

# Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines

\*Dan Turner, †Arie Levine, ‡Johanna C. Escher, §Anne M. Griffiths, ||Richard K. Russell, ¶Axel Dignass, #Jorge Amil Dias, \*\*Jiri Bronsky, ††Christian P. Braegger, †††Salvatore Cucchiara, †††Lissy de Ridder, §§Ulrika L. Fagerberg, ||||Séamus Hussey, ¶¶Jean-Pierre Hugot, ###Sanja Kolacek, \*\*\*Kaija Leena Kolho, †††Paolo Lionetti, ††††Anders Pærregaard, §§§Alexander Potapov, \*\*\*Risto Rintala, |||||Daniela E. Serban, ¶¶¶Annamaria Staiano, |||||Brian Sweeny, ####Gigi Veerman, \*\*\*\*Gabor Veres, ††††David C. Wilson, and †††††Frank M. Ruemmele

## ABSTRACT

**Background and Aims:** Pediatric ulcerative colitis (UC) shares many features with adult-onset disease but there are some unique considerations; therefore, therapeutic approaches have to be adapted to these particular needs. We aimed to formulate guidelines for managing UC in children based on a systematic review (SR) of the literature and a robust consensus process. The present article is a product of a joint effort of the European Crohn's and Colitis Organization (ECCO) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN).

**Methods:** A group of 27 experts in pediatric IBD participated in an iterative consensus process including 2 face-to-face meetings, following an open call to ESPGHAN and ECCO members. A list of 23 predefined

questions were addressed by working subgroups based on a SR of the literature.

**Results:** A total of 40 formal recommendations and 68 practice points were endorsed with a consensus rate of at least 89% regarding initial evaluation, how to monitor disease activity, the role of endoscopic evaluation, medical and surgical therapy, timing and choice of each medication, the role of combined therapy, and when to stop medications. A management flowchart, based on the Pediatric Ulcerative Colitis Activity Index (PUCAI), is presented.

**Conclusions:** These guidelines provide clinically useful points to guide the management of UC in children. Taken together, the recommendations offer a standardized protocol that allows effective, timely management and

Received June 15, 2012; accepted June 22, 2012.

From the \*Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Jerusalem, and the †Wolfson Medical Center, Tel-Aviv University, Tel-Aviv, Israel, the ‡ErasmusMC-Sophia Children's Hospital, Rotterdam, The Netherlands, the §The Hospital for Sick Children, University of Toronto, Toronto, Canada, the ||Yorkhill Hospital, Glasgow, UK, the ¶Agaplesion Markus Hospital, Frankfurt/Main, Germany, the #Hospital S. João, Porto, Portugal, the \*\*2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic, the ††University Children's Hospital, Zurich, Switzerland, the †††Pediatric Gastroenterology and Liver Unit, "La Sapienza" University, Rome, Italy, the §§Centre for Clinical Research, Västmanland County Hospital, Västerås, Karolinska Institutet, Stockholm, Sweden, ||||Our Lady's Children's Hospital, Crumlin Dublin, Ireland, the ¶¶Univ Paris-Diderot-Sorbonne Paris-Cité, Hôpital Robert Debré, Paris, France, the ###Children's Hospital, Medical Center "Sestre Milosrdnice," Zagreb University Medical School, Croatia, the \*\*\*Children's Hospital, Helsinki, University Central Hospital and University of Helsinki, Finland, the †††University of Florence, Meyer Hospital, Florence, Italy, the ††††Hvidovre University Hospital, Copenhagen, Denmark, the §§§Children's Health Russian Academy of Medical Sciences, Moscow, Russia, the |||||University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania, the ¶¶¶University of Naples "Federico II," Italy, ####UZ Brussels, Belgium, the \*\*\*\*Semmelweis University, Budapest, Hungary, ††††Child Life and Health, University of Edinburgh, UK, and the †††††Université Paris Descartes, Sorbonne Paris Cité, APHP, Hôpital Necker Enfants Malades, Paris, France.

Address correspondence and reprint requests to Dan Turner, MD, PhD, Shaare Zedek Medical Center, Jerusalem, Israel (e-mail: turnerjd2001@gmail.com). All authors contributed equally to this work.

R.K.R. is supported by a NHS Research Scotland career fellowship award. The work of the IBD team at Yorkhill, Glasgow, was supported by the Catherine McEwan Foundation and the Yorkhill IBD fund. R.K.R. received consultation fee, research grant, or honorarium, from MSD, Abbott, Dr Falk, Ferring, and Nestle; A.M.G. received consultation fee, research support, or speaking fee from Centocor, Janssen, Merck, Abbott, and Shire; J.C.E. received consultation fee and research grant from MSD and Janssen Biologics; J.A.D. received consultation fee from Advisory Boards for MSD, Abbott; L.d.R. received consultation fee from MSD and Shire; J.B. received consultation fee from MSD; U.L.F. received lecture fee or travel grant from Tillotts AB, Otsuka Pharma Scandinavia AB, and Schering-Plough AB; A.P. received speaker's fee from MSD, and is a consultant for Swedish Orphan Biovitrum (Shire); K.L.K. received consultation fee from Abbott, MSD, and Tillotts Pharma; A.D. served as scientific advisory member for Ferring, MSD, Centocor, Abbott, UCB, PDL, Shire, and received lecture honoraria from Ferring, Falk Foundation, MSD, Merckle Recordati, Abbott, UCB, Shire, Otsuka, Vifor, and Immundiagnostik; S.K. received honorarium from MSD, Abbott, Nestle, and Nutricia; D.T. received consultation fee, research grant, or honorarium, from MSD, Shire, Janssen, Hospital for Sick Children (PUCAI royalties), Proctor & Gamble, and Johnson & Johnson; A.L. received consultation fee, research grants, or honoraria, from MSD, Falk, Janssen, and Nestle; G.V. is a consultant to MSD, Shire, and Danone; D.C.W. received consultation fees or honoraria from MSD, Abbott, Ferring, and Nestle; F.M.R. received consultation fees, research grants, or lecture honoraria from Abbott, Biocodex, Centocor, Danone, Falk Foundation, Ferring, Johnson & Johnson, MeadJohnson, MSD, Nestlé, and Shire.

The other authors report no conflicts of interest.

Copyright © 2012 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0b013e3182662233

monitoring of the disease course, while acknowledging that each patient is unique.

**Key Words:** children, clinical guidelines, European Crohn's and Colitis Organization, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition, management, Pediatric Ulcerative Colitis Activity Index, ulcerative colitis

(JPGN 2012;55: 340–361)

**U**lcerative colitis (UC) is a chronic relapsing inflammatory condition of the colon, extending continuously from the rectum proximally to a varying degree. No single criterion can accurately diagnose UC. Typically, UC is suspected in a patient presenting with bloody diarrhea, tenesmus, abdominal pain, and, when symptoms become severe, weight loss, fatigue, and vomiting. The incidence of pediatric-onset UC, which forms roughly 15% to 20% of patients of all ages with UC, ranges between 1 and 4 of 100,000/year in most North American and European regions (1–3).

Childhood-onset UC is extensive in 60% to 80% of all cases, twice as often as in adults (4). Because disease extent has been consistently associated with disease severity, it is not surprising that pediatric-onset UC has a worse disease course, with a 30% to 40% colectomy rate at 10 years, as compared with 20% in adults (4,5), although rates as low as 10% also have been reported in other pediatric studies (6,7). Approximately 25% to 30% of children with UC will require admission for an acute exacerbation before transitioning to adult care, almost twice as often as seen in adult-onset disease during a similar period (8,9). Children also have unique age-related considerations, such as growth, puberty, nutrition, and bone mineral density (BMD) accretion during adolescence, as well as differing psychosocial needs and development.

We aimed to develop guidelines for managing UC in children based on a systematic review (SR) of the literature and a robust consensus process of an international working group of specialists in pediatric IBD from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO), following an open call. These consensus guidelines 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 (10) and similar topics are covered here only briefly, referencing the extensive ECCO review. **These guidelines relate only to ambulatory children and not to the management of children hospitalized with acute severe colitis**, which was covered in the pediatric ESPGHAN and ECCO guidelines on acute severe colitis (11).

## METHODS

A list of 23 questions addressing the management of UC in children was first developed, each appraised independently based on review of the evidence by 2 group members (Appendix 1). The subgroup's recommendations were iterated by e-mail with the steering committee until refined. The review of the evidence included both pediatric and adult data because pediatric data were often scarce (12). Electronic searches were performed in early 2011 using MEDLINE, Embase, CINAHL, and the Cochrane Controlled Trials Register, and updated in early 2012. The search strategies used are available upon request. Clinical guidelines, SRs, clinical trials, cohort studies, case-control studies, diagnostic studies, surveys, letters, narrative reviews, and case series were used. The grading of evidence was performed according to the Oxford Centre for Evidence-based Medicine (Appendix 2).

Recommendations were discussed by the working group at 2 face-to-face meetings during ESPGHAN annual meeting (Sorrento, May 2011) and during UEGW (Stockholm, October 2011). The meetings were complemented by an e-mail Delphi process with the entire group until agreement was reached. All statements and practice points were supported by at least 89% of the group and, in most cases, reflect almost full consensus. The guidelines include recommendations (boxed in the text) and "practice points" that reflect common practice in which evidence is lacking.

## MONITORING AND PREDICTION

**Baseline Investigations at Diagnosis and Differential Diagnosis (Table 1) (96% consensus)**

1. **The diagnosis of pediatric UC should be based on a combination of history, physical examination, and ileocolonoscopy with histology on multiple biopsies, performed by a gastroenterologist with pediatric expertise [EL5, RG D]**
2. **Upper endoscopy is recommended in all cases to exclude Crohn disease [EL2b, RG C]**
3. **Initial laboratory investigations should include a full blood count, liver enzymes, albumin, erythrocyte sedimentation rate (ESR), iron status, and C-reactive protein (CRP) [EL5, RG D; adults EL2b, RG B]**
4. **Stool culture is mandatory to exclude infectious diarrhea; testing for *Clostridium difficile* toxin is recommended on at least 3 independent stool samples [EL4, RG C]; additional stool tests may be necessary for patients who report recent travels [EL5, RG D]**
5. **In children younger than 2 years, additional immunological investigations and allergy testing may be necessary to exclude colitis related to primary immunodeficiency or allergic conditions [EL5, RG D]**

### Practice Points:

1. Imaging of the small bowel is recommended to exclude Crohn disease (CD) and should be performed particularly in patients with atypical phenotypes.
2. Blood inflammatory markers in children with active colitis may be normal, especially in mild disease.
3. Fecal inflammatory parameters, most notably calprotectin but also lactoferrin and S100A12, effectively differentiate colitis from noninflammatory diarrhea; however, in the vast majority of cases, bloody diarrhea is present, which indicates colonic inflammation. Therefore, fecal markers are not usually necessary as part of the diagnostic workup of UC, unless used to determine baseline values for future reference.
4. Serological markers (eg, anti-neutrophil cytoplasmic antibody, anti-saccharomyces cerevisiae antibody) can be useful for differentiating UC from CD; the diagnosis of UC should be reevaluated in cases of positive anti-saccharomyces cerevisiae antibody.
5. Immunological testing for atypical presentation and for children younger than 2 years includes lymphocyte phenotyping (T, B, NK, NK-T cells), immunoglobulin levels, as well as functional analyses of lymphocytic responses to antigens/mitogens and neutrophils, including chronic granulomatous disease (CGD). Allergic testing in infants is based mainly on a trial of food withdrawal. Testing for the interleukin (IL)-10 axis should be considered for those younger than 1 year, and may be based on functional or genetic analyses.

TABLE 1. Main differential diagnosis of pediatric UC

Differential diagnosis	Clinical presentation	Investigation
Infectious colitis (frequent)	Acute onset, often with fever and occasionally with vomiting. Rarely lasts >3 wk	Stool samples for microbial investigations including <i>C difficile</i> and parasites; tuberculosis and <i>Yersinia</i> testing when indicated
Allergic colitis (frequent in young infants)	Eczema, history of milk protein allergy, family history of atopy	Specific/total IgE, skin prick testing, colonic biopsies (eosinophilic infiltration, lymphonodular hyperplasia), trial of elimination of cow's-milk protein and other allergens
Vasculitis (rare)	Associated extraintestinal inflammation (eg, skin, joints and eyes)	HLA-B5, skin biopsies, serological markers
Immunodeficiency states (rare)	Onset of colitis within the first months of life, often with perianal involvement; skin folliculitis or eczema; other fungal or bacterial infections	Consult an immunologist in every case of early onset colitis (eg, IL-10R and IL-10 genotyping and/or functional testing, NBT testing or chemotaxis testing or genetic testing (CGD), CVID, Wiskott-Aldrich syndrome, and others)

CGD = chronic granulomatous disease; CVID = common variable immune deficiency; NBT = nitroblue-tetrazolium test; UC = ulcerative colitis.

It is beyond the scope of the present article to review all of the evidence for the diagnosis and classification of UC, which was addressed in the Porto criteria for the diagnosis of pediatric IBD (13), the Paris pediatric modification of the Montreal classification of IBD (14), and a NASPGHAN working group review (15). Briefly, the historical perception that considered UC as a superficial inflammatory disease uniformly involving the rectum and progressing contiguously to varying degrees of the colon only is simplistic. Macroscopic rectal sparing may be seen in approximately 5% to 30% of patients, many of whom have "relative" (mild patchy disease) rather than "absolute" macroscopic rectal sparing (13,14,16–18). Prospectively collected data from the large ESPGHAN EuroKids registry demonstrated macroscopic rectal sparing in 5% of children at diagnosis (19). Young children at disease onset may show more rectal sparing, macroscopically patchy disease, or have normal or minimally disturbed crypt architecture (17), which occur primarily in children 10 years or younger (20). Mild limited cecal erythema (ie, cecal patch) may be present in both children and adults with UC (20,21). Mild nonerosive ileitis in the presence of severe pancolitis may be diagnosed as backwash ileitis associated with UC and microscopically may show villous atrophy, increased mononuclear cells, and scattered crypt abscesses (22). Gastritis is commonly seen with UC whether focal or diffuse, and erosions may be present (23); however, frank gastric ulcers, erosive duodenitis, or esophagitis is rare in UC, found in <1% of 261 children with newly diagnosed UC from the EuroKids registry (19). In that registry, diagnostic yield of upper gastrointestinal endoscopy was 7.5%, indicating that in 1 of 13 children with colitis, a diagnosis of CD could be made based on the upper endoscopy findings (24).

Because there are multiple findings that may be inconsistent with UC, it is important to complete a full ileocolonoscopy and upper endoscopy with serial biopsies for diagnosing pediatric IBD. In patients with acute severe colitis, a diagnostic sigmoidoscopy may be used as the initial test for evaluation, but a follow-up colonoscopy should be subsequently performed. Because histology is atypical in a significant number of children, small bowel imaging should be considered in pediatric patients to exclude CD.

Colonic inflammation in young infants (especially younger than 1 year) may reflect allergic colitis or an immunodeficiency, even as an isolated finding. Although these children should have an allergic evaluation, only a trial of elimination diet can confirm the diagnosis of allergic colitis (25). Before confirming the diagnosis of

early-onset IBD, classical and subtle immunodeficiencies should be excluded (Table 1) (26–28).

#### Assessing and Predicting Disease Activity (96% Consensus)

- 1. Endoscopic evaluation is recommended at diagnosis, before major treatment changes and when the clinical assessment is in question; endoscopic evaluation in children is not routinely recommended during flares, which are not severe or during clinical remission aside from cancer surveillance [EL5, RG D]**

#### Practice Points:

- Achieving complete remission is associated with improved long-term outcomes; however, there is no evidence to suggest that endoscopic verification of mucosal healing is significantly superior to clinical judgment of remission for this purpose.
- The Pediatric Ulcerative Colitis Activity Index (PUCAI; Appendix 3) is a validated score of clinical disease activity that does not include endoscopy or laboratory markers and is easy to perform on a daily basis. Generally, a PUCAI < 10 indicates remission, 10 to 34 mild disease activity, 35 to 64 moderate, and ≥65 points severe. A clinically significant response is indicated by a drop in PUCAI of at least 20 points. In practice, clinicians may benchmark their decision on response by these general cutoff values, but these can vary individually.
- In drug trials, the PUCAI score can be used as a noninvasive primary outcome measure that has proven to be a valid and responsive index, including high correlation with colonoscopy.
- Before management changes in active disease, it must be ensured that symptoms are the result of disease activity and not of other clinical problems such as irritable bowel syndrome [IBS], dysmotility, bacterial overgrowth, disease complications (eg, stenosis), celiac, 5-aminosalicylic acid (5-ASA) intolerance, or infection with *C difficile* or cytomegalovirus [CMV].
- Complete blood cell count (CBC), albumin, liver enzymes, and inflammatory markers should be performed periodically.

6. Calprotectin levels >100 to 150  $\mu\text{g/g}$  indicate mucosal inflammation. Its role in predicting clinical relapse needs to be further studied prospectively head-to-head with clinical variables, before it can be used to dictate a change in therapy.

The ECCO adult guidelines recommend endoscopic reassessment at relapse, for steroid-dependent or steroid-refractory UC or when considering colectomy (29); however, endoscopic assessment of disease activity has several major limitations. First, endoscopic scoring depends on the subjective assessment of mucosal properties with generally low interobserver reliability (30). Second, endoscopic appearance lags behind clinical improvement, thereby underestimating response to treatment (31). Endoscopy in children is mostly performed under general anesthesia and is considered more invasive than in adults. Finally, although mucosal healing has been shown to predict favorable clinical outcome in UC (32–34), it has yet to be proven that endoscopy is superior to clinical judgment for predicting clinically important outcomes. Indeed, in the combined ACT cohorts (466 adults with UC treated with either infliximab or placebo), endoscopic healing had no predictive value among the subset of patients with clinical remission after 8 weeks of therapy (32). Clinical judgment of response to steroid treatment in UC has been shown to predict long-term, clinically important outcomes, both in adults (35) and in children (8,36). This probably stems from the strong correlation between physician's clinical assessment of disease activity and mucosal inflammation in UC, unlike that seen in CD ( $r=0.77-0.79$  in 76 children and 86 adults) ((37) and unpublished data from D.T.). Treatment changes based on endoscopy were more frequent in children with CD compared with UC (38). Taken together, and incorporating the unique pediatric considerations, it does not seem justified to recommend endoscopic assessment routinely in pediatric UC solely for assessing disease activity or response to treatment or at relapse. Endoscopic evaluation, however, is indispensable in questionable clinical scenarios, before major treatment changes, and for diagnosing complications (eg, stenosis, dysplasia) and superinfections.

The PUCAI is a noninvasive multi-item measure that has been shown to be valid, reliable, and responsive to short-term changes in several clinical trials and cohort studies (39,40). The PUCAI has been proven to have excellent correlation with the invasive Mayo score ( $r=0.95$ ), physician global assessment ( $r=0.91$ ), and colonoscopic appearance ( $r=0.76-0.8$ ) (37,39). The PUCAI score ranges from 0 to 85 points and is the sum of scores of daily abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity level. Cutoff scores for remission, mild, moderate, and severe disease have been replicated in 3 independent cohorts with sensitivity and specificity of >90% (37,39,40).

At the time of presentation, serum inflammatory markers are higher in CD compared with UC (41,42). In a cohort of 512 children newly diagnosed as having UC, 54% of those with mild disease had normal results on all 4 common assays (ie, hemoglobin, albumin, platelet, and ESR), compared with 21% of children with mild CD (41). Both ESR and CRP were completely normal in 34% and 5% to 10% of 451 children with mild and moderate to severe disease activity, respectively (43). Correlation with colonic inflammation was only fair, with a slight superiority of CRP. In most patients, either CRP or ESR alone was sufficient to reflect disease activity over time, once it is determined which of the markers is elevated.

Fecal calprotectin levels above the cutoff of 100  $\mu\text{g/g}$  have been shown to correlate with mucosal inflammation on endoscopy in UC in the range of 0.5 to 0.8 (44–49). Although

1 small study showed that the correlation of the Rachmilewitz index was lower (44), most noninvasive clinical indices show similar correlation with endoscopy, with  $\rho$  ranging from 0.65 to 0.8 (37). Although fecal calprotectin is superior to markers of inflammation in the blood (50), it is not known whether routine assessment of calprotectin in all patients is superior to simple clinical assessment in children; however, the authors stressed its importance because they use calprotectin routinely. In the acute severe setting, the clinical PUCAI predicted short-term clinical response better than 5 fecal biomarkers in children (51,52). Fecal biomarkers may certainly be useful in some cases in which the association of symptoms with mucosal inflammation is in question, such as with nonbloody diarrhea. Further research is required to compare the performance of fecal biomarkers to clinical judgment before recommending the use of fecal biomarkers for routine monitoring of disease activity in all patients.

## MEDICAL MANAGEMENT

### Oral 5-ASA and Rectal Therapy (93% consensus)

- Oral 5-ASA regimens are recommended as first-line induction therapy for mild to moderately active pediatric UC [EL2b, RG B; adults EL1b, RG A] and for maintenance of remission [EL5, RG D; adults EL1a, RG A] regardless of other initial treatments**
- Monotherapy with topical 5-ASA may be effective in selected children with mild to moderate proctitis; however, this is a rare pediatric phenotype [EL 2b, RG B; adults E1b, RG A]**
- Combining oral 5-ASA with topical 5-ASA is more effective than oral alone [EL5, RG D; adults EL1b, RG B]. Therefore, whenever tolerated, 5-ASA enemas (or rectal steroids if 5-ASA is not tolerated) should be offered along with oral therapy for induction of remission even in extensive disease [EL5, RG D; adults EL1a, RG A]**
- Rectal 5-ASA is superior and should be preferred over rectal steroid therapy [EL2b, RG B; adults EL1a, RG A]**

### Practice Points:

- There is no evidence that any delivery system of mesalazine (controlled release and pH dependent) is superior to the other.
- Mesalazine and sulfasalazine are the 5-ASAs of choice. Oral mesalazine is dosed 60 to 80  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  in 2 daily doses up to 4.8 g daily. Although not evidence based, doses of 100 mg/kg are sometimes used. Rectal 5-ASA is dosed 25 mg/kg up to 1 g once daily. Sulfasalazine is dosed 40 to 70  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  oral in 2 divided doses with a maximal dose of 4 g/day, and again, higher doses are in use. The maximal combined oral and rectal dose should not usually exceed the standard oral dose by >50% or 6.4 g/day in adults.
- Although pediatric data are lacking, there are several adult trials showing that once-daily dosing of 5-ASA is equally effective as twice daily.
- The maintenance dose should be similar to the dose used for induction therapy, but lower doses may be considered after a period of sustained remission (not lower than 40 mg/kg or 2.4 g/day; the minimum effective dose in adults is 1.2 g/day).
- There is no firm evidence to support the superiority of sulfasalazine over mesalazine. Sulfasalazine may be particularly helpful in patients with associated arthropathy; it is considerably less expensive and is the only formulation available in liquid form. It is, however, associated with more adverse effects. Gradual dose increase of sulfasalazine

- >7 to 14 days may decrease the rate of dose-dependent adverse effects, such as headaches and gastrointestinal upset.
6. Lack of response to oral mesalazine within 2 weeks is an indication to consider an alternative treatment as an addition of topical therapy (if not started already) or oral corticosteroids.
  7. Maintenance of 5-ASA should be continued indefinitely unless intolerant, given its high effectiveness and excellent safety profile.
  8. Acute intolerance to 5-ASA may resemble a flare of colitis. Response to withdrawal of 5-ASA and recurrence upon rechallenge provide the clue to this diagnosis, which precludes further use of any 5-ASA-containing drug.
  9. Rectal therapy should be offered to the child but cannot be forced because effective alternatives exist. Single daily dosing of rectal 5-ASA may enhance compliance without affecting clinical outcomes.

5-ASA delivery systems can be divided into azo-compounds (sulfasalazine, olsalazine, and balsalazide), controlled release (Pentasa), pH dependent (either pH 6 [Salofalk, Mesasal, Claversal] or pH 7 [Asacol, Mesren, Ipcol]), and a combination of pH-dependent and controlled release (Mezavant and Lialda). Site of delivery for the azo-compounds is the colon (cleavage by bacteria), for the pH-dependent distal to the distal ileum, and for the controlled release from the duodenum (53,54).

Two recent Cochrane reviews (55,56) and another meta-analysis (57) showed that 5-ASA compounds are effective in adults for both induction and maintaining remission compared with placebo. Eleven RCTs compared 5-ASA with placebo for induction of remission (2086 patients), with relative risk (RR) of 0.79 (95% confidence interval [CI] 0.73–0.85; number needed to treat [NNT] 6). Overall, 40% of patients achieved remission compared with 20% in the placebo group. Eleven RCTs compared 5-ASA with placebo (1502 patients) for maintenance of remission, with RR 0.65 (95% CI 0.55–0.76; NNT 4). Overall, 40% of patients on 5-ASA relapsed versus 63% with placebo >6 to 12 months (57). A recent meta-analysis showed that mucosal healing was achieved by 37% of 3977 patients using oral 5-ASA, and 50% of 2513 patients using rectal 5-ASA (58). There was no difference in mucosal healing rate between the various 5-ASA agents.

Four small pediatric clinical trials (59–62) and a few retrospective studies (63–65) confirmed that 5-ASA is effective for inducing remission in mild to moderate UC in children, achieving endoscopic remission in 27% after 12 weeks (59). There are no pediatric trials evaluating combined oral and rectal 5-ASAs, nor of the effectiveness of 5-ASA in maintaining remission.

The Cochrane meta-analysis showed a trend to benefit the newer 5-ASA preparations (in terms of both efficacy and minimizing adverse effects) over sulfasalazine for inducing remission, but sulfasalazine was superior for maintaining remission (55,56). In contrast, the recent meta-analysis showed no difference for both inducing and maintaining remission (57). One pediatric double-blinded randomized clinical trial (RCT) showed that olsalazine 30 mg · kg<sup>-1</sup> · day<sup>-1</sup> induced clinical response in 39% versus 79% with sulfasalazine 60 mg · kg<sup>-1</sup> · day<sup>-1</sup> after 3 months in 56 children with mild to moderate UC (61). Results from another pediatric trial suggested equivalent efficacy of mesalazine and sulfasalazine in maintaining remission in either UC or Crohn colitis (64). A dedicated meta-analysis comparing the efficacy of sulfasalazine versus newer 5-ASA included 20 RCTs and showed no major differences in efficacy and adverse events (66).

No pediatric dose-finding trials of aminosalicylates are available. The pediatric dosing is extrapolated from adults based on 3 studies showing that pharmacokinetics in children is

comparable with adults (63,65,67). Doses >2.4 g may be beneficial for extensive colitis (68) and, as suggested in the ASCEND trials, also in patients with more active disease (69–71). Because pediatric-onset UC is associated with a more severe and extensive phenotype, higher doses on average may be needed to treat children with UC. In adults, 2.4 g/day may be superior to lower doses for maintaining remission, especially in extensive disease (68), but no pediatric data are available. Wiersma et al (67) have shown that a single mesalazine dose is probably safe and this is well studied in adults (72–75); however, trials to support once-daily dosing in children, although under way, have not yet been completed.

Although 5-ASA agents are considered safe (76), several pediatric case reports described rare adverse effects, such as interstitial nephritis (77), pneumonitis (78), and pericarditis (owing to hypersensitivity) (79). Interstitial nephritis is a rare but serious complication of an aminosalicylate (77). Sulfasalazine may inhibit the intestinal transport of folic acid (80). Acute intolerance to 5-ASA is seen in 3% of adult patients and may resemble a flare of colitis (10). Although not evidence based, many clinicians believe that creatinine, full blood count, and urinalysis should be monitored every 3 to 6 months during aminosalicylate therapy, and blood folate levels annually (10,77).

Topical mesalazine induced remission in active proctitis and distal colitis in 31% to 80% (median 67%) versus 7% to 11% placebo, in a meta-analysis of 11 trials including 778 adult patients (81). Mesalazine foam enemas, gel enemas, and liquid enemas appear to achieve similar outcomes in terms of remission, tolerance, and safety in adults, although the liquid enemas are perceived to cover a larger part of the bowel (82–84). 5-ASA suppositories (up to 24 months) are superior to placebo for maintaining remission in adults (85–87). In pediatrics, 500 mg daily mesalazine suppositories were effective in improving disease activity at 3 and 6 weeks in children with mild to moderate ulcerative proctitis (62). Either 5-ASA or hydrocortisone enemas resulted in a higher remission rate than placebo in 29 children with isolated left-sided colitis (88). Unlike in adults, however, only ~5% of children present with isolated proctitis (4,19), and although higher rates also have been reported (5), the risk for progressing to a more extensive phenotype is higher than that in adults (4). Therefore, rectal monotherapy is suitable for a few pediatric patients and, as a general rule, should be used in combination with an oral medication.

Rectal 5-ASA was not significantly superior to oral 5-ASA for symptomatic improvement in the Cochrane meta-analysis (odds ratio [OR] 2.25, 95% CI 0.53–9.54, *P* = 0.27), in contrast to that suggested by previous meta-analyses (89–91). No significant benefit of high-dose over low-dose rectal 5-ASA (mesalazine 500 mg daily up to 4 g/day) has been observed. Either single daily or divided daily dosing of 5-ASA suppositories is equally effective for inducing remission (92,93). Finally, rectal steroids are an effective alternative to rectal 5-ASA in patients intolerant of 5-ASA (88). Other rectal therapies proposed anecdotally include cyclosporine, tacrolimus, short-chain fatty acids, probiotics, and beclomethasone 17,21-dipropionate (BDP).

A number of studies indicate that dual therapy with oral and rectal 5-ASA is superior to either alone in patients with mild to moderate UC (94). Adding 1 g daily mesalazine enemas enhanced clinical improvement and remission at 4 and 8 weeks in adults with mild to moderate UC treated with oral mesalazine 4 g daily (95). Adjunctive intermittent 5-ASA enemas reduced frequency of relapse compared with oral 5-ASA monotherapy in adults with UC in remission (96).

For topical therapy to be successful, children and their parents need extra support, education, and reassurance to allay concerns and to ensure optimal compliance. The treatment of

a given child with enemas should balance the clinical benefits, psychological distress, and the viable oral alternatives.

#### Oral Steroids (96% consensus)

1. **Oral steroids are effective for inducing remission in pediatric UC [EL2a, RG C; adults EL1b, RG C] but not for maintaining remission [EL5, RG D]**
2. **Oral steroids are recommended in moderate disease with systemic symptoms and selected children with severe disease without systemic symptoms, or in those failing to achieve remission with optimal 5-ASA therapy. Most of those with severe disease should be admitted for intravenous steroid therapy [EL5, RG D; adults EL1b, RG B]**
3. **The dose of prednisone/prednisolone should be 1 mg/kg up to 40 mg once daily in most children [EL2a, RG B]**
4. **Steroid dependency in children should not be tolerated; steroid-sparing strategies should be used [EL 4, GR C]**

#### Practice Points:

1. Prednisone (the prodrug of prednisolone) or prednisolone (the biologically active steroid) may be used orally with comparable doses. Oral budesonide is not recommended for UC. Recent data suggest that oral and rectally administered BDP, a new corticosteroid with topical action, may be as effective as prednisone in mild to moderate UC.
2. A single total dose in the morning is advisable to reduce potential harmful suppression of growth.
3. In steroid refractoriness (ie, nonresponse to oral steroids within 7–14 days), optimal dosing and compliance with treatment should be confirmed. Other explanations for the symptoms (as outlined in the Assessing and Predicting Disease Activity section) should be excluded.
4. Steroid dependency is defined as remission with corticosteroids but recurrence of symptoms when the dose is lowered or within 3 months following complete taper, or if steroids cannot be stopped within 14 to 16 weeks. Steroid dependency should be avoided by escalating the existing maintenance therapy or by adding topical therapy.
5. We constructed a pediatric steroid tapering table (Table 2) based on common practice and group consensus.

Steroids are introduced in up to 80% of children with UC mainly within 3 months of diagnosis, with a 50% to 90% short-term response rate (7,31,97). Mucosal healing with corticosteroids is more often achieved in UC than in CD, but it lags behind clinical improvement. After 8 weeks of steroid therapy in 20 children with UC, mucosal healing has been achieved in 40%, whereas 90% showed clinical improvement (31). The majority of adult patients with UC respond to steroids within 2 to 3 weeks (98). In children, it is particularly important to evaluate the response earlier to start timely tapering and reduce the dose and duration of treatment. It is imperative to avoid unnecessary steroid exposure to minimize growth retardation and other steroid-related adverse effects. Steroid therapy may lower calprotectin levels as disease activity improves, but normalization is infrequent (99). Thus, an increased level of calprotectin does not necessitate ongoing steroid therapy if the patient is in clinical remission.

There are no dose-finding trials of steroids in pediatric UC. In adults, a 20-mg daily dose of oral prednisone is less effective than 40 mg in inducing remission; 60 mg was as effective as 40 mg but with more adverse events (98). Splitting the daily dose is not

more effective than a single dose (100). Children with UC may have a higher steroid-related complication rate compared with adults, including osteoporosis, glaucoma, and cataracts, even when adjusted to weight-based steroid doses (101). Mood disorders and sleep disturbance are common during steroid treatment. In most asymptomatic cases, there is no need to add acid suppression during standard steroid treatment. This should be considered in upper gastrointestinal disease or when nonsteroidal anti-inflammatory drugs (NSAIDs) are in use.

Steroid dependency implies initial clinical response to systemic corticosteroid treatment, but the inability to achieve and/or maintain a steroid-free clinical remission. Steroid dependency during a 1-year follow-up has been reported in 45% of children with UC requiring corticosteroids at diagnosis, higher than that reported in adults (7,97). Strategies to avoid steroid dependency include optimization of 5-ASA, adjuvant therapy with enemas, and consideration of escalating therapy to thiopurines or infliximab. Adherence to therapy should be ensured, especially in adolescents. Colectomy should be considered when medical strategies have not resolved steroid dependency.

BDP is a new corticosteroid with topical action. RCTs in adults showed its effectiveness in UC both in oral and topical routes (102–104). A pediatric trial showed that the week 12 remission rate among 15 children receiving 5 mg/day of BDP is 80% compared with only 33% in 15 children receiving 5-ASA (59). There are preliminary data on the extended-release formulation of budesonide inducing clinical improvement in adults with active left-sided colitis but no pediatric data (105).

#### Antibiotics and Probiotics (Excluding Pouchitis) (96% consensus)

1. **There is insufficient evidence to recommend routine antibiotic or probiotic therapy to ambulatory pediatric patients with UC for induction or maintenance of remission [EL5, RG D; adults EL2b, RG B]**
2. **Probiotics, however, may be considered in children with mild UC intolerant to 5-ASA, or as an adjuvant therapy in those with mild residual activity despite standard therapy [EL1b, RG B; adults EL1b, GR A]**

#### Practice Points:

1. Efficacy of probiotics in pediatric and adult UC trials has been demonstrated for VSL#3 (Table 3 for daily dosing) and *Escherichia coli* Nissle.
2. Probiotics should be used with caution in severely immunocompromised patients or those with intravenous catheters because sepsis has been reported. Bloating, flatulence, and nausea may be associated with VSL#3.

There have been no controlled trials of adjunctive antibiotics to induce or maintain remission in pediatric UC, but several small adult studies suggested some benefit with differing regimens. Oral tobramycin (107,108), oral rifaximin (109), and a combination regimen of oral amoxicillin, metronidazole, and tetracycline (110) had an adjunctive effect to successfully induce remission in ambulatory adults with UC. Ciprofloxacin (<14 days) did not induce remission in adults with mild to severe UC (111), but 6-month treatment seemed beneficial in maintaining remission in adults with moderate to severe disease (112). Rifaximin increased the remission rate in a small retrospective study of 11 children (113).

TABLE 2. Prednisone tapering plan (numbers reflect daily milligrams)

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
60*	50	40	35	30	25	20	15	10	5	0
50*	40	40	35	30	25	20	15	10	5	0
45*	40	40	35	30	25	20	15	10	5	0
40	40	30	30	25	25	20	15	10	5	0
35	35	30	30	25	20	15	15	10	5	0
30	30	30	25	20	15	15	10	10	5	0
25	25	25	20	20	15	15	10	5	5	0
20	20	20	15	15	12.5	10	7.5	5	2.5	0
15	15	15	12.5	10	10	7.5	7.5	5	2.5	0

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). If there is no significant clinical improvement in patients with moderate to severe colitis (ie, PUCAI decrease in <20 points) after 7 to 14 days, or an increase in PUCAI ≥ 20 points at any time, then consider treatment escalation after excluding other causes for steroid-refractory disease (see text).

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 start weaning again more slowly; PUCAI > 60 or increase in PUCAI by at least 20 points at any time, consider treatment escalation. In any case, avoid steroid dependency by timely escalation of maintenance therapy.

The risk for exacerbation is smaller with prednisone doses >20 mg, but the risk for adverse events is then higher. Thus, tapering should be instituted early with larger decrements initially and slower decrements at lower doses. Shortening each stage from 7 to 5 days may be considered in selected cases. With lower doses, alternate-day treatment may reduce the risk of adverse events. Consider the possibility of adrenal insufficiency, even many months after tapering off steroids.

A recent SR of RCTs suggested an overall beneficial effect of antibiotics for induction of remission in adult UC (114). Nine RCTs, involving 662 patients with active UC (2 of whom were in the acute severe setting), found a statistically significant benefit of antibiotics for inducing remission (RR 0.64; 95% CI 0.43–0.96); however, a funnel plot suggested publication bias, and a great variety of the antibiotics was used. Pediatric trials are required to decipher the potential benefits, if any, of antibiotics for UC in children before they can be recommended.

Probiotics have been evaluated for induction and maintenance of remission in UC. One pediatric and 3 adult trials did not find a significant difference between *E coli* Nissle 1917 and mesalazine for maintaining remission in UC (10,115). Although the ECCO guidelines in adults state that this probiotic may be a viable alternative to 5-ASA for maintaining remission in mild to moderate UC (10), a Cochrane review highlighted major methodological limitations in these studies, preventing any conclusion (116).

A small pediatric trial suggested that *E coli* Nissle is also effective in inducing remission in UC (115). In an open pilot study, remission was induced in 10 of 18 children with UC treated with VSL#3 in conjunction with 5-ASA, low doses of corticosteroids, or immunomodulators (117). A small trial of 29 children treated with 5-ASA showed that the combination with VSL#3 was superior to placebo in inducing and maintaining 1-year remission (Table 3 tabulates the daily dosing) (106). These studies build on the adult literature, which show a benefit for VSL#3 in inducing remission in UC (117–120).

TABLE 3. Pediatric VSL#3 dosing by Miele et al (106)

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

In other small trials, different probiotics were suggested to be effective in inducing remission (*Saccharomyces boulardii* (121), *Bifidobacterium longum* plus the prebiotic Synergy (122), and *B breve*, *B bifidum* plus *Lactobacillus acidophilus* (123)) and maintaining remission (*Lactobacillus* GG (124), and Probio-Tec AB-25 (125)). One recent pediatric trial showed that rectal enemas of *Lactobacillus reuteri* were superior to placebo in facilitating mesalazine-induced remission in UC (126).

**Immunomodulators (89% consensus)**

1. Thiopurines (azathioprine or mercaptopurine) are recommended for maintaining remission in children with 5-ASA intolerance or those with frequently relapsing (2–3 relapses per year) or steroid-dependent disease, despite the use of maximal 5-ASA treatment [EL3b, RG C; adults EL1b, RG B]; thiopurines are ineffective for induction of remission [EL3b, RG C]
2. Thiopurines are recommended for maintenance treatment after inducing remission by steroids during acute severe colitis because the likelihood for an aggressive disease course is higher [EL4, RG C; adults: EL2b, RG B]; however, 5-ASA maintenance monotherapy may be considered in 5-ASA-naïve children with acute severe colitis responding rapidly to steroids [EL5, RG D]
3. Cyclosporine or tacrolimus started during an episode of acute severe colitis should be discontinued after 4 months, bridging to thiopurines [EL4, RG C]
4. The presently available evidence is insufficient to recommend the use of methotrexate in pediatric UC [EL5, RG D; adults EL4, RG C]

**Practice Points:**

1. The therapeutic effect of thiopurines may take up to 10 to 14 weeks after the start of treatment.
2. The dose may be adjusted to approximately 2.5 mg/kg of azathioprine and 1 to 1.5 mg/kg of mercaptopurine, in a single daily dose.

3. The determination of thiopurine methyltransferase (TPMT) genotype or phenotype (TPMT activity), if available, is encouraged to identify patients at greater risk for early profound myelosuppression. Dose should be reduced in heterozygous patients or in those with low activity. Thiopurines should not be used in children who are homozygous for TPMT polymorphisms or those with extremely low TPMT activity. Myelosuppression may still occur in the presence of normal TPMT activity, and therefore regular monitoring of blood counts and liver tests are recommended in all cases.
4. Thiopurines should be discontinued in clinically significant myelosuppression or pancreatitis. Reintroduction of thiopurines after leukopenia can be considered at a lower dose after carefully assessing the risks and benefits and after measuring TPMT activity/genotype and following metabolites. Switching between azathioprine and mercaptopurine may be successful in acute flu-like and gastrointestinal adverse events.
5. The measurement of metabolites of thiopurines (ie, 6-methyl mercaptopurine [6-MMP] and 6-thioguanine [6-TG]) may be helpful in patients failing therapy to assess compliance and to assess the nature of possible toxicity (ie, leukopenia or elevated liver enzymes).
6. Continuation of 5-ASA after introduction of thiopurines may have some advantages, but there is insufficient evidence to clearly recommend it.
7. Oral tacrolimus (FK-506) may be used in selected outpatient children with UC as a bridge to thiopurines.
8. Methotrexate should be considered only in the rare patients with UC who fail to respond or are intolerant of thiopurines, when other alternatives are not available.
9. Vaccination status should be assessed in all children. An attempt should be made to immunize with live vaccines >6 weeks before starting immunosuppressive agents, but immunization should not delay necessary medications to control the disease.

A Cochrane review included 6 adult RCTs involving 286 patients and showed that azathioprine was superior to placebo for the maintenance of remission in UC (OR 0.41, 95% CI 0.24–0.70) (127) with roughly 60% effectiveness (NNT 5) (128,129). A prospective registry data of 133 children with UC reported a 1-year steroid-free remission rate of 49%, irrespective of whether thiopurines were introduced at disease onset (130). Other retrospective studies in children confirmed the benefit of thiopurines in maintaining remission and steroid sparing (131–133), with a median time to achieve steady state of thiopurine levels of 55 days (134). An SR in adults including 2 RCTs on 130 patients with active UC showed no statistically significant benefit of thiopurines for inducing remission (129).

The superiority of AZA to maintain remission in UC compared with 5-ASA has been documented in 2 small RCTs. In the first, Ardizzone et al (135) enrolled 72 steroid-dependent adults with UC to receive either 2 mg · kg<sup>-1</sup> · day<sup>-1</sup> of AZA or 3.2 g/day of 5-ASA, whereas prednisolone was tapered >8 weeks. Clinical and endoscopic remission at 6 months was achieved in 53% of the AZA group versus 19% in the 5-ASA group. In the second study, 34 adult patients with UC were randomized to receive 1.5 mg/kg of mercaptopurine (n = 15), 15 mg of methotrexate (n = 12), or 3 g/day of 5-ASA (n = 8) (136). Sustained remission rates at 30, 48, and 106 weeks were 79%, 64%, and 50% in the mercaptopurine group versus 25%, 0%, and 0% in the 5-ASA group, respectively. Nevertheless, considering the efficacy and safety of aminosalicylates for the maintenance of remission, thiopurines should be reserved for patients intolerant of 5-ASA and children who developed an acute

severe colitis episode for whom the risk of a more aggressive disease course is higher.

One placebo-controlled trial in 70 adults with UC showed no benefit for adding 1.5 g/day of olsalazine to 2.2 mg · kg<sup>-1</sup> · day<sup>-1</sup> of azathioprine to maintain a 2-year remission, and there were more adverse events and noncompliance in the 5-ASA-treated group (137); however, the dose was small and olsalazine may have more adverse effects than the other 5-ASA regimens and lower effectiveness (57). It cannot be stated whether there is an additional advantage to combining 5-ASA with a thiopurine, but it is not unreasonable to do so, given the excellent safety profile of 5-ASA and its high effectiveness in UC, including cancer prevention. Clinicians should be aware that 5-ASA may partially inhibit TPMT activity and, therefore, may increase 6-TG levels (138,139). Increasing the number of daily pills may also decrease compliance.

In a retrospective study of 107 children with IBD (of whom 30 had UC) a high discontinuation rate of 30% was noted when using azathioprine at a dose of 3 mg · kg<sup>-1</sup> · day<sup>-1</sup>, mainly because of adverse events (140). In another study, treatment was discontinued because of an adverse effect in 17 (18%) of 95 treated children (141). Dose-independent adverse reactions include fever, pancreatitis, rash, arthralgias, nausea, vomiting, and diarrhea. Dose-dependent toxicities include leukopenia, thrombocytopenia, infections, and hepatitis (142). Pancreatitis is the most common hypersensitivity reaction, occurring in 3% to 4% of adults and children, and almost always within the first several weeks of therapy. Infections are the main risk for immunosuppressed adults (143,144) and children (145,146), although severe infections are uncommon. Pediatricians should focus on immunizations at diagnosis; guidelines for the prevention of infections in pediatric IBD have been published (147). Once immunosuppressive therapy has been initiated, inactivated vaccines should be administered, including annual influenza, pneumococcal vaccine, and HPV. Finally, thiopurines increase the risk for non-Hodgkin lymphoma 4-fold on average (148) but the risk is smaller at younger ages, approximating 4.4 of 10,000 patient years (149). In contrast, the rare but almost uniformly fatal hepatosplenic T-cell lymphoma (HSTCL) has been recognized to occur in young adult or adolescent boys with IBD, with roughly 50% having received thiopurine therapy alone, and 50% thiopurines with anti-TNF (tumor necrosis factor) (~40 IBD cases reported by the end of 2010). Kotlyar et al (150) have estimated the risks of this fatal neoplasm in men younger than 35 years to be 1 in 7404 with thiopurines, and 1 in 3534 if receiving a combination of thiopurines and anti-TNF.

A meta-analysis involving adult and pediatric studies suggests a strong association between 6-TG blood levels and maintenance of remission (151). Mutations of the *TMPT* gene influence the pharmacodynamics of thiopurines, but some studies have failed to identify a clear benefit of TPMT genotyping (152). Monitoring of metabolites may help to identify nonadherent patients and optimize dose, although there is a large interindividual variation that makes it difficult to define a single therapeutic window (153). Concomitant use of allopurinol with reduced dose of azathioprine may provide a valid therapeutic option in cases of hyperactive TPMT resulting in high 6-MMP and low 6-TG (154,155).

Studies on methotrexate for UC are small and have inconsistent outcomes. In 2 adult trials, oral methotrexate at a dose of 12.5 (156) or 15 mg/week (157) was ineffective in inducing and maintaining remission in UC compared with placebo. Another small RCT showed that methotrexate at a dose of 15 mg/week was superior to 5-ASA but inferior to thiopurines in maintaining 2-year remission in UC (136). The 3-, 6-, and 12-month remission rates determined by the PUCAI were 28% to 31% in 1 retrospective pediatric study including 32 children with UC

(of whom 28 intolerant or refractory to thiopurines) treated with intramuscular methotrexate at a mean dose of  $13.7 \pm 3.6$  mg·m<sup>-1</sup>·week<sup>-1</sup> (158). Two prospective placebo-controlled studies regarding the efficacy of methotrexate in adult patients with UC are under way.

Oral tacrolimus seems to achieve a short-term success rate (ie, avoidance of colectomy) in the range of 60% to 80% in pediatric acute severe colitis (159). Oral administration of tacrolimus in an ambulatory child without acute severe colitis seems to have steroid-sparing effects in steroid dependency (160), but more studies are warranted. Oral tacrolimus is typically used as a bridge to thiopurine therapy owing to its rapid onset of action, and discontinued after 3 to 5 months to minimize adverse effects (161).

#### Biological Agents (93% consensus)

1. **Infliximab should be considered for treatment of children with persistently active, or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines** [EL1b, RG B; adults EL1b, RG B]
2. **Infliximab may be considered for steroid-refractory (whether oral or intravenous) disease. If infliximab has been initiated during an acute episode in a thiopurine-naïve patient, then it can be used as a bridge to thiopurine. In that case, infliximab may be discontinued after approximately 4 to 8 months** [EL4, RG C; adults EL1b, RG B]
3. **Adalimumab should only be used in those who lost response or were intolerant of infliximab** [EL4, RG C; adults EL1b, RG B]

#### Practice Points:

1. Infliximab is presently the first-line biological agent in pediatric UC and should be administered at 5 mg/kg (3 induction doses >6 weeks followed by 5 mg/kg every 8 weeks for maintenance); individualization of dosing may be needed.
2. Measuring infliximab levels and antibodies to infliximab can optimize treatment when failing to maintain remission. If there are low levels and negative antibodies, then dose escalation may be indicated. Undetectable infliximab levels in the presence of antibodies may indicate loss of response and the need for dose escalation or switching to a different drug. Normal infliximab level suggests primary nonresponse or an alternative diagnosis as a cause of symptoms (as outlined above).
3. Extrapolating from the adult literature and pediatric case series, adalimumab should be started at 100 mg/m<sup>2</sup> up to 160 mg, followed by 50 mg/m<sup>2</sup> up to 80 mg after 2 weeks and then 25 mg/m<sup>2</sup> up to 40 mg every other week; dose individualization may be needed.
4. There is no good evidence to support combining infliximab with thiopurines in children with UC who failed thiopurine treatment. Biological agents are, however, used by some pediatric gastroenterologists in combination with thiopurines for at least the first 4 to 8 months of therapy, even if the child has been a nonresponder to thiopurines. The balance of safety versus benefits of combination treatment needs to be fully explained.
5. It is unknown whether 5-ASA offers an advantage in combination with biological agents, but given the potential benefit (including possible cancer chemoprevention) and the

high safety, it is not unreasonable to recommend a combined therapy.

A Cochrane review on adult UC trials concluded that infliximab is effective in inducing clinical remission, promoting mucosal healing, and reducing the need for colectomy in patients with active UC whose disease has not responded to conventional treatment (162). According to the randomized, double-blind, placebo-controlled ACT-1 and ACT-2 trials, infliximab seems to be effective for induction and maintenance of remission in ambulatory adult patients with moderate to severe UC (163). In both trials combined, 728 patients received placebo or infliximab (5 or 10 mg/kg) intravenously at weeks 0, 2, and 6, then every 8 weeks and followed to week 54 (ACT-1) or 30 (ACT-2). Clinical remission rates at weeks 8, 30, and 52 in the combined infliximab arms compared with placebo were 33% versus 10%, 33% versus 13%, and 35% versus 17%, respectively. Steroid-free remission at week 30 was 22% in the infliximab arms versus 13% in the placebo arm.

Comparable results were found in a pediatric T-72 RCT (164). Forty-five of 60 (75%) ambulatory children with moderate to severe UC (excluding those hospitalized with acute severe UC) responding to a standard 5 mg/kg 3-dose induction protocol were randomized to continue to receive infliximab 5 mg/kg either every 8 or every 12 weeks. Dose was escalated to 10 mg/kg in 20 of 45 (44%) children who lost response during the 54-week follow-up period in both arms, but such patients were considered treatment failures in the primary analysis. The clinical (PUCAI < 10 points) and complete mucosal healing rates (Mayo endoscopic subscore 0) were both 33% at week 8; clinical remission rates in the q8 versus q12 weeks were 8/20 (40%) versus 4/21 (19%) at week 30, and 8/21 (38%) versus 4/22 (18%) at week 54.

Other level 2 pediatric evidence exists to support infliximab use in pediatric UC. A meta-analysis showed that the pooled long-term success rate of infliximab in 6 series including 126 children with acute severe colitis was 64% (159). Of 53 infliximab-treated children with UC in the North American registry (44% with acute severe colitis), corticosteroid-free remission was observed in 38% and 21% of patients at 12 and 24 months, respectively (165). The likelihood of avoiding colectomy at 2 years was 61%.

One RCT of adalimumab to induce remission in adults with UC has been published (ULTRA 1) (166). A total of 390 anti-TNF-naïve ambulatory adult patients with moderate to severe UC despite treatment with corticosteroids and/or immunosuppressants were treated with a 4-dose induction protocol of 160/80/40/40 mg versus 80/40/40/40 versus placebo every other week, subcutaneously. The 8-week clinical remission rate was 19% in the high-dose arm compared with 10% in the low-dose arm and 9% with placebo ( $P=0.031$ ). In the 52-week follow-up study (ULTRA 2) of 494 adult patients with moderate to severe UC, the use of adalimumab was shown to be safe and effective in maintaining remission compared with placebo with remission rates of 17% and 9%, respectively (167). Of note, the 52-week remission rates in patients with prior anti-TNF exposure were only 10% and 3%, respectively. Adalimumab usage in pediatric UC has been presented mainly as case reports (146).

Both the SONIC trial in adult CD (168) and its counterpart in adult UC, the SUCCESS trial (169), included mainly thiopurine-naïve patients in whom the combination of infliximab and azathioprine was shown to be superior to monotherapy with azathioprine or infliximab alone. Combination therapy must be weighed against the possible adverse effects, including the risk of lymphoma (as discussed in the Immunomodulators section), especially because there is no good evidence to support combination therapy after thiopurine failure. On the contrary, although

concomitant immunomodulators reduced infusion reactions and immunogenicity of infliximab in the combined ACCENT-1, ACCENT-2, ACT-1, and ACT-2 trials, it did not improve clinical outcomes or pharmacokinetics (170). Identical results of lack of benefit to combined therapy have been reported in the pediatric T72 trial of infliximab in UC (164). In an RCT in adults with CD, stopping thiopurines after 6 months of combination therapy did not reduce the 2-year clinical or endoscopic outcomes (171). Similarly, long-term colectomy rate did not differ between monotherapy or combined therapy in 52 children with UC treated with infliximab (165). In thiopurine-naïve children, infliximab can be used as a bridging agent for thiopurines in steroid-refractory patients, and then combination therapy is customarily given for 4 to 8 months (11). One pediatric study reports on successful weaning of infliximab in 12 patients on combination therapy (172).

Dose intensification (increasing infliximab dose to 10 mg/kg or shortening dosing interval to 4 to 6 weeks) may be necessary in those losing response over time (164,173). Optimizing use of infliximab may be facilitated by access to drug levels and ability to measure antibodies to infliximab (174). Most clinical trials have not shown major safety issues, other than infusion reactions and allergic responses. Uncommon adverse events including major infections, demyelinating diseases, cutaneous eruptions, and lymphoma, when used in conjunction with thiopurines (as discussed above), however, have been reported (175). The discussion above for immunomodulators regarding infections and vaccines applies also to the biological agents and even more so when used in conjunction with other immunomodulatory agents.

#### Other Investigational Interventions

##### Practice Points:

1. Granulocyte/monocyte apheresis remains a controversial treatment strategy and cannot be recommended routinely. It may be a remote treatment option for induction and maintenance of remission in children with ongoing mild to moderate active UC when no other medical options exist.
2. Omega-3 supplement is not effective in inducing or maintaining remission in UC even in large doses.

Treatments that act by removal of leukocytes and other components of the immune system from the blood after filtering (leukocytapheresis, granulocytapheresis, granulocyte/monocyte apheresis) have been used to treat active UC, particularly in Asia and Scandinavia. Two strategies have been used with 1 using granulocyte/monocyte apheresis (Adacolumn) and 1 using leukocytapheresis (Cellsorba).

A meta-analysis including 7 adult clinical trials concluded that granulocyte/monocyte apheresis was a useful treatment for active UC, although specific methodological issues among most of the RCTs limited the generalizability of the studies, and that higher-quality RCTs were needed (176). A large adult RCT demonstrated no benefit of apheresis compared with a sham infusion (177). Six pediatric case series using heterogeneous methodology have been published, including 71 children, most with mild to moderate disease (178–183), yielding remission in 32 of 71 (45%), response in 20 of 71 (28%), and no response in 19 of 71 (27%) usually (but not always) after an initial course of 5 cycles >5 weeks. An open-label European pediatric trial is ongoing.

The use of leukocytapheresis has been limited thus far to open-label studies in adults with almost no pediatric data (184). One small adult study that randomized patients to either granulocyte/monocyte apheresis or leukocytapheresis showed no significant difference between the 2 treatments (185).

The use of intravenous immunoglobulins to treat active steroid-dependent UC (and CD) has been described in a small pediatric case series with limited effect (186). A case report has described amelioration of UC in a child infected with *Enterobius vermicularis* (187). Initial small open-label studies suggested that worm therapy was safe (188). There has been 1 RCT of worms (*Trichuris suis*) in 54 adult patients with UC, which showed a statistically significant benefit for treatment compared with placebo at 12 weeks (189). More data are required before this therapy can be considered, especially in children. A meta-analysis found that omega-3 supplement is ineffective for maintaining remission in UC (190). Fecal transplantation is an anecdotal therapy without data to support its use in children.

## SURGICAL CONSIDERATIONS

### Elective Surgery for Pediatric UC (96% consensus)

1. **Elective colectomy may be indicated in children with active or steroid-dependent UC despite maximal treatment with 5-ASA, thiopurines, and anti-TNF therapy, or the finding of colonic dysplasia [EL5, RG D; adults EL 4, RG C]**
2. **In general, restorative proctocolectomy (ileoanal pouch or ileal pouch-anal anastomosis), especially the J-pouch, is preferred over straight pull-through (ileoanal) or ileorectal anastomosis for elective surgery of pediatric UC [EL2b, RG B]**
3. **The laparoscopic surgical approach can be used safely in children with low complication rates and superior cosmetic results [EL2b, RG B]**

##### Practice Points:

1. The disease should be reevaluated thoroughly before referral to colectomy, including repeated ileocolonoscopy and ruling out other causes for the symptoms.
2. The role of ileorectal anastomosis is controversial but may be considered in girls who are primarily concerned about the reduced fecundity associated with restorative proctocolectomy. High early failure rates have been reported and a lifelong follow-up of the retained rectal stump is required.
3. A 2-stage operation (colectomy and pouch formation with ileostomy in the first stage, and closure of the stoma at the second stage) is the most common approach for elective surgery for UC. A 3-stage operation (ie, splitting the first operation into colectomy first and then pouch formation) should be considered in patients with high-dose steroids or those experiencing severe malnutrition, and when the diagnosis of CD has not been excluded completely.
4. Restorative proctocolectomy without protecting ileostomy (ie, 1-stage operation) may be safe in selected children without any risk factors (eg, high-dose steroids). Anticipated tension at the anastomosis site precludes this option.
5. There is no need for preoperative bowel preparation.
6. Preoperative high-dose steroids and questionably infliximab are associated with increased surgical complications; thiopurines or calcineurin inhibitors are probably not.
7. The risks of thromboembolic complications are low in ambulatory pediatric patients with UC, and routine thromboembolic prophylaxis cannot be recommended.

Colectomy should be discussed as a viable alternative in children who experience ongoing symptoms despite multiple

immunosuppressive medications, especially if steroid dependent. The most frequent indication for colectomy in ambulatory children with UC is a chronic ongoing disease, at times steroid dependent; in adults, dysplasia is also a common indication (191). In general, effective doses of immunomodulatory agents and infliximab should be attempted in most cases before referral to colectomy in ambulatory mild to moderate UC. In those losing response to infliximab, adalimumab may be considered before colectomy.

Most pediatric surgeons treating patients with UC prefer pouch surgery over straight pull-through, but there are few pediatric data to support this. Most series report better continence after the pouch procedure. A pediatric meta-analysis consisting of 5 studies and 306 patients suggested that the straight ileoanal pull-through was associated with a higher failure risk (15% for straight pull-through vs 8% for pouch procedure), and perianal sepsis (20% vs 10%), as well as a higher stool frequency (OR 2.63, 95% CI 1.34–3.92) (192). A multicenter study including 112 children with straight ileoanal pull-through and 91 with a J-pouch showed similar early and late complication rates (193). Stool frequency was higher in the straight pull-through group, although the difference became less apparent with longer follow-up (mean daily stool frequency at 24 months: 6.2 for the pouch procedure vs 8.4 for the straight pull-through). Because the quality of life in children with restorative proctocolectomy is inversely related to stool frequency and continence (194), this difference is clinically important; however, the pouch procedure is associated with risk for pouchitis (see below).

A 2-stage operation is favored by most pediatric surgeons in elective colectomy (192). One-stage repair may be feasible in selected children with low disease activity, good nutritional status, and not treated with steroids but it is associated with an increased complication rate (195,196). A 3-stage surgery is performed mainly in patients who require emergency colectomy for refractory acute severe attack or in malnourished patients and those treated with high-dose corticosteroids. With any chosen procedure, a laparoscopic-assisted procedure is feasible and safe in adults (197,198) and in children (199,200).

Ileorectal anastomosis is not often performed. Earlier reports showed high failure rates, and there is a lifelong need for endoscopic surveillance of the rectal stump. Adult studies have shown that in selected cases, ileorectal anastomosis is safe, with better continence function than pouch formation (201); however, there was a higher urgency rate; the quality of life was similar and approximately half required resection of the rectum in 20 years. Nonetheless, this surgery may be considered, especially in young female patients considering future fecundity. In a meta-analysis the risk of female infertility was increased from 15% among 411 girls with UC without ileal pouch-anal anastomosis (IPAA) to 48% in 481 girls after IPAA (202,203). It should be emphasized that many of the “infertile” cases will eventually achieve pregnancy with supportive treatments. It is unlikely that there would be a difference in fertility problems between straight pull-through and pouch procedures because the degree of pelvic dissection is similar; however, fecundity is probably better preserved after ileorectal anastomosis (204). An open discussion with a girl requiring colectomy and her caregivers stating the pros and cons of each procedure is mandatory before any surgical intervention.

Preoperative steroid therapy (>20 mg in adults), hypoalbuminemia, and malnutrition are associated with increased surgical complication rates (205), but waiting for the reversal of their effects before surgery is not recommended in the acute setting (206). A meta-analysis of 5 studies found a higher postoperative short-term complication rate in 706 adults treated with infliximab before colectomy (207). In a population-based case-control study, the risk of venous thromboembolic events in UC was increased

across all age groups, but the absolute rate was much higher in the older population (27 deep vein thrombosis [DVT] cases per 10,000 person-years in the 0- to 20-year-old group (odds ratio 10 [95% CI 3.4–29.3]) vs 207/10,000 in the older than 60-years-old group (208)).

#### Pouchitis (100% consensus)

1. **When pouchitis is suspected for the first time, endoscopy with mucosal biopsies should be performed to confirm the diagnosis** [EL3b, RG C; adults EL3a, RG B]
2. **The first-line therapy of pouchitis should be a 14-day course of antibiotics; ciprofloxacin seems to be more effective than metronidazole** [EL5, RG C; adults EL1b, RG A]; **in persistent cases, combined metronidazole and ciprofloxacin or oral budesonide can be given** [EL5, RG C; adults EL2b, RG B]
3. **Probiotics may be used for maintaining antibiotic-induced remission in recurrent pouchitis** [EL5, RG C; adults EL1b, RG B]
4. **Topical mesalazine is an effective treatment for inflammation of the residual rectal cuff, known as cuffitis** [EL 5, RG D; adults EL4, RGD]

#### Practice Points:

1. In chronic (>4 weeks) or refractory pouchitis-like symptoms, other diagnoses should be sought, including cuffitis, missed CD, anastomotic ulcer, irritable pouch syndrome, infectious pouchitis, and anastomotic stenosis.
2. Fecal calprotectin can reflect the degree of pouch inflammation.
3. Metronidazole (20–30 mg · kg<sup>-1</sup> · day<sup>-1</sup> in 3) divided doses and/or ciprofloxacin (30 mg · kg<sup>-1</sup> · day<sup>-1</sup> up to 1 g/day in 2 divided doses) for 14 days are common dosing strategies for pouchitis. Dosing of VSL#3 for recurrent pouchitis in 2 adult RCT was 1800 billion bacteria once daily (4 sachets of 450 billion bacteria).
4. Although VSL#3 (900 billion bacteria daily) also may be effective for preventing the first episode of pouchitis, this is not justified because many children will never develop pouchitis.
5. Immunosuppressants or infliximab may be considered in refractory pouchitis.

Pouchitis, an idiopathic inflammation of the ileal reservoir, is the most common complication of IPAA, occurring at least once in pediatric series from 30% to 75% of patients (193,194,209–211). In a cohort of 151 children, 54 (36%) had no pouchitis, 73 (48%) had 1 episode of acute pouchitis, 11 (7%) developed chronic pouchitis, and 13 (9%) pouch failure for intractable disease or poor pouch function (210). In children younger than 10 years, pouchitis is reported in up to 75% of patients (212).

Clinical symptoms of pouchitis include looser and frequent stools with or without blood, abdominal cramps, tenesmus, urgency, abdominal discomfort, and seldom even fever (213). Symptoms of pouch dysfunction are, however, not specific. Restorative proctocolectomy, especially with the stapling technique, leaves a remnant of rectal mucosa between the dental line and the anastomosis. Residual rectal cuff inflammation, known as cuffitis, may cause symptoms similar to those of pouchitis, especially bleeding. In an open trial performed in adults, mesalazine suppositories have shown efficacy in cuffitis (214). Other pouchitis-mimickers include missed CD and anastomotic ulcer or stenosis. Development of terminal ileitis, also known as prepouch ileitis, can occur in children

(215), and it does not necessarily confirm the diagnosis of CD. Other differential diagnoses include ischemia and rare infections such as CMV and *C difficile*. Moreover, “irritable pouch syndrome” is characterized by increased stool frequency and cramping with normal endoscopy and histology of the pouch (216). Therefore, initial clinical suspicion of pouchitis should be confirmed by endoscopic evaluation of the pouch with mucosal biopsies. Macroscopic findings include diffuse or patchy erythema, edema, granularity, friability, loss of vascular pattern, spontaneous or contact bleeding, erosion, and ulcerations. Unlike in UC, erosions and ulcerations of pouchitis may be discontinuous, and small ulceration should not be overinterpreted as CD. Mucosal biopsies should be obtained from the pouch and from the afferent ileal loop but not from the staple line. Histology of pouchitis includes acute and chronic inflammation, crypt abscesses, and ulcerations.

Risk factors for developing pouchitis reported in the adult literature include extensive UC, backwash ileitis, extraintestinal manifestations (EIMs; especially primary sclerosing cholangitis [PSC]), being a nonsmoker, and the use of NSAIDs (217). Anti-neutrophil cytoplasmic antibody positivity has been associated with pouchitis in adults but not in children (218).

Antibiotic treatment is considered the first-line treatment for pouchitis. Metronidazole is associated with a rapid response, but ciprofloxacin may be more effective, with fewer adverse events (219). Combined antibiotic therapy is an option for chronic pouchitis. Small adult trials suggested that chronic pouchitis may be treated with combination of ciprofloxacin and imidazole or rifaximin, or oral budesonide 9 mg daily for 8 weeks (217). Infliximab has shown efficacy in refractory pouchitis and CD-related complication of the pouch in an adult case series (220).

Two double-blind placebo-controlled trials performed in adults showed effectiveness of the probiotic mixture VSL#3 in maintaining remission in patients with chronic pouchitis (221,222). VSL#3 was superior to placebo in 1 study for preventing pouchitis, although in another it did not show added benefit (219).

## OTHER MANAGEMENT CONSIDERATIONS

### EIMs With a Focus on Arthritis and PSC (100% consensus)

1. **A diagnosis of pauciarticular arthritis (type 1; affecting <5 large joints) is made on clinical grounds, and treatment is primarily directed at inducing remission of intestinal disease** [EL 4, RG D; adults: EL3b, RG C]
2. **When arthritis is present, sulfasalazine is the appropriate 5-ASA drug for maintenance treatment of UC** [EL 4, RG D; adults EL1a, RG B]

#### Practice Points:

1. A discussion regarding EIM other than arthritis and PSC is similar to adults and may be found in the adult ECCO guidelines, including recommendations for follow-up colonoscopies and cancer surveillance (217).
2. Magnetic resonance cholangiography is the first-line investigation for PSC in children, but the interpretation may be difficult in young infants.

EIMs occur in up to 30% of pediatric patients with UC potentially involving the skin, joints, hepatobiliary system, and eyes. Some are clearly related to intestinal disease activity (ie, erythema nodosum, peripheral arthritis), whereas others occur independently (ie, pyoderma gangrenosum, uveitis, ankylosing spondylitis, and PSC) (223). Data from 2 pediatric registries in the United States (224,225) and Europe (223) indicate that  $\geq 1$  EIMs

are present at diagnosis in 6% to 17% of pediatric patients with UC, especially in children older than 5 years, with an increase of almost 50% with disease evolution (226–229). EIMs are more likely to occur in patients with extensive colitis (225).

Joint disease in IBD may be axial (sacroiliitis or ankylosing spondylitis), causing inflammatory lower back pain or peripheral arthritis (type 1: pauciarticular, large joints or type 2: polyarticular, affecting particularly the metacarpophalangeal joints). In children as in adults, peripheral arthritis is more common than axial 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 (224), 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 (230). The sulfapyridine component of sulfasalazine has an anti-inflammatory effect on both the colonic mucosa and the joints (231).

PSC is 3 times more likely to occur in UC compared with CD (225), and is associated with older age in children (225). PSC may precede the onset of IBD symptoms by years but may also evolve in patients with UC after colectomy. The cumulative incidence of PSC in pediatric IBD was reported to be 1.6% at 10 years after diagnosis (224). Although EIMs are generally associated with a more severe course of disease, this is not true for PSC (225). ERCP is difficult to perform, particularly in small children. MRCP may show a characteristic pattern of irregular bile ducts, with zones of both narrowing and dilatation (232). PSC may progress to liver cirrhosis, ultimately necessitating liver transplantation. Patients with PSC and UC have a greater risk of malignancies such as colorectal cancer and cholangiocarcinoma (8%–30% of patients with UC with long-standing PSC) (233,234). Patients with a diagnosis of PSC during childhood may have a more severe course of disease (234). In adults with PSC, ursodeoxycholic acid is reported to improve abnormal liver function tests (235) and may improve outcome. Recent recommendations for adult patients suggest ursodeoxycholic acid dose of 10 to 15 mg · kg<sup>-1</sup> · day<sup>-1</sup> and warn against high-dose treatment, which may be harmful (236–238). There are no studies of treatment of PSC in children.

### Growth, Bone, and Nutrition (100% consensus)

1. **The nutritional status and growth of children with UC must be monitored regularly; nutritional support should be provided when required** [EL 5, RG D]
2. **Enteral or parenteral nutrition is inappropriate for primary disease treatment in UC** [Pediatric EL4, RG C; Adult EL 2b, RG B]
3. **Special diets or dietary supplementations are not effective to induce or maintain remission in pediatric UC, and at times carry a risk of nutritional deficiencies** [Pediatric EL 5, RG D; Adult EL 3b, RG C]
4. **Bone mineral status should be assessed using dual-energy x-ray absorptiometry (DEXA), particularly in children with highly active UC and who are receiving prolonged, or repeated, treatment with corticosteroids** [EL 2a, RG B].

#### Practice Points:

1. In children with UC without excessive steroid use, height velocity is usually normal.
2. Continuation of regular diet is recommended during mild to moderately active disease.
3. If oral intake is poor because of anorexia in active disease, enteral nutrition or high-energy supplements may be indicated.

4. Patients with UC are much less prone to impaired bone density compared with patients with CD.
5. Adequate nutrition, weight-bearing exercise, adequate disease control, avoidance of smoking, and steroid-sparing strategies should all be used to promote bone health.

Undernutrition and particularly growth failure are less common in children with UC compared with patients with CD, but nutritional deficiencies can develop quickly during periods of active disease (239). In newly diagnosed IBD, low BMI was seen in ~8% of children with UC, whereas short stature was noted only in CD (240). As a rule, children with UC reach their expected adult height (241,242).

It has been documented that bowel rest or exclusive enteral nutrition does not have any therapeutic role in acute UC (243–245), although bowel rest can alleviate abdominal pain, when severe. For pediatric patients, there is a small retrospective study showing that total parenteral nutrition and bowel rest did not improve the outcome (246). In a pediatric prospective study, 74 of 128 (58%) were not eating solid food by the third admission day for acute severe colitis, but this was not associated with improved outcome after controlling for disease activity (D.T., unpublished data). There is no dietary approach proven to reduce the risk of either developing or preventing a relapse of UC.

Peak bone mass attained during late childhood, adolescence, and early adulthood is the most important determinant of life-long skeletal health. Children with IBD are particularly prone to disturbed bone health because of increased circulating inflammatory cytokines, malnutrition, delayed puberty, decreased physical activity, treatment with corticosteroids, and in girls, primary or secondary amenorrhea (247,248). Severe osteopenia was present in 3% to 6% in UC compared with 12% to 18% in CD (249–251).

According to recently published clinical guidelines, DEXA is the preferred screening tool for bone density measurement in children and adolescents, provided that age- and sex-matched *z* scores are used (252). Because DEXA measures BMD in 2 dimensions, it is recommended that in children with linear growth delay (heights *z* score < -2.0) DEXA results should also be adjusted for height (252). It has been suggested that DEXA should be performed in all children newly diagnosed as having IBD and repeated in cases of severe disease course, including suboptimal growth velocity, prolonged malnutrition, amenorrhea, delayed puberty, and long or repeated treatments with steroids (252); however, these recommendations are not evidence based.

Children with IBD are particularly at risk for vitamin D deficiency, but this was not found to be associated with osteopenia (253). Therefore, the significance of hypovitaminosis D in young patients with UC merits further study. Nonetheless, it is widely accepted that vitamin D levels be routinely measured and treated when appropriate, especially in children with decreased BMD. Age-appropriate nutrition support, weight-bearing exercise, and adequate disease control using steroid-sparing strategies (248,250,252) are also advocated to improve bone formation.

#### Psychosocial Support and Adherence to Therapy (100% consensus)

1. **Psychological intervention should be offered to patients in need because it improves quality of life (QOL), coping, and depression** (Pediatric EL2b, RG B; Adults EL3b, RG C)
2. **Nonadherence to medication should be also considered in children and adolescents, particularly during unstable disease course** (Pediatric EL3a, RG B; Adults EL2a, RG B)

#### Practice Points:

1. Every clinic visit made by children and adolescents with IBD must include attention to psychological problems as part of the consultation.
2. Pediatric IBD programs should be ready to offer psychological interventions according to individual needs and local resources, involving qualified specialists.
3. Adherence may be evaluated by interviews of both the adolescent and parents, drug monitoring (eg, thiopurine metabolite level), and prescription refill rates.
4. 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 and providing pillboxes.

Several recent SRs, including a Cochrane review, have concluded that adolescents with IBD, especially boys, have reduced health-related quality of life, including anxiety, depression, social problems, and low self-esteem (254–257). The problems seem to be associated with more severe disease course, whereas most children with mild IBD report psychosocial functioning comparable with healthy controls (258,259). No evidence exists that psychosocial problems contribute to the etiology of UC; however, observational data from primarily the adult literature provide support to the impression that psychosocial stress is a risk factor for relapse (217). Certain drugs used for treatment of UC, such as corticosteroids, may induce change in mood and even psychiatric disturbances to which children are particularly sensitive. A Cochrane review found that psychological interventions resulted in improvements in coping and depression among adolescents (256).

Nonadherence in IBD is an important and frequent problem, reported in 50% to 66% of children (254,260), especially in adolescence. The presence of nonadherence is related to increased disease activity in adolescents (260). Individual studies among adolescents with IBD have reported barriers identical to those identified among adults as well as more pediatric-specific barriers: fear of adverse events of medication, belief that the disease is inactive, belief that the medication is not working, >1 daily medication (254), forgetfulness, interference with other activities, difficulty in swallowing pills (261), lack of motivation, and parent-child conflict (262).

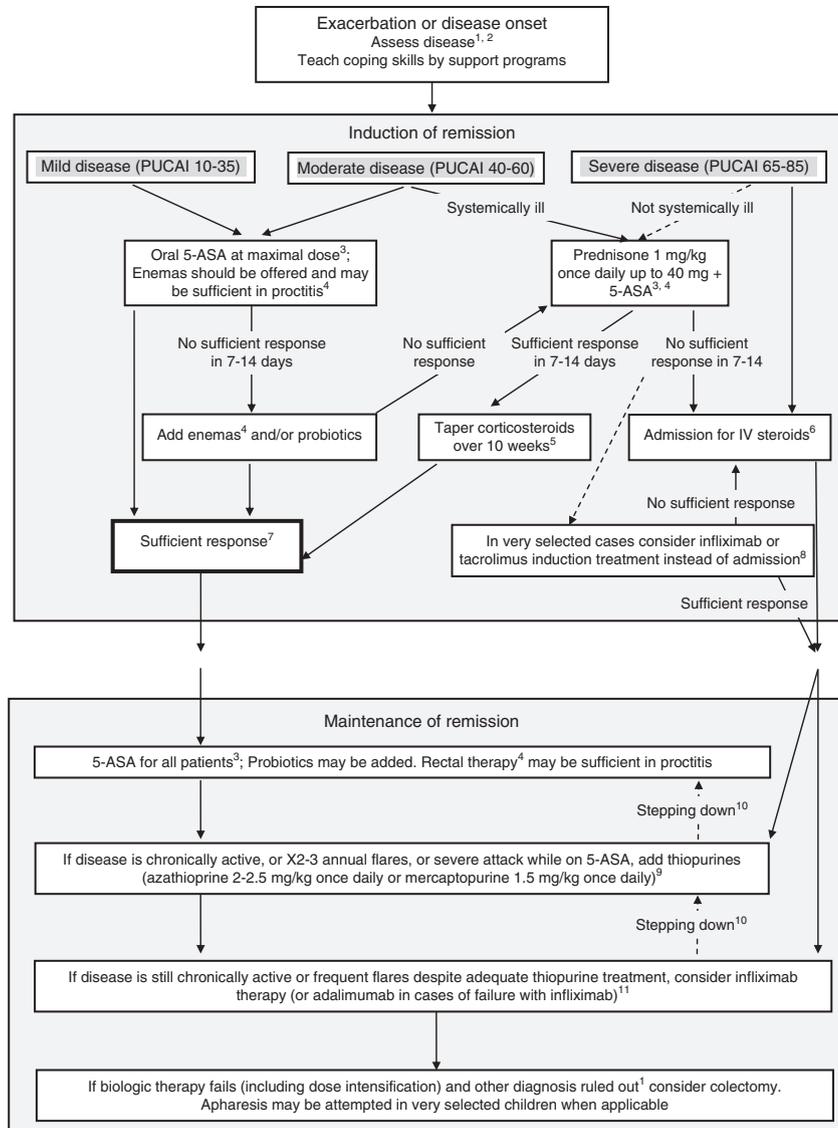
#### Transitional Care (100% consensus)

1. **Every adolescent should be included in transition programs that could be adapted according to the local organization of pediatric and adult facilities** [EL5, RG D]
2. **The adolescent should be encouraged to assume increasing responsibility for treatment and to visit the clinic at least once without being accompanied by the parents** [EL5, RG D]

#### Practice Points:

1. Whenever feasible, at least 1 joint clinic in which the adolescent is seen by both a pediatric and an adult gastroenterologist is recommended.
2. The time of transition should be individually adapted according to psychosocial readiness. Most adolescents will benefit from a transition program during the 16- to 18-year-old age period.

Pediatric IBD services differ from those for adults. Children are usually offered endoscopy under general anesthesia and are



**FIGURE 1.** Joint European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)-European Crohn's and Colitis Organization (ECCO) therapeutic paradigm for pediatric ulcerative colitis (UC). Medical therapies in UC should be divided into those that induce remission (5-aminosalicylic acid [5-ASA], corticosteroids, anti-tumor necrosis factor [TNF] therapy, calcineurin inhibitors, and likely probiotics), and those that maintain remission (5-ASA, thiopurines, anti-TNF therapy, and selected probiotics). <sup>1</sup>In any state of active disease, the following must be ruled out: infectious colitis (including cytomegalovirus [CMV] and *C. difficile*), 5-ASA-related colitis, lactose intolerance, irritable bowel syndrome, wrong diagnosis, celiac disease, and the like. <sup>2</sup>Unlike in adults, endoscopic evaluation of the rectal mucosa is conceived to be more invasive for routine monitoring of disease activity and response to therapy in children. Therefore, these should be based on noninvasive indirect markers of disease activity. Cutoff values of the Pediatric UC Activity Index (PUCAI) for remission, mild, moderate, and severe disease activity have been previously validated in 3 independent cohorts. <sup>3</sup>5-ASA is dosed 60 to 80 mg · kg<sup>-1</sup> · day<sup>-1</sup> up to 4.8 g daily. In clinical practice, higher doses of up to 100 mg/kg are often used effectively but without strong supporting evidence. Recent data in adults suggest that once-daily 3 g 5-ASA is at least as effective as twice-daily dosing. <sup>4</sup>5-ASA enemas (25 mg/kg up to 1 g) 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 work for more extensive colitis. <sup>5</sup>If there is lack of improvement (ie, PUCAI decrease of <20 points) after 7 to 10 days or an increase in PUCAI ≥20 points at any time, consider admission for intravenous steroids or outpatient treatment with anti-TNF therapy, or less often tacrolimus. Steroid dependency should be declared in children achieving remission with corticosteroids but who experience return of symptoms when dosage is lowered or within 3 months following complete taper, or if steroids cannot be stopped within 14 to 16 weeks. Maintenance therapy should be then escalated. <sup>6</sup>Turner et al (11) <sup>7</sup>Response is defined as a drop in PUCAI of at least 20 points; however, the goal of induction therapy is eventually complete clinical remission (PUCAI <10). <sup>8</sup>For example, previous intolerance or resistance to steroids, or when infliximab is indicated anyway for maintenance treatment after failing thiopurines. <sup>9</sup>Measuring thiopurine methyltransferase (genotyping or enzymatic activity) at baseline, and 6-TG and 6-MMP levels after 2 to 3 months, may aid in optimizing thiopurine dosing. <sup>10</sup>If infliximab has been used in thiopurine-naïve disease, thiopurines may be added and infliximab discontinued after 4 to 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 complete remission. <sup>11</sup>There is no evidence to support adding thiopurines to infliximab in thiopurine-failure children; however, some discontinue thiopurines after 4 to 8 months of combined therapy.

accompanied by parents or caretakers during hospital visits as well as during making decisions for therapy. Pediatric gastroenterologists are experienced in growth and pubertal development and the psychological aspects of puberty, and potentially also the problems of nonadherence to medication. In general, they also run a more child-friendly and relaxed practice. Several suggestions for transition programs have been published, but none has been formally evaluated (263). Most programs involve a joint clinic by both a pediatric and an adult gastroenterologist, at least once, at ages 16 to 18 years. A dedicated IBD nurse may further improve the process of transition.

An SR evaluated 10 transition programs (none in IBD) focusing on the patient (educational program, skills training), staff (joint pediatric and adult clinics), and service delivery (telephone support and enhanced follow-up) (264). Although widely recommended, the efficacy of a specific IBD transition program remains to be proven formally. Until then, each program can determine the most suitable transition setup according to the local practice of both pediatric and adult care.

## SYNTHESIS AND SUMMARY

This consensus process yielded 40 formal recommendations and 68 practice points, along with practical tables, based on SR of the literature (Fig. 1).

Guidance for the management of pediatric UC is summarized in an algorithm (Fig. 1). The goal of treatment in active disease should be complete remission (as opposed to response), but usually this can be assessed clinically without the need for endoscopic verification. The choice of treatment in adults is a factor of both the disease severity and disease extent (10), but because limited distal disease is uncommon in children, pediatric treatment strategy depends mainly on disease severity. Aminosalicylates are considered first-line therapy for inducing and maintaining remission of mild to moderate UC. Steroids should be used only as induction agents. If the patient does not clearly respond to oral steroids within 1 to 2 weeks, then admission for intravenous corticosteroids should be considered. In refractory nonsevere cases, an alternative to admission may include outpatient treatment with infliximab (especially in those who failed thiopurines and 5-ASA); in selected patients, oral tacrolimus may be considered. Reasons for refractoriness include poor adherence, inadequate dosing, prescribing the wrong drug for the clinical scenario, unrecognized complications (eg, stenosis, superinfection), or inappropriate diagnosis (eg, IBS, lactose intolerance, CD, celiac disease).

Most patients who received intravenous corticosteroids should be weaned to thiopurines, and if 5-ASA naïve, subsequently to 5-ASA after a long period of complete remission. All children with UC must be treated with a maintenance therapy indefinitely. It should be noted that 2 studies in adults showed an increased risk of relapse and colectomy in patients who discontinued azathioprine (265,266). Anti-TNF is indicated for nonresponse, loss of response, or intolerance of 5-ASA and thiopurine maintenance therapy. Patients needing anti-TNF induction should continue this therapy and, if thiopurine naïve, may be subsequently stepped down to thiopurines after a period of 4 to 8 months of complete remission. 5-ASA may be given as an adjuvant therapy with thiopurines and even anti-TNF, although there is little evidence to support this notion. Infliximab should be discontinued in those with primary nonresponse after 2 to 3 infusions, loss of response despite dose intensification strategies, and severe infusion reactions. Drug discontinuation may also be considered in children with sustained remission, evidenced by clinical assessment and endoscopic evaluation, although specific timing of this is unclear. The pros and cons of combination therapies have been discussed within each section.

Finally, in UC, colectomy is always a viable option that 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, but serve 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.

## QUALIFYING STATEMENT

These guidelines may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. These guidelines are intended to be an educational device to provide information that may assist clinicians in providing care to patients. These guidelines are not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may require taking a course of action that varies from 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. Henderson P, Hansen R, Cameron FL, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis* 2012;18:999–1005.
3. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;146:35–40.
4. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114–22.
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 Jr, 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. 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.
9. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010;4:431–7.
10. Travis SPL, Stange EF, Lémann M, et al. European evidence-based consensus on the management of ulcerative colitis: current management. *J Crohn Colitis* 2008;2:24–62.
11. 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.
12. Wilson DC, Thomas AG, Croft NM, et al. Systematic review of the evidence base for the medical treatment of paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2010;50:S14–34.
13. IBD Working Group of the European Society for Paediatric Gastroenterology Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria. *J Pediatr Gastroenterol Nutr*. 2005;41:1–7.
14. 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.

15. Bousvaros A, Antonioli DA, Colletti RB, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr* 2007;44:653–74.
16. Rajwal SR, Puntis JW, McClean P, et al. Endoscopic rectal sparing in children with untreated ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2004;38:66–9.
17. Glickman JN, Bousvaros A, Farraye FA, et al. Pediatric patients with untreated ulcerative colitis may present initially with unusual morphologic findings. *Am J Surg Pathol* 2004;28:190–7.
18. Markowitz J, Kahn E, Grancher K, et al. Atypical rectosigmoid histology in children with newly diagnosed ulcerative colitis. *Am J Gastroenterol* 1993;88:2034–7.
19. Levine A, de Bie CL, Turner D, et al. Atypical disease phenotypes in paediatric ulcerative colitis: 5-year analyses of the EUROKIDS registry. *Inflamm Bowel Dis*. 2012 May 8. [Epub ahead of print]
20. Robert ME, Tang L, Hao LM, et al. Patterns of inflammation in mucosal biopsies of ulcerative colitis: perceived differences in pediatric populations are limited to children younger than 10 years. *Am J Surg Pathol* 2004;28:183–9.
21. Kim B, Barnett JL, Kleer CG, et al. Endoscopic and histological patchiness in treated ulcerative colitis. *Am J Gastroenterol* 1999;94:3258–62.
22. Haskell H, Andrews CW Jr, Reddy SI, et al. Pathologic features and clinical significance of “backwash” ileitis in ulcerative colitis. *Am J Surg Pathol* 2005;29:1472–81.
23. Tobin JM, Sinha B, Ramani P, et al. Upper gastrointestinal mucosal disease in pediatric Crohn disease and ulcerative colitis: a blinded, controlled study. *J Pediatr Gastroenterol Nutr* 2001;32:443–8.
24. de Bie CI, Buderus S, Sandhu BK, et al. Diagnostic workup of paediatric patients with inflammatory bowel disease in Europe: results of a 5-year audit of the EUROKIDS registry. *J Pediatr Gastroenterol Nutr* 2012;54:374–80.
25. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's milk protein allergy in infants and children: a practical guideline of the GI-committee of ESPGHAN. *J Pediatr Gastroenterol Nutr*. 2012;55:221–229.
26. Glocker EO, Frede N, Perro M, et al. Infant colitis—it's in the genes. *Lancet* 2010;376:1272.
27. 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.
28. 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.
29. Stange EF, Travis SP, Vermeire S, et al. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. *J Crohns Colitis* 2008;2:1–23.
30. 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.
31. 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.
32. 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.
33. 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.
34. Froslic 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.
35. Gustavsson A, Järnerot G, Hertervig E, et al. A 2-year follow-up of the Swedish-Danish Infliximab/placebo trial in steroid resistant acute ulcerative colitis. *Gastroenterology* 2007;132:A983.
36. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology* 2010;138:2282–91.
37. 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.
38. Thakkar K, Lucia CJ, Ferry GD, et al. Repeat endoscopy affects patient management in pediatric inflammatory bowel disease. *Am J Gastroenterol* 2009;104:722–7.
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. Turner D, Hyams J, Markowitz J, et al. Appraisal of the Pediatric Ulcerative Colitis Activity Index (PUCAI). *Inflamm Bowel Dis* 2009;15:1218–23.
41. Mack DR, Langton C, Markowitz J, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. *Pediatrics* 2007;119:1113–9.
42. 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.
43. 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.
44. Schoepfer AM, Trummel M, 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.
45. D'Inca R, Dal Pont E, Di Leo V, et al. Calprotectin and lactoferrin in the assessment of intestinal inflammation and organic disease. *Int J Colorectal Dis* 2007;22:429–37.
46. Hanai H, Takeuchi K, Iida T, et al. Relationship between fecal calprotectin, intestinal inflammation, and peripheral blood neutrophils in patients with active ulcerative colitis. *Dig Dis Sci* 2004;49:1438–43.
47. Roseth AG, Aadland E, Jahnsen J, et al. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. *Digestion* 1997;58:176–80.
48. 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.
49. Bunn SK, Bisset WM, Main MJ, et al. Fecal calprotectin: validation as a noninvasive measure of bowel inflammation in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001;33:14–22.
50. Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. *Am J Gastroenterol* 2012;107:941–49.
51. Turner D, Leach ST, Mack D, et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicenter comparison of predicting outcomes and monitoring response. *Gut* 2010;59:1207–12.
52. Sylvester FA, Turner D, Draghi A 2nd, et al. Fecal osteoprotegerin may guide the introduction of second-line therapy in hospitalized children with ulcerative colitis. *Inflamm Bowel Dis* 2011;17:1726–30.
53. Harris MS, Lichtenstein GR. Review article: delivery and efficacy of topical 5-aminosalicylic acid (mesalazine) therapy in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2011;33:996–1009.
54. Lichtenstein GR, Kamm MA. Review article: 5-aminosalicylate formulations for the treatment of ulcerative colitis—methods of comparing release rates and delivery of 5-aminosalicylate to the colonic mucosa. *Aliment Pharmacol Ther* 2008;28:663–73.
55. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006:CD000543.
56. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006:CD000544.
57. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:601–16.
58. Romkens TE, Kampschreur MT, Drenth JP, et al. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. *Inflamm Bowel Dis* 2012 Mar 14. [Epub ahead of print]

59. 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.
60. 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.
61. 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.
62. 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.
63. Christensen LA, Fallingborg J, Jacobsen BA, et al. Bioavailability of 5-aminosalicylic acid from slow release 5-aminosalicylic acid drug and sulfasalazine in normal children. *Dig Dis Sci* 1993;38:1831–6.
64. Barden L, Lipson A, Pert P, et al. Mesalazine in childhood inflammatory bowel disease. *Aliment Pharmacol Ther* 1989;3:597–603.
65. Tolia V, Massoud N, Klotz U. Oral 5-aminosalicylic acid in children with colonic chronic inflammatory bowel disease: clinical and pharmacokinetic experience. *J Pediatr Gastroenterol Nutr* 1989;8:333–8.
66. 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.
67. 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.
68. Paoluzi OA, Iacopini F, Pica R, et al. Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-year follow-up study. *Aliment Pharmacol Ther* 2005;21:1111–9.
69. 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;137:1934–43.
70. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100:2478–85.
71. 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.
72. Kruis W, Kiudelis G, Racz I, et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009;58:233–40.
73. Williams C, Panaccione R, Ghosh S, et al. Optimizing clinical use of mesalazine (5-aminosalicylic acid) in inflammatory bowel disease. *Therap Adv Gastroenterol* 2011;4:237–48.
74. Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008;57:893–902.
75. Ford AC, Khan KJ, Sandborn WJ, et al. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:2070–7.
76. Loftus EV Jr, Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2004;19:179–89.
77. Arend LJ, Springate JE. Interstitial nephritis from mesalazine: case report and literature review. *Pediatr Nephrol* 2004;19:550–3.
78. 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.
79. 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.
80. Selhub J, Dhar GJ, Rosenberg IH. Inhibition of folate enzymes by sulfasalazine. *J Clin Invest* 1978;61:221–4.
81. Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. *Aliment Pharmacol Ther* 1995;9:293–300.
82. Cortot A, Maetz D, Degoutte E, et al. Mesalamine foam enema versus mesalamine liquid enema in active left-sided ulcerative colitis. *Am J Gastroenterol* 2008;103:3106–14.
83. Malchow H, Gertz B. A new mesalazine foam enema (Claversal foam) compared with a standard liquid enema in patients with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:415–23.
84. Gionchetti P, Ardizzone S, Benvenuti ME, et al. A new mesalazine gel enema in the treatment of left-sided ulcerative colitis: a randomized controlled multicentre trial. *Aliment Pharmacol Ther* 1999;13:381–8.
85. d'Albasio G, Paoluzi P, Campieri M, et al. Maintenance treatment of ulcerative proctitis with mesalazine suppositories: a double-blind placebo-controlled trial. The Italian IBD Study Group. *Am J Gastroenterol* 1998;93:799–803.
86. Hanauer S, Good LI, Goodman MW, et al. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol* 2000;95:1749–54.
87. Marteau P, Crand J, Foucault M, et al. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut* 1998;42:195–9.
88. Odera G, Giuliani B, Santini B, et al. Topical treatment with 5-ASA and hydrocortisone. *Riv Ital Pediatr* 1986;12:674–8.
89. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010;CD004115.
90. Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263–76.
91. Regueiro M, Loftus EV Jr, Steinhart AH, et al. Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. *Inflamm Bowel Dis* 2006;12:979–94.
92. Lamet M, Ptak T, Dallaire C, et al. Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study. *Inflamm Bowel Dis* 2005;11:625–30.
93. 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. *Digest Dis Sci* 2011;56:513–22.
94. Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:513–9.
95. 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.
96. Yokoyama H, Takagi S, Kuriyama S, et al. Effect of weekend 5-aminosalicylic acid (mesalazine) enema as maintenance therapy for ulcerative colitis: results from a randomized controlled study. *Inflamm Bowel Dis* 2007;13:1115–20.
97. 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.
98. Baron JH, Connell AM, Kanaghinis TG, et al. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *Br Med J* 1962;2:441–3.
99. Kolho KL, Raivio T, Lindahl H, et al. Fecal calprotectin remains high during glucocorticoid therapy in children with inflammatory bowel disease. *Scand J Gastroenterol* 2006;41:720–5.
100. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978;13:833–7.
101. 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.
102. Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclomethasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002;16:1109–16.

103. Manguso F, Balzano A. Meta-analysis: the efficacy of rectal beclomethasone dipropionate vs. 5-aminosalicylic acid in mild to moderate distal ulcerative colitis. *Aliment Pharmacol Ther* 2007;26:21–9.
104. Campieri M, Adamo S, Valpiani D, et al. Oral beclomethasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003;17:1471–80.
105. D'Haens GR, Kovacs A, Vergauwe P, et al. Preliminary efficacy and safety study of a new budesonide-MMX(R) 9 mg extended-release tablets in patients with active left-sided ulcerative colitis. *J Crohns Colitis* 2010;4:153–60.
106. 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.
107. Burke DA, Axon AT, Clayden SA, et al. The efficacy of tobramycin in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 1990;4:123–9.
108. Lobo AJ, Burke DA, Sobala GM, et al. Oral tobramycin in ulcerative colitis: effect on maintenance of remission. *Aliment Pharmacol Ther* 1993;7:155–8.
109. Gionchetti P, Rizzello F, Ferrieri A, et al. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. *Dig Dis Sci* 1999;44:1220–1.
110. David M, Weiner, MD - urologist, treatment with Sildenafil online nation therapy for ulcerative colitis: a double-blind placebo-controlled multicenter trial. *Am J Gastroenterol* 2010;105:1820–9.
111. Mantzaris GJ, Archavlis E, Christoforidis P, et al. A prospective randomized controlled trial of oral ciprofloxacin in acute ulcerative colitis. *Am J Gastroenterol* 1997;92:454–6.
112. Turunen UM, Farkkila MA, Hakala K, et al. Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study. *Gastroenterology* 1998;115:1072–8.
113. Muniyappa P, Gulati R, Mohr F, et al. Use and safety of rifaximin in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009;49:400–4.
114. 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.
115. 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.
116. Naidoo K, Gordon M, Fagbemi AO, et al. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2011; CD007443
117. 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.
118. Bibiloni R, Fedorak RN, Tannock GW, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol* 2005;100:1539–46.
119. Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2010;105:2218–27.
120. Sood A, Midha V, Makharia GK, et al. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:1202–9.
121. Guslandi M, Giollo P, Testoni PA. A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003;15:697–8.
122. Furrle E, Macfarlane S, Kennedy A, et al. Synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005;54:242–9.
123. Kato K, Mizuno S, Umesaki Y, et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther* 2004;20:1133–41.
124. Zocco MA, dal Verme LZ, Cremonini F, et al. Efficacy of *Lactobacillus GG* in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 2006;23:1567–74.
125. Wildt S, Nordgaard I, Hansen U, et al. A randomised double-blind placebo-controlled trial with *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. lactis BB-12 for maintenance of remission in ulcerative colitis. *J Crohns Colitis* 2011;5:115–21.
126. 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.
127. Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;CD000478
128. 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.
129. 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.
130. 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.
131. 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.
132. 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.
133. Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. *J Pediatr* 1990;117:809–14.
134. 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.
135. Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006;55:47–53.
136. Mate-Jimenez J, Hermida C, Cantero-Perona J, et al. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur Gastroenterol Hepatol* 2000;12:1227–33.
137. 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.
138. 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.
139. Andrews JM, Travis SPL, 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.
140. Fuentes D, Torrente F, Keady S, et al. High-dose azathioprine in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;17:913–21.
141. Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. *Gastroenterology* 1998;115:813–21.
142. 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.
143. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;4:621–30.
144. Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;3:47–91.
145. De Greef E, Vandenplas Y, Veereman-Wauters G. Opportunistic infections in paediatric inflammatory bowel disease patients. *Arch Dis Child* 2011;91:5–7.

146. Russell RK, Wilson ML, Loganathan S, et al. A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:946–53.
147. Veereman-Wauters G, de Ridder L, Veres G, et al. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. *J Pediatr Gastroenterol Nutr* 2012 Feb 10. [Epub ahead of print]
148. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;54:1121–5.
149. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; 374:1617–25.
150. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011; 9:36–41.
151. Osterman MT, Kundu R, Lichtenstein GR, et al. Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology* 2006;130:1047–53.
152. Gazouli M, Pachoula I, Panayotou I, et al. Thiopurine S-methyltransferase genotype and the use of thiopurines in paediatric inflammatory bowel disease Greek patients. *J Clin Pharm Ther* 2010;35:93–7.
153. Ooi CY, Bohane TD, Lee D, et al. Thiopurine metabolite monitoring in paediatric inflammatory bowel disease. *Aliment Pharmacol Ther* 2007; 25:941–7.
154. 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.
155. Rahