moderate ulcerative colitis: a randomized, placebo-controlled trial. *J Crohns Colitis* 2017;11:785–91.
119. Uchida K, Araki T, Toiyama Y, et al. Preoperative steroid-related complications in Japanese pediatric patients with ulcerative colitis. *Dis Colon Rectum* 2006;49:74–9.
120. Sidoroff M, Kolho KL. Glucocorticoids in pediatric inflammatory bowel disease. *Scand J Gastroenterol* 2012;47:745–50.
121. Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. *J Crohns Colitis* 2017;11:3–25.
122. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.
123. Ahmet A, Kim H, Spier S. Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. *Allergy Asthma Clin Immunol* 2011;7:13.
124. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet* 2014;383:2152–67.
125. Sidoroff M, Kolho KL. Screening for adrenal suppression in children with inflammatory bowel disease discontinuing glucocorticoid therapy. *BMC Gastroenterol* 2014;14:51.
126. Sidoroff M, Kolho KL. Glucocorticoid sensitivity in inflammatory bowel disease. *Ann Med* 2012;44:578–87.
127. Quax RA, Manenschijn L, Koper JW, et al. Glucocorticoid sensitivity in health and disease. *Nat Rev Endocrinol* 2013;9:670–86.
128. Shipkova M, Armstrong VW, Wieland E, et al. Differences in nucleotide hydrolysis contribute to the differences between erythrocyte 6-thioguanine nucleotide concentrations determined by two widely used methods. *Clin Chem* 2003;49:260–8.
129. Gisbert JP, Linares PM, McNicholl AG, et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. *Aliment Pharmacol Ther* 2009;30:126–37.
130. Timmer A, Patton PH, Chande N, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (5):2016:CD000478.
131. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:630–42.
132. Sood R, Ansari S, Clark T, et al. Long-term efficacy and safety of azathioprine in ulcerative colitis. *J Crohns Colitis* 2015;9:191–7.
133. Hyams JS, Lerer T, Mack D, et al. Outcome following thiopurine use in children with ulcerative colitis: a prospective multicenter registry study. *Am J Gastroenterol* 2011;106:981–7.
134. Aloi M, D'Arcangelo G, Bramuzzo M, et al. Effect of early versus late azathioprine therapy in pediatric ulcerative colitis. *Inflamm Bowel Dis* 2016;22:1647–54.
135. Barabino A, Torrente F, Ventura A, et al. Azathioprine in paediatric inflammatory bowel disease: an Italian multicentre survey. *Aliment Pharmacol Ther* 2002;16:1125–30.
136. Kader HA, Mascarenhas MR, Piccoli DA, et al. Experiences with 6-mercaptopurine and azathioprine therapy in pediatric patients with severe ulcerative colitis. *J Pediatr Gastroenterol Nutr* 1999;28:54–8.
137. Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. *J Pediatr* 1990;117: 809–14.
138. Tajiri H, Tomomasa T, Yoden A, et al. Efficacy and safety of azathioprine and 6-mercaptopurine in Japanese pediatric patients with ulcerative colitis: a survey of the Japanese Society for Pediatric Inflammatory Bowel Disease. *Digestion* 2008;77:150–4.
139. Pozler O, Chladek J, Maly J, et al. Steady-state of azathioprine during initiation treatment of pediatric inflammatory bowel disease. *J Crohns Colitis* 2010;4:623–8.
140. Chhaya V, Pollok RC, Cecil E, et al. Impact of early thiopurines on surgery in 2770 children and young people diagnosed with inflammatory bowel disease: a national population-based study. *Aliment Pharmacol Ther* 2015;42:990–9.
141. Mantzaris GJ, Sfakianakis M, Archavlis E, et al. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol* 2004;99: 1122–8.
142. Szumlanski CL, Weinshilboum RM. Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995;39: 456–9.
143. Andrews JM, Travis SP, Gibson PR, et al. Systematic review: does concurrent therapy with 5-ASA and immunomodulators in inflammatory bowel disease improve outcomes? *Aliment Pharmacol Ther* 2009;29:459–69.
144. Luan ZJ, Li Y, Zhao XY, et al. Treatment efficacy and safety of low-dose azathioprine in chronic active ulcerative colitis patients: a meta-analysis and systemic review. *J Dig Dis* 2016;17:652–9.
145. Grossman AB, Noble AJ, Mamula P, et al. Increased dosing requirements for 6-mercaptopurine and azathioprine in inflammatory bowel disease patients six years and younger. *Inflamm Bowel Dis* 2008;14:750–5.
146. Stocco G, Martelossi S, Arrigo S, et al. Multicentric case-control study on azathioprine dose and pharmacokinetics in early-onset pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2017;23: 628–34.
147. Fuentes D, Torrente F, Keady S, et al. High-dose azathioprine in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;17:913–21.
148. Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. *Gastroenterology* 1998;115:813–21.
149. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease: azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. *Am J Gastroenterol* 1996;91:423–33.
150. Connell WR, Kamm MA, Ritchie JK, et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut* 1993;34:1081–5.
151. Kennedy NA, Rhatigan E, Arnott ID, et al. A trial of mercaptopurine is a safe strategy in patients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis. *Aliment Pharmacol Ther* 2013;38: 1255–66.
152. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol* 2015;13:847–58e4; quiz e48-50.
153. Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. *J Gastroenterol Hepatol* 2013;28:24–30.
154. Yabe M, Medeiros LJ, Daneshbod Y, et al. Hepatosplenic T-cell lymphoma arising in patients with immunodysregulatory disorders: a study of 7 patients who did not receive tumor necrosis factor-alpha inhibitor therapy and literature review. *Ann Diagn Pathol* 2017;26: 16–22.
155. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. *Gastroenterology* 2015;149:907–17e7.
156. Gazouli M, Pachoula I, Panayotou I, et al. Thiopurine methyltransferase genotype and thiopurine S-methyltransferase activity in Greek children with inflammatory bowel disease. *Ann Gastroenterol* 2012;25:249–53.

157. De Ridder L, Van Dieren JM, Van Deventer HJ, et al. Pharmacogenetics of thiopurine therapy in paediatric IBD patients. *Aliment Pharmacol Ther* 2006;23:1137–41.
158. Gerich ME, Quiros JA, Marcin JP, et al. A prospective evaluation of the impact of allopurinol in pediatric and adult IBD patients with preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. *J Crohns Colitis* 2010;4:546–52.
159. Rahhal RM, Bishop WP. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2008;14:1678–82.
160. Pavlidis P, Stamoulos P, Abdulrehman A, et al. Long-term safety and efficacy of low-dose azathioprine and allopurinol cotherapy in inflammatory bowel disease: a large observational study. *Inflamm Bowel Dis* 2016;22:1639–46.
161. Ihekweazu FD, Kellermayer R. Allopurinol: a useful adjunct to thiopurine therapy for pediatric ulcerative colitis in the biologic era. *J Pediatr Gastroenterol Nutr* 2014;59:22–4.
162. Konidari A, Anagnostopoulos A, Bonnett LJ, et al. Thiopurine monitoring in children with inflammatory bowel disease: a systematic review. *Br J Clin Pharmacol* 2014;78:467–76.
163. Nguyen TV, Vu DH, Nguyen TM, et al. Exploring associations of 6-thioguanine nucleotide levels and other predictive factors with therapeutic response to azathioprine in pediatric patients with IBD using multilevel analysis. *Inflamm Bowel Dis* 2013;19:2404–10.
164. Hanai H, Iida T, Takeuchi K, et al. Thiopurine maintenance therapy for ulcerative colitis: the clinical significance of monitoring 6-thioguanine nucleotide. *Inflamm Bowel Dis* 2010;16:1376–81.
165. Wong DR, Coenen MJ, Vermeulen SH, et al. Early assessment of thiopurine metabolites identifies patients at risk of thiopurine-induced leukopenia in inflammatory bowel disease. *J Crohns Colitis* 2017;11:175–84.
166. Lee MN, Kang B, Choi SY, et al. Relationship between azathioprine dosage, 6-thioguanine nucleotide levels, and therapeutic response in pediatric patients with IBD treated with azathioprine. *Inflamm Bowel Dis* 2015;21:1054–62.
167. Ooi CY, Bohane TD, Lee D, et al. Thiopurine metabolite monitoring in paediatric inflammatory bowel disease. *Aliment Pharmacol Ther* 2007;25:941–7.
168. Gupta P, Gokhale R, Kirschner BS. 6-mercaptopurine metabolite levels in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001;33:450–4.
169. Banerjee S, Bishop WP. Evolution of thiopurine use in pediatric inflammatory bowel disease in an academic center. *J Pediatr Gastroenterol Nutr* 2006;43:324–30.
170. Nguyen TV, Nguyen TM, Lachaux A, et al. Usefulness of thiopurine metabolites in predicting azathioprine resistance in pediatric IBD patients. *J Clin Pharmacol* 2013;53:900–8.
171. Cassinotti A, Actis GC, Duca P, et al. Maintenance treatment with azathioprine in ulcerative colitis: outcome and predictive factors after drug withdrawal. *Am J Gastroenterol* 2009;104:2760–7.
172. Kennedy NA, Kalla R, Warner B, et al. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates, with predictive factors in 237 patients. *Aliment Pharmacol Ther* 2014;40:1313–23.
173. Chande N, Wang Y, MacDonald JK, et al. Methotrexate for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (8):2014:CD006618.
174. Wang Y, MacDonald JK, Vandermeer B, et al. Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (8):2015:CD007560.
175. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. *Gastroenterology* 2016;150:380–8e4.
176. Aloi M, Di Nardo G, Conte F, et al. Methotrexate in paediatric ulcerative colitis: a retrospective survey at a single tertiary referral centre. *Aliment Pharmacol Ther* 2010;32:1017–22.
177. Baumgart DC, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. *Cochrane Database Syst Rev* (3):2008:CD007216.
178. Ogata H, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006;55:1255–62.
179. Landy J, Wahed M, Peake ST, et al. Oral tacrolimus as maintenance therapy for refractory ulcerative colitis—an analysis of outcomes in two London tertiary centres. *J Crohns Colitis* 2013;7:e516–21.
180. Ziring DA, Wu SS, Mow WS, et al. Oral tacrolimus for steroid-dependent and steroid-resistant ulcerative colitis in children. *J Pediatr Gastroenterol Nutr* 2007;45:306–11.
181. Navas-Lopez VM, Blasco Alonso J, Serrano Nieto MJ, et al. Oral tacrolimus for pediatric steroid-resistant ulcerative colitis. *J Crohns Colitis* 2014;8:64–9.
182. Truffinet O, Martinez-Vinson C, Guerriero E, et al. Tacrolimus exerts only a transient effectiveness in refractory pediatric crohn disease: a case series. *J Pediatr Gastroenterol Nutr* 2017;64:721–5.
183. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (3):2006:CD005112.
184. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392–400e3.
185. Turner D, Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. *Inflamm Bowel Dis* 2011;17:440–9.
186. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 2010;105:1430–6.
187. Larsen MD, Qvist N, Nielsen J, et al. Use of anti-TNFalpha agents and time to first-time surgery in paediatric patients with ulcerative colitis and Crohn's disease. *J Crohns Colitis* 2016;10:650–6.
188. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7.
189. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:257–65e1-3.
190. Thorlund K, Druyts E, Mills EJ, et al. Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naive to anti-TNF therapy: an indirect treatment comparison meta-analysis. *J Crohns Colitis* 2014;8:571–81.
191. Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther* 2017;45:1291–302.
192. Ananthakrishnan AN, Cagan A, Cai T, et al. Comparative effectiveness of infliximab and adalimumab in Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2016;22:880–5.
193. Vahabnezhad E, Rabizadeh S, Dubinsky MC. A 10-year, single tertiary care center experience on the durability of infliximab in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2014;20:606–13.
194. Volonaki E, Mutalib M, Kiparissi F, et al. Adalimumab as a second-line biological therapy in children with refractory ulcerative colitis. *Eur J Gastroenterol Hepatol* 2015;27:1425–8.
195. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:85–95quiz e14-5.
196. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96–109e1.
197. Turner D, Veereman G, Hyams J, et al. A multicentre open-label study assessing pharmacokinetics, efficacy, and safety of subcutaneous golimumab in paediatric patients with moderately-severely active ulcerative colitis. *J Crohns Colitis* 2016;10(suppl 1):S364–5.
198. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
199. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2016;14:543–9.

200. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology* 2014;147:1296–307e5.
201. Imaeda H, Bamba S, Takahashi K, et al. Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. *J Gastroenterol* 2014;49:674–82.
202. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014;63:1721–7.
203. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; 12:80–84e2.
204. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther* 2014;40:620–8.
205. Adedokun OJ, Xu Z, Marano CW, et al. Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 PURSUIT induction and maintenance studies. *J Crohns Colitis* 2017;11:35–46.
206. Papamichael K, Baert F, Tops S, et al. Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis. *J Crohns Colitis* 2017;11:53–9.
207. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016;14:550–7e2.
208. Zittan E, Kabakchiev B, Milgrom R, et al. Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease. *J Crohns Colitis* 2016;10:510–5.
209. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2015;13:514–21e4.
210. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology* 2017;153: 827–34.
211. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015;13:522–30e2.
212. Klaasen R, Wijbrandts CA, Gerlag DM, et al. Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis Rheum* 2011;63:359–64.
213. Feber J, Al-Matrafi J, Farhadi E, et al. Prednisone dosing per body weight or body surface area in children with nephrotic syndrome: is it equivalent? *Pediatr Nephrol* 2009;24:1027–31.
214. Kelsen JR, Grossman AB, Pauly-Hubbard H, et al. Infliximab therapy in pediatric patients 7 years of age and younger. *J Pediatr Gastroenterol Nutr* 2014;59:758–62.
215. Adedokun OJ, Xu Z, Padgett L, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. *Inflamm Bowel Dis* 2013;19:2753–62.
216. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol* 2009;65:1211–28.
217. Ordas I, Mould DR, Feagan BG, et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012;91:635–46.
218. Fasanmade AA, Adedokun OJ, Olson A, et al. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010;48:297–308.
219. Gecse KB, Vegh Z, Lakatos PL. Optimizing biological therapy in Crohn's disease. *Expert Rev Gastroenterol Hepatol* 2016;10: 37–45.
220. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Aliment Pharmacol Ther* 2016;43:1293–9.
221. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014;20: 2247–59.
222. Nanau RM, Cohen LE, Neuman MG. Risk of infections of biological therapies with accent on inflammatory bowel disease. *J Pharm Pharm Sci* 2014;17:485–531.
223. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA* 2017;318:1679–86.
224. Eickstaedt JB, Killpack L, Tung J, et al. Psoriasis and psoriasiform eruptions in pediatric patients with inflammatory bowel disease treated with anti-tumor necrosis factor alpha agents. *Pediatr Dermatol* 2017;34:253–60.
225. Alexandre B, Vandermeeren Y, Dewit O, et al. Optic neuritis associated or not with TNF antagonists in patients with inflammatory bowel disease. *J Crohns Colitis* 2016;10:541–8.
226. Jacobstein DA, Markowitz JE, Kirschner BS, et al. Premedication and infusion reactions with infliximab: results from a pediatric inflammatory bowel disease consortium. *Inflamm Bowel Dis* 2005; 11:442–6.
227. Lahdenne P, Wikström AM, Aalto K, et al. Prevention of acute adverse events related to infliximab infusions in pediatric patients. *Arthritis Care Res (Hoboken)* 2010;62:785–90.
228. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol* 2012;107:1409–22.
229. Andersen NN, Jess T. Risk of infections associated with biological treatment in inflammatory bowel disease. *World J Gastroenterol* 2014;20:16014–9.
230. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol* 2016;14:Error: FPage (1385) is higher than LPage (97e10)!.
231. Lawrance IC, Radford-Smith GL, Bampton PA, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. *J Gastroenterol Hepatol* 2010;25:1732–8.
232. Raaschou P, Simard JF, Holmqvist M, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *Bmj* 2013;346:f1939.
233. Mercer LK, Askling J, Raaschou P, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis* 2017;76:386–91.
234. Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease. *Gastroenterology* 2017;152:1901–14e3.
235. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
236. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol* 2017;15:Error: FPage (229) is higher than LPage (39e5)!.
237. Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (8):2014:CD007571.
238. Yarur A, Bruss A, Jain A, et al. Higher vedolizumab levels are associated with deep remission in patients with Crohn's disease and ulcerative colitis on maintenance therapy with vedolizumab [Abstract]. *European Crohn's and Colitis Organisation 2017 Annual Meeting* 2017:DOP020.

239. Schulze H, Esters P, Hartmann F, et al. A prospective cohort study to assess the relevance of Vedolizumab drug level monitoring in IBD patients [Abstract]. *European Crohn's and Colitis Organisation 2017 Annual Meeting* 2017:P521.
240. Williet N, Paul S, Del Tedesco E, et al. Serum vedolizumab assay at week 6 predicts sustained clinical remission and lack of recourse to optimisation in inflammatory bowel disease. *ECCO Annual Meeting* 2016:Abst632.
241. Ledder O, Assa A, Levine A, et al. Vedolizumab in pediatric inflammatory bowel disease: a retrospective multi-center experience from the Paediatric IBD Porto group of ESPGHAN. *J Crohns Colitis* 2017;11:1230–7.
242. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab therapy in severe pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2016;22:2425–31.
243. Singh N, Rabizadeh S, Jossen J, et al. Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2016;22:2121–6.
244. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis* 2015;21:2879–85.
245. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med* 2014;160:704–11.
246. Ikeda H, Ishimaru Y, Takayasu H, et al. Efficacy of granulocyte apheresis in pediatric patients with ulcerative colitis: a pilot study. *J Pediatr Gastroenterol Nutr* 2006;43:592–6.
247. Martin de Carpi J, Vilar P, Prieto G, et al. Safety and efficacy of granulocyte and monocyte adsorption apheresis in paediatric inflammatory bowel disease: a prospective pilot study. *J Pediatr Gastroenterol Nutr* 2008;46:386–91.
248. Ruuska T, Wewer V, Lindgren F, et al. Granulocyte-monocyte adsorptive apheresis in pediatric inflammatory bowel disease: results, practical issues, safety, and future perspectives. *Inflamm Bowel Dis* 2009;15:1049–54.
249. Tanaka T, Okanobu H, Kuga Y, et al. Clinical and endoscopic features of responders and non-responders to adsorptive leucocytapheresis: a report based on 120 patients with active ulcerative colitis. *Gastroenterol Clin Biol* 2010;34:687–95.
250. Tomomasa T, Kobayashi A, Kaneko H, et al. Granulocyte adsorptive apheresis for pediatric patients with ulcerative colitis. *Dig Dis Sci* 2003;48:750–4.
251. Tomomasa T, Tajiri H, Kagimoto S, et al. Leukocytapheresis in pediatric patients with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2011;53:34–9.
252. Sandborn WJ. Preliminary data on the use of apheresis ininflammatory bowel disease. *Inflamm Bowel Dis* 2006;12(suppl 1):S15–21.
253. Dignass AU, Kilander A, Pukitis A, et al. Clinical trial: five or ten cycles of granulocyte-monocyteapheresis show equivalent efficacy and safety in ulcerative colitis. *Aliment Pharmacol Ther* 2010;31: 1286–95.
254. Kruis W, Dignass A, Steinhagen-Thiessen E, et al. Open label trial of granulocyte apheresis suggests therapeutic efficacy in chronically activesteroid refractory ulcerative colitis. *World J Gastroenterol* 2005;11:7001–6.
255. Sawada K, Suzuki Y, Bamba T, et al. Leukocytapheresis in ulcerative colitis: results of a multicenter double-blind prospective case-control study with sham apheresis as placebo treatment. *Am J Gastroenterol* 2005;100:1362–9.
256. Sawada K, Muto T, Shimoyama T, et al. Multicenter randomized controlled trial for the treatment of ulcerative colitis with a leukocytapheresis column. *Curr Pharm Des* 2003;9:307–21.
257. Yokoyama Y, Matsuoka K, Kobayashi T, et al. A large-scale, prospective, observational study of leukocytapheresis for ulcerative colitis: treatment outcomes of 847 patients in clinical practice. *J Crohns Colitis* 2014;8:981–91.
258. Sands BE, Katz S, Wolf DC, et al. A randomised, double-blind, sham-controlled study of granulocyte/monocyte apheresis for moderate to severe Crohn's disease. *Gut* 2013;62:1288–94.
259. Thanaraj S, Hamlin PJ, Ford AC. Systematic review: granulocyte/monocyte adsorptive apheresis for ulcerative colitis. *Aliment Pharmacol Ther* 2010;32:1297–306.
260. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal ficrobiota fransplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA* 2016;315:142–9.
261. Kunde S, Pham A, Bonczyk S, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013; 56:597–601.
262. Suskind DL, Singh N, Nielson H, et al. Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2015;60:27–9.
263. Kellermayer R, Nagy-Szakal D, Harris RA, et al. Serial fecal microbiota transplantation alters mucosal gene expression in pediatric ulcerative colitis. *Am J Gastroenterol* 2015;110:604–6.
264. Vandenplas Y, Veereman G, van der Werff Ten Bosch J, et al. Fecal microbial transplantation in early-onset colitis: caution advised. *J Pediatr Gastroenterol Nutr* 2015;61:e12–4.
265. Hourigan SK, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. *Pediatr Res* 2016;80:2–6.
266. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006;444:1027–31.
267. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012;107:1079–87.
268. Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis* 2015;2:ofv004.
269. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* 2015; 149:102–9e6.
270. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology* 2015;149:110–8e4.
271. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;389:1218–28.
272. Henker J, Muller S, Laass MW, et al. Probiotic *Escherichia coli* Nissle 1917 (EcN) for successful remission maintenance of ulcerative colitis in children and adolescents: an open-label pilot study. *Z Gastroenterol* 2008;46:874–5.
273. Kruis W, Schutz E, Fric P, et al. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 1997;11:853–8.
274. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004;53:1617–23.
275. Rembacken BJ, Snelling AM, Hawkey PM, et al. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;354:635–9.
276. Losurdo G, Iannone A, Contaldo A, et al. *Escherichia coli* Nissle 1917 in ulcerative colitis treatment: systematic review and meta-analysis. *J Gastrointestin Liver Dis* 2015;24:499–505.
277. Naidoo K, Gordon M, Fagbemi AO, et al. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (12):2011:CD007443.
278. Miele E, Pascarella F, Giannetti E, et al. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol* 2009;104: 437–43.
279. Huynh HQ, deBruyn J, Guan L, et al. Probiotic preparation VSL#3 induces remission in children with mild to moderate acute ulcerative colitis: a pilot study. *Inflamm Bowel Dis* 2009;15:760–8.
280. Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. *Inflamm Bowel Dis* 2014;20:1562–7.
281. Cinque B, La Torre C, Lombardi F, et al. VSL#3 probiotic differently influences IEC-6 intestinal epithelial cell status and function. *J Cell Physiol* 2017;232:3530–9.
282. Cinque B, La Torre C, Lombardi F, et al. Production conditions affect the in vitro anti-tumoral effects of a high concentration multi-strain probiotic preparation. *PLoS One* 2016;11:e0163216.

283. Oliva S, Di Nardo G, Ferrari F, et al. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2012;35:327–34.
284. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:661–73.
285. Wang SL, Wang ZR, Yang CQ. Meta-analysis of broad-spectrum antibiotic therapy in patients with active inflammatory bowel disease. *Exp Ther Med* 2012;4:1051–6.
286. Suskind DL, Wahbeh G, Burpee T, et al. Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study. *J Pediatr Gastroenterol Nutr* 2013;56:277–9.
287. Hanai HIT, Takeuchi K, et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;4: 1502–6.
288. Lang A, Salomon N, Wu JC, et al. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin Gastroenterol Hepatol* 2015;13:1444–9e1.
289. Singla V, Pratap Mouli V, Garg SK, et al. Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis—a randomized, placebo-controlled, pilot study. *J Crohns Colitis* 2014;8:208–14.
290. Langhorst J, Wulfert H, Lauche R, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohn Colitis* 2015;9:86–106.
291. Ng SC, Lam YT, Tsoi KK, et al. Systematic review: the efficacy of herbal therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:854–63.
292. Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther* 2004;19:739–47.
293. Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases—a systematic review. *Br J Nutr* 2012; 107(suppl 2):S240–52.
294. Turner D, Shah PS, Steinhart AH, et al. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): a systematic review and meta-analyses. *Inflamm Bowel Dis* 2011; 17:336–45.
295. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* (18):2007:CD006443.
296. Merkley SA, Beaulieu DB, Horst S, et al. Use of intravenous immunoglobulin for patients with inflammatory bowel disease with contraindications or who are unresponsive to conventional treatments. *Inflamm Bowel Dis* 2015;21:1854–9.
297. Winter DA, Karolewska-Bochenek K, Lazowska-Przeorek I, et al. Pediatric IBD-unclassified is less common than previously reported: results of an 8-year audit of the EUROKIDS Registry. *Inflamm Bowel Dis* 2015;21:2145–53.
298. Aloi M, Birimberg-Schwartz L, Buderus S, et al. Treatment options and outcomes of pediatric IBDU compared with other IBD Subtypes: a retrospective multicenter study from the IBD Porto Group of ESPGHAN. *Inflamm Bowel Dis* 2016;22:1378–83.
299. Polites SF, Potter DD, Moir CR, et al. Long-term outcomes of ileal pouch-anal anastomosis for pediatric chronic ulcerative colitis. *J Pediatr Surg* 2015;50:1625–9.
300. Ozdemir Y, Kiran RP, Erem HH, et al. Functional outcomes and complications after restorative proctocolectomy and ileal pouch anal anastomosis in the pediatric population. *J Am Coll Surg* 2014; 218:328–35.
301. Lillehei CW, Leichtner A, Bousvaros A, et al. Restorative proctocolectomy and ileal pouch-anal anastomosis in children. *Dis Colon Rectum* 2009;52:1645–9.
302. Pakarinen MP, Natunen J, Ashorn M, et al. Long-term outcomes of restorative proctocolectomy in children with ulcerative colitis. *Pediatrics* 2009;123:1377–82.
303. Mortellaro VE, Green J, Islam S, et al. Occurrence of Crohn's disease in children after total colectomy for ulcerative colitis. *J Surg Res* 2011;170:38–40.
304. Gray BW, Drongowski RA, Hirschl RB, et al. Restorative proctocolectomy without diverting ileostomy in children with ulcerative colitis. *J Pediatr Surg* 2012;47:204–8.
305. Dolgin SE, Shlasko E, Gorfine S, et al. Restorative proctocolectomy in children with ulcerative colitis utilizing rectal mucosectomy with or without diverting ileostomy. *J Pediatr Surg* 1999;34:837–9discussion 39-40.
306. Ryan DP, Doody DP. Restorative proctocolectomy with and without protective ileostomy in a pediatric population. *J Pediatr Surg* 2011;46:200–3.
307. Marceau C, Alves A, Ouaissi M, et al. Laparoscopic subtotal colectomy for acute or severe colitis complicating inflammatory bowel disease: a case-matched study in 88 patients. *Surgery* 2007;141: 640–4.
308. Lazzerini M, Bramuzzo M, Maschio M, et al. Thromboembolism in pediatric inflammatory bowel disease: systematic review. *Inflamm Bowel Dis* 2011;17:2174–83.
309. Carter FM, McLeod RS, Cohen Z. Subtotal colectomy for ulcerative colitis: complications related to the rectal remnant. *Dis Colon Rectum* 1991;34:1005–9.
310. Linden BC, Bairdain S, Zurakowski D, et al. Comparison of laparoscopic-assisted and open total proctocolectomy and ileal pouch anal anastomosis in children and adolescents. *J Pediatr Surg* 2013;48: 1546–50.
311. Diamond IR, Gerstle JT, Kim PC, et al. Outcomes after laparoscopic surgery in children with inflammatory bowel disease. *Surg Endosc* 2010;24:2796–802.
312. Pini-Prato A, Faticato MG, Barabino A, et al. Minimally invasive surgery for paediatric inflammatory bowel disease: personal experience and literature review. *World J Gastroenterol* 2015;21:11312–20.
313. Markel TA, Lou DC, Pfefferkorn M, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. *Surgery* 2008; 144:540–5.
314. Schaufler C, Lerer T, Campbell B, et al. Preoperative immunosuppression is not associated with increased postoperative complications following colectomy in children with colitis. *J Pediatr Gastroenterol Nutr* 2012;55:421–4.
315. Hait EJ, Bousvaros A, Schuman M, et al. Pouch outcomes among children with ulcerative colitis treated with calcineurin inhibitors before ileal pouch anal anastomosis surgery. *J Pediatr Surg* 2007; 42:31–5.
316. Kennedy R, Potter DD, Moir C, et al. Pediatric chronic ulcerative colitis: does infliximab increase post-ileal pouch anal anastomosis complications? *J Pediatr Surg* 2012;47:199–203.
317. Billioud V, Ford AC, Tedesco ED, et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. *J Crohns Colitis* 2013;7:853–67.
318. Narula N, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNFalpha treatment and post-operative complications in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; 37:1057–64.
319. Tilney HS, Constantinides V, Ioannides AS, et al. Pouch-anal anastomosis vs straight ileoanal anastomosis in pediatric patients: a meta-analysis. *J Pediatr Surg* 2006;41:1799–808.
320. Seetharamaiah R, West BT, Ignash SJ, et al. Outcomes in pediatric patients undergoing straight vs J pouch ileoanal anastomosis: a multicenter analysis. *J Pediatr Surg* 2009;44:1410–7.
321. Davis C, Alexander F, Lavery I, et al. Results of mucosal proctectomy versus extrarectal dissection for ulcerative colitis and familial polyposis in children and young adults. *J Pediatr Surg* 1994;29:305–9.
322. Luukkonen P, Jarvinen H. Stapled vs hand-sutured ileoanal anastomosis in restorative proctocolectomy. A prospective, randomized study. *Arch Surg* 1993;128:437–40.
323. Shannon A, Eng K, Kay M, et al. Long-term follow up of ileal pouch anal anastomosis in a large cohort of pediatric and young adult patients with ulcerative colitis. *J Pediatr Surg* 2016;51:1181–6.
324. Orlanski-Meyer E, Topf-Olivestone C, Shtayer E, et al. Short and long-term surgical outcomes and Pouch function following proctocolectomy and pouch formation in Paediatric UC: A multicentre-retrospective cohort study from the Porto IBD working group of ESPGHAN. *ESPGHAN Annual Meeting, Prague* 2017Abstr G-P-308.

325. Orlanski-Meyer E, Topf-Olivestone C, Ledder O, et al. Pouchitis in paediatric UC: a multicentre longitudinal cohort study from the Porto IBD working group of ESPGHAN. *ESPGHAN Annual Meeting, Prague* 2017Abstr G-O-038.
326. Nasseri Y, Melmed G, Wang HL, et al. Rigorous histopathological assessment of the colectomy specimen in patients with inflammatory bowel disease unclassified does not predict outcome after ileal pouch-anal anastomosis. *Am J Gastroenterol* 2010;105:155–61.
327. Murrell ZA, Melmed GY, Ippoliti A, et al. A prospective evaluation of the long-term outcome of ileal pouch-anal anastomosis in patients with inflammatory bowel disease-unclassified and indeterminate colitis. *Dis Colon Rectum* 2009;52:872–8.
328. Myrelid P, Oresland T. A reappraisal of the ileo-rectal anastomosis in ulcerative colitis. *J Crohns Colitis* 2015;9:433–8.
329. Hull TL, Joyce MR, Geisler DP, et al. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. *Br J Surg* 2012;99:270–5.
330. Bartels SA, D'Hoore A, Cuesta MA, et al. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg* 2012;256:1045–8.
331. Beyer-Berjot L, Maggiori L, Birnbaum D, et al. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Ann Surg* 2013;258:275–82.
332. Uzzan M, Cosnes J, Amiot A, et al. Long-term follow-up after ileorectal anastomosis for ulcerative colitis: A GETAID/GETAID chirurgie multicenter retrospective cohort of 343 Patients. *Ann Surg* 2017;266:1029–34.
333. Burns EM, Bottle A, Aylin P, et al. Volume analysis of outcome following restorative proctocolectomy. *Br J Surg* 2011;98:408–17.
334. Koivusalo A, Pakarinen MP, Rintala RJ. Surgical complications in relation to functional outcomes after ileoanal anastomosis in pediatric patients with ulcerative colitis. *J Pediatr Surg* 2007;42:290–5.
335. Patton D, Gupta N, Wojcicki JM, et al. Postoperative outcome of colectomy for pediatric patients with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2010;51:151–4.
336. Knod JL, Holder M, Cortez AR, et al. Surgical outcomes, bowel habits and quality of life in young patients after ileoanal anastomosis for ulcerative colitis. *J Pediatr Surg* 2016;51:1246–50.
337. Dharmaraj R, Dasgupta M, Simpson P, et al. Predictors of pouchitis after ileal pouch-anal anastomosis in children. *J Pediatr Gastroenterol Nutr* 2016;63:e58–62.
338. Perrault J. Pouchitis in children: therapeutic options. *Curr Treat Options Gastroenterol* 2002;5:389–97.
339. Slatter C, Girgis S, Huynh H, et al. Pre-pouch ileitis after colectomy in paediatric ulcerative colitis. *Acta Paediatr* 2008;97:381–3.
340. Shen B, Achkar JP, Lashner BA, et al. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol* 2002;97:972–7.
341. Goldstein NS, Sanford WW, Bodzin JH. Crohn's-like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. *Am J Surg Pathol* 1997;21:1343–53.
342. Setti Carraro PG, Talbot IC, Nicholls JR. Patterns of distribution of endoscopic and histological changes in the ileal reservoir after restorative proctocolectomy for ulcerative colitis. A long-term follow-up study. *Int J Colorectal Dis* 1998;13:103–7.
343. Warren BF, Shepherd NA. The role of pathology in pelvic ileal reservoir surgery. *Int J Colorectal Dis* 1992;7:68–75.
344. Pemberton JH. The problem with pouchitis. *Gastroenterology* 1993;104:1209–11.
345. Ben-Bassat O, Tyler AD, Xu W, et al. Ileal pouch symptoms do not correlate with inflammation of the pouch. *Clin Gastroenterol Hepatol* 2014;12:831–7e2.
346. Shen B, Achkar JP, Lashner BA, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001;121:261–7.
347. Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc* 1994;69:409–15.
348. Heuschen UA, Autschbach F, Allemeyer EH, et al. Long-term follow-up after ileoanal pouch procedure: algorithm for diagnosis, classification, and management of pouchitis. *Dis Colon Rectum* 2001;44:487–99.
349. Shen B, Achkar JP, Connor JT, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis Colon Rectum* 2003;46:748–53.
350. Abdelrazeq AS, Kandiyil N, Botterill ID, et al. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. *Colorectal Dis* 2008;10:805–13.
351. Hata K, Watanabe T, Shinozaki M, et al. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. *Scand J Gastroenterol* 2003;38:1055–8.
352. Sandborn WJ, Landers CJ, Tremaine WJ, et al. Antineutrophil cytoplasmic antibody correlates with chronic pouchitis after ileal pouch-anal anastomosis. *Am J Gastroenterol* 1995;90:740–7.
353. Lipman JM, Kiran RP, Shen B, et al. Perioperative factors during ileal pouch-anal anastomosis predict pouchitis. *Dis Colon Rectum* 2011;54:311–7.
354. Merrett MN, Mortensen N, Kettlewell M, et al. Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis. *Gut* 1996;38:362–4.
355. Carter MJ, Di Giovine FS, Cox A, et al. The interleukin 1 receptor antagonist gene allele 2 as a predictor of pouchitis following colectomy and IPAA in ulcerative colitis. *Gastroenterology* 2001;121:805–11.
356. Meier CB, Hegazi RA, Aisenberg J, et al. Innate immune receptor genetic polymorphisms in pouchitis: is CARD15 a susceptibility factor? *Inflamm Bowel Dis* 2005;11:965–71.
357. Tyler AD, Milgrom R, Xu W, et al. Antimicrobial antibodies are associated with a Crohn's disease-like phenotype after ileal pouch-anal anastomosis. *Clin Gastroenterol Hepatol* 2012;10:507–12e1.
358. Wu XR, Ashburn J, Remzi FH, et al. Male gender is associated with a high risk for chronic antibiotic-refractory pouchitis and ileal pouch anastomotic sinus. *J Gastrointest Surg* 2016;20:631–9.
359. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;53:108–14.
360. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:305–9.
361. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003;124:1202–9.
362. Pronio A, Montesani C, Butteroni C, et al. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative colitis is associated with expansion of mucosal regulatory cells. *Inflamm Bowel Dis* 2008;14:662–8.
363. Pineton de Chambrun GP, Torres J, Darfeuille-Michaud A, et al. The role of anti(myco)bacterial interventions in the management of IBD: is there evidence at all? *Dig Dis* 2012;30:358–67.
364. Holubar SD, Cima RR, Sandborn WJ, et al. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev* (6):2010:CD001176.
365. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis* 2001;7:301–5.
366. Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther* 2007;25:1231–6.
367. Biancone L, Michetti P, Travis S, et al. European evidence-based consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis* 2008;2:63–92.
368. Ferrante M, D'Haens G, Dewit O, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. *Inflamm Bowel Dis* 2010;16:243–9.
369. Barreiro-de Acosta M, Garcia-Bosch O, Souto R, et al. Efficacy of infliximab rescue therapy in patients with chronic refractory pouchitis: a multicenter study. *Inflamm Bowel Dis* 2012;18:812–7.
370. Calabrese C, Gionchetti P, Rizzello F, et al. Short-term treatment with infliximab in chronic refractory pouchitis and ileitis. *Aliment Pharmacol Ther* 2008;27:759–64.
371. Barreiro-de Acosta M, Garcia-Bosch O, Gordillo J, et al. Efficacy of adalimumab rescue therapy in patients with chronic refractory pouchitis previously treated with infliximab: a case series. *Eur J Gastroenterol Hepatol* 2012;24:756–8.

372. Greuter T, Biedermann L, Rogler G, et al. Alicaforsen, an antisense inhibitor of ICAM-1, as treatment for chronic refractory pouchitis after proctocolectomy: a case series. *United European Gastroenterol J* 2016;4:97–104.
373. Nygaard K, Bergan T, Bjorneklett A, et al. Topical metronidazole treatment in pouchitis. *Scand J Gastroenterol* 1994;29:462–7.
374. Miglioli M, Barbara L, Di Febo G, et al. Topical administration of 5-aminosalicylic acid: a therapeutic proposal for the treatment of pouchitis. *N Engl J Med* 1989;320:257.
375. Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.
376. Aloi M, Cucchiara S. Extradigestive manifestations of IBD in pediatrics. *Eur Rev Med Pharmacol Sci* 2009;13(suppl 1):23–32.
377. Jose FA, Garnett EA, Vittinghoff E, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2009;15:63–8.
378. Dotson JL, Hyams JS, Markowitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. *J Pediatr Gastroenterol Nutr* 2010;51:140–5.
379. Hyams JS. Extraintestinal manifestations of inflammatory bowel disease in children. *J Pediatr Gastroenterol Nutr* 1994;19:7–21.
380. Hyams JS. Crohn's disease in children. *Pediatr Clin North Am* 1996;43:255–77.
381. Winesett M. Inflammatory bowel disease in children and adolescents. *Pediatr Ann* 1997;26:227–34.
382. Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin North Am* 2003;32:967–95.
383. Bonner GF, Fakhri A, Vennamaneni SR. A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004;10:751–7.
384. Orchard TR, Jewell DP. Conditions of the eyes and joints associated with inflammatory bowel disease. In: Targan SR, Shanahan F, Karp LC, eds. *Inflammatory Bowel Disease: Translating Basic Science Into Clinical Practice.* Chichester, UK: John Wiley & Sons Ltd.; 2010: 573–604.
385. van Dijkhuizen EH, Wulffraat NM. Prediction of methotrexate efficacy and adverse events in patients with juvenile idiopathic arthritis: a systematic literature review. *Pediatr Rheumatol Online J* 2014;12:51.
386. Horneff G. Update on biologicals for treatment of juvenile idiopathic arthritis. *Expert Opin Biol Ther* 2013;13:361–76.
387. Ponsioen CY. Diagnosis, differential diagnosis, and epidemiology of primary sclerosing cholangitis. *Dig Dis* 2015;33(suppl 2):134–9.
388. Deneau MR, El-Matary W, Valentino PL, et al. The natural history of primary sclerosing cholangitis in 781 children: a multicenter, international collaboration. *Hepatology* 2017;66:518–27.
389. Charatcharoenwitthaya P, Lindor KD. Primary sclerosing cholangitis: diagnosis and management. *Curr Gastroenterol Rep* 2006;8:75–82.
390. Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995;22:1404–8.
391. Fevery J, Henckaerts L, Van Oirbeek R, et al. Malignancies and mortality in 200 patients with primary sclerosering cholangitis: a long-term single-centre study. *Liver Int* 2012;32:214–22.
392. Cullen SN, Chapman RW. The medical management of primary sclerosing cholangitis. *Semin Liver Dis* 2006;26:52–61.
393. Singh S, Khanna S, Pardi DS, et al. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2013;19:1631–8.
394. Pardi DS, Loftus EV Jr, Kremers WK, et al. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology* 2003;124:889–93.
395. Eaton JE, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Am J Gastroenterol* 2011;106:1638–45.
396. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med* 1997;336:691–5.
397. Sjoqvist U, Tribukait B, Ost A, et al. Ursodeoxycholic acid treatment in IBD-patients with colorectal dysplasia and/or DNA-aneuploidy: a prospective, double-blind, randomized controlled pilot study. *Anticancer Res* 2004;24 (5B):3121–7.
398. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009;50:808–14.
399. Rahimpour S, Nasiri-Toosi M, Khalili H, et al. A triple blinded, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of oral vancomycin in primary sclerosing cholangitis: a pilot study. *J Gastrointestin Liver Dis* 2016;25:457–64.
400. Buness C, Lindor KD, Miloh T. Oral vancomycin therapy in a child with primary sclerosing cholangitis and severe ulcerative colitis. *Pediatr Gastroenterol Hepatol Nutr* 2016;19:210–3.
401. Ali AH, Carey EJ, Lindor KD. Current research on the treatment of primary sclerosing cholangitis. *Intractable Rare Dis Res* 2015;4:1–6.
402. Davies YK, Tsay CJ, Caccamo DV, et al. Successful treatment of recurrent primary sclerosing cholangitis after orthotopic liver transplantation with oral vancomycin. *Case Rep Transplant* 2013;2013:314292.
403. Tabibian JH, Weeding E, Jorgensen RA, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis—a pilot study. *Aliment Pharmacol Ther* 2013;37:604–12.
404. Lindor KD. New treatment strategies for primary sclerosing cholangitis. *Dig Dis* 2011;29:113–6.
405. Mieli-Vergani G, Vergani D. Unique features of primary sclerosing cholangitis in children. *Curr Opin Gastroenterol* 2010;26:265–8.
406. Abarbanel DN, Seki SM, Davies Y, et al. Immunomodulatory effect of vancomycin on Treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis. *J Clin Immunol* 2013;33:397–406.
407. Navaneethan U, Kochhar G, Venkatesh PG, et al. Duration and severity of primary sclerosing cholangitis is not associated with risk of neoplastic changes in the colon in patients with ulcerative colitis. *Gastrointest Endosc* 2012;75:1045–54e1.
408. Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? *World J Gastroenterol* 2012;18:3839–48.
409. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Chromoendoscopy for surveillance in inflammatory bowel disease does not increase neoplasia detection compared with conventional colonoscopy with random biopsies: results from a large retrospective study. *Am J Gastroenterol* 2015;110:1014–21.
410. Pappa H, Thayu M, Sylvester F, et al. Skeletal health of children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011;53:11–25.
411. Shepherd D, Day AS, Leach ST, et al. Single High-Dose Oral Vitamin D3 Therapy (Stoss): a solution to vitamin D deficiency in children with inflammatory bowel disease? *J Pediatr Gastroenterol Nutr* 2015;61:411–4.
412. Rocha R, Santana GO, Almeida N, et al. Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. *Br J Nutr* 2009;101:676–9.
413. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;88:995–1000.
414. Markowitz J, Grancher K, Rosa J, et al. Growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1993;16:373–80.
415. Turunen P, Ashorn M, Auvinen A, et al. Long-term health outcomes in pediatric inflammatory bowel disease: a population-based study. *Inflamm Bowel Dis* 2009;15:56–62.
416. Miele E, Shamir R, Aloi M, et al. Nutrition in paediatric inflammatory bowel disease: a position paper on behalf of The Porto IBD Group of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2018;66:687–708.
417. Green TJ, Issenman RM, Jacobson K. Patients' diets and preferences in a pediatric population with inflammatory bowel disease. *Can J Gastroenterol* 1998;12:544–9.
418. Lewis JD, Abreu MT. Diet as a trigger or therapy for inflammatory bowel diseases. *Gastroenterology* 2017;152:398–414e6.
419. Ahmed SF, Horrocks IA, Patterson T, et al. Bone mineral assessment by dual energy X-ray absorptiometry in children with inflammatory bowel disease: evaluation by age or bone area. *J Pediatr Gastroenterol Nutr* 2004;38:276–80.

420. Gokhale R, Favus MJ, Karrison T, et al. Bone mineral density assessment in children with inflammatory bowel disease. *Gastroenterology* 1998;114:902–11.
421. Sylvester FA, Wyzga N, Hyams JS, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2007;13:42–50.
422. Walther F, Fusch C, Radke M, et al. Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. *J Pediatr Gastroenterol Nutr* 2006;43:42–51.
423. Bak-Drabik K, Adamczyk P, Chobot A, et al. Bone status assessed by quantitative ultrasound in children with inflammatory bowel disease: a comparison with DXA. *Expert Rev Gastroenterol Hepatol* 2016; 10:1305–12.
424. Pappa HM, Gordon CM, Saslowsky TM, et al. Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics* 2006;118:1950–61.
425. Lu C, Yang J, Yu W, et al. Association between 25(OH)D level, ultraviolet exposure, geographical location, and inflammatory bowel disease activity: a systematic review and meta-analysis. *PLoS One* 2015;10:e0132036.
426. Werkstetter KJ, Pozza SB, Filipiak-Pittroff B, et al. Long-term development of bone geometry and muscle in pediatric inflammatory bowel disease. *Am J Gastroenterol* 2011;106:988–98.
427. Hyams JS, Wyzga N, Kreutzer DL, et al. Alterations in bone metabolism in children with inflammatory bowel disease: an in vitro study. *J Pediatr Gastroenterol Nutr* 1997;24:289–95.
428. Franchimont N, Putzeys V, Collette J, et al. Rapid improvement of bone metabolism after infliximab treatment in Crohn's disease. *Aliment Pharmacol Ther* 2004;20:607–14.
429. Thayu M, Leonard MB, Hyams JS, et al. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol* 2008;6:1378–84.
430. Ryan BM, Russel MG, Schurgers L, et al. Effect of antitumour necrosis factor-alpha therapy on bone turnover in patients with active Crohn's disease: a prospective study. *Aliment Pharmacol Ther* 2004;20:851–7.
431. Miheller P, Muzes G, Racz K, et al. Changes of OPG and RANKL concentrations in Crohn's disease after infliximab therapy. *Inflamm Bowel Dis* 2007;13:1379–84.
432. Whitten KE, Leach ST, Bohane TD, et al. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 2010;45:399–405.
433. Greenley RN, Stephens M, Doughty A, et al. Barriers to adherence among adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16:36–41.
434. Greenley RN, Hommel KA, Nebel J, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Pediatr Psychol* 2011;35:857–69.
435. Timmer A, Preiss JC, Motschall E, et al. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database of Systematic Reviews (Online)* (2)2011CD006913.
436. Ross SC, Strachan J, Russell RK, et al. Psychosocial functioning and health-related quality of life in paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011;53:480–8.
437. Engstrom I. Parental distress and social interaction in families with children with inflammatory bowel disease. *J Am Acad Child Adolesc Psychiatry* 1991;30:904–12.
438. Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med* 2004;66:79–84.
439. Rufo PA, Denson LA, Sylvester FA, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. *J Pediatr Gastroenterol Nutr* 2012;55:93–108.
440. Hommel KA, Denson LA, Baldassano RN. Oral medication adherence and disease severity in pediatric inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2011;23:250–4.
441. Hommel KA, Baldassano RN. Brief report: barriers to treatment adherence in pediatric inflammatory bowel disease. *J Pediatr Psychol* 2010;35:1005–10.
442. Reed-Knight B, Lewis JD, Blount RL. Association of disease, adolescent, and family factors with medication adherence in pediatric inflammatory bowel disease. *J Pediatr Psychol* 2011;36:308–17.
443. Ruemmele FM, Turner D. Differences in the management of pediatric and adult onset ulcerative colitis—lessons from the joint ECCO and ESPGHAN consensus guidelines for the management of pediatric ulcerative colitis. *J Crohns Colitis* 2014;8:1–4.
444. Goodhand J, Hedin CR, Croft NM, et al. Adolescents with IBD: the importance of structured transition care. *J Crohns Colitis* 2011;5:509–19.
445. van Rheenen PF, Aloi M, Biron IA, et al. European Crohn's and colitis organisation topical review on transitional care in inflammatory bowel disease. *J Crohns Colitis* 2017;11:1032–8.
446. Oliva-Hemker M, Hutfless S, Al Kazzi ES, et al. Clinical presentation and five-year therapeutic management of very early-onset inflammatory bowel disease in a large North American cohort. *J Pediatr* 2015;167:527–32e1-3.
447. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD—a metaanalysis. *J Crohns Colitis* 2009;3:277–81.
448. Kammermeier J, Dziubak R, Pescarin M, et al. Phenotypic and genotypic characterisation of inflammatory bowel disease presenting before the age of 2 years. *J Crohns Colitis* 2017;11:60–9.
449. Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014;147:990–1007e3.
450. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–9.
451. Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. *Gastroenterology* 2014;147:803–13e7; quiz e14-5.
452. Begue B, Verdier J, Rieux-Laucat F, et al. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. *Am J Gastroenterol* 2011;106:1544–55.
453. Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009;361:2033–45.
454. Glocker EO, Frede N, Perro M, et al. Infant colitis—it's in the genes. *Lancet* 2010;376:1272.
455. Damen GM, van Krieken JH, Hoppenreijs E, et al. Overlap, common features, and essential differences in pediatric granulomatous inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2010;51:690–7.
456. Dhillon SS, Fattouh R, Elkadri A, et al. Variants in nicotinamide adenine dinucleotide phosphate oxidase complex components determine susceptibility to very early onset inflammatory bowel disease. *Gastroenterology* 2014;147:680–9e2.
457. Pachlopnik Schmid J, Canioni D, Moshous D, et al. Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency). *Blood* 2011;117:1522–9.
458. Aguilar C, Lenoir C, Lambert N, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers. *J Allergy Clin Immunol* 2014;134:1131–41e9.
459. Lemoine R, Pachlopnik-Schmid J, Farin HF, et al. Immune deficiency-related enteropathy-lymphocytopenia-alopecia syndrome results from tetratricopeptide repeat domain 7A deficiency. *J Allergy Clin Immunol* 2014;134:1354–64.
460. Bigorgne AE, Farin HF, Lemoine R, et al. TTC7A mutations disrupt intestinal epithelial apicobasal polarity. *J Clin Invest* 2013;124:328–37.
461. Fernandez I, Patey N, Marchand V, et al. Multiple intestinal atresia with combined immune deficiency related to TTC7A defect is a multiorgan pathology: study of a French-Canadian-based cohort. *Medicine (Baltimore)* 2014;93:e327.
462. Fabre A, Charroux B, Martinez-Vinson C, et al. SKIV2L mutations cause syndromic diarrhea, or trichohepatoenteric syndrome. *Am J Hum Genet* 2012;90:689–92.
463. Fabre A, Martinez-Vinson C, Roquelaure B, et al. Novel mutations in TTC37 associated with tricho-hepato-enteric syndrome. *Hum Mutat* 2011;32:277–81.
464. Torgerson TR, Linane A, Moes N, et al. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. *Gastroenterology* 2007;132:1705–17.
465. Moes N, Rieux-Laucat F, Begue B, et al. Reduced expression of FOXP3 and regulatory T-cell function in severe forms of early-onset autoimmune enteropathy. *Gastroenterology* 2010;139:770–8.

466. Wildin RS, Ramsdell F, Peake J, et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet* 2001;27:18–20.
467. Baud O, Goulet O, Canioni D, et al. Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. *N Engl J Med* 2001;344:1758–62.
468. Engelhardt KR, Shah N, Faizura-Yeop I, et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013;131:825–30.
469. Shouval DS, Biswas A, Goettel JA, et al. Interleukin-10 receptor signaling in innate immune cells regulates mucosal immune tolerance and anti-inflammatory macrophage function. *Immunity* 2014;40:706–19.
470. Neven B, Mamessier E, Bruneau J, et al. A Mendelian predisposition to B cell lymphoma caused by IL-10R deficiency. *Blood* 2013;122:3713–22.
471. D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2218–24.
472. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. *Inflamm Bowel Dis* 2013;19:332–41.
473. Scaioli E, Scagliarini M, Cardamone C, et al. Clinical application of faecal calprotectin in ulcerative colitis patients. *Eur J Gastroenterol Hepatol* 2015;27:1418–24.
474. Dranga M, Mihai C, Drug V, et al. A rapid test for assessing disease activity in ulcerative colitis. *Turk J Gastroenterol* 2016;27:149–55.
475. Langhorst J, Elsenbruch S, Koelzer J, et al. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol* 2008;103:162–9.
476. Falvey JD, Hoskin T, Meijer B, et al. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflamm Bowel Dis* 2015;21:824–31.
477. Guardiola J, Lobatón T, Rodríguez-Alonso L, et al. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. *Clin Gastroenterol Hepatol* 2014;12:1865–70.
478. Lin W, Wong J, Tung C, et al. Fecal calprotectin correlated with endoscopic remission for Asian inflammatory bowel disease patients. *World J Gastroenterol* 2015;21:13566–73.
479. Lobaton T, Rodriguez-Moranta F, Lopez A, et al. A new rapid quantitative test for fecal calprotectin predicts endoscopic activity in ulcerative colitis. *Inflamm Bowel Dis* 2013;19:1034–42.
480. Samant H, Desai D, Abraham P, et al. Fecal calprotectin and its correlation with inflammatory markers and endoscopy in patients from India with inflammatory bowel disease. *Indian J Gastroenterol* 2015;34:431–5.
481. Xiang JY, Ouyang Q, Li GD, et al. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. *World J Gastroenterol* 2008;14:53–7.
482. Nancey S, Boschetti G, Moussata D, et al. Neopterin is a novel reliable fecal marker as accurate as calprotectin for predicting endoscopic disease activity in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2013;19:1043–52.
483. Takashima S, Kato J, Hiraoka S, et al. Evaluation of mucosal healing in ulcerative colitis by fecal calprotectin vs. fecal immunochemical test. *Am J Gastroenterol* 2015;110:873–80.
484. Sandborn WJ, Panés J, Zhang H, et al. Correlation between concentrations of fecal calprotectin and outcomes of patients with ulcerative colitis in a phase 2 trial. *Gastroenterology* 2016;150:96–102.
485. Kolho KL, Sipponen T. The long-term outcome of anti-tumor necrosis factor-alpha therapy related to fecal calprotectin values during induction therapy in pediatric inflammatory bowel disease. *Scand J Gastroenterol* 2014;49:434–41.
486. De Vos M, Louis EJ, Jahnsen J, et al. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. *Inflamm Bowel Dis* 2013;19:2111–7.
487. Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009;15:1190–8.
488. Ho GT, Lee HM, Brydon G, et al. Fecal calprotectin predicts the clinical course of acute severe ulcerative colitis. *Am J Gastroenterol* 2009;104:673–8.
489. Lasson A, Simren M, Stotzer PO, et al. Fecal calprotectin levels predict the clinical course in patients with new onset of ulcerative colitis. *Inflamm Bowel Dis* 2013;19:576–81.
490. Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut* 2005;54:364–8.
491. D'Inca R, Dal Pont E, Di Leo V, et al. Can calprotectin predict relapse risk in inflammatory bowel disease? *Am J Gastroenterol* 2008; 103:2007–14.
492. Garcia-Sanchez V, Iglesias-Flores E, Gonzalez R, et al. Does fecal calprotectin predict relapse in patients with Crohn's disease and ulcerative colitis? *J Crohns Colitis* 2010;4:144–52.
493. Hosseini SV, Jafari P, Taghavi SA, et al. Fecal calprotectin is an accurate tool and correlated to seo index in prediction of relapse in iranian patients with ulcerative colitis. *Iran Red Crescent Med J* 2015;17:e22796.
494. Jauregui-Amezaga A, Lopez-Ceron M, Aceituno M, et al. Accuracy of advanced endoscopy and fecal calprotectin for prediction of relapse in ulcerative colitis: a prospective study. *Inflamm Bowel Dis* 2014; 20:1187–93.
495. Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, et al. Fecal calprotectin as predictor of relapse in patients with inflammatory bowel disease under maintenance infliximab therapy. *J Clin Gastroenterol* 2016;50:147–51.
496. Tursi A, Elisei W, Picchio M, et al. Accuracy of rapid fecal calprotectin test in monitoring inflammatory bowel diseases under treatment with TNFα antagonists. *Dig Dis Sci* 2015;60:1406–13.
497. Theede K, Holck S, Ibsen P, et al. Fecal calprotectin predicts relapse and histological mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2016;22:1042–8.
498. F A, Filippi J, Boschetti G, et al. Accuracies of fecal calprotectin, lactoferrin, M2-pyruvate kinase, neopterin and zonulin to predict the response to infliximab in ulcerative colitis. *Dig Liver Dis* 2017;49:11–6.

APPENDIX 1: THE PEDIATRIC ULCERATIVE COLITIS ACTIVITY INDEX (PUCAI)

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

For user's guide and cutoff values for response, remission, mild, moderate, and severe disease activity, refer to the original study (39).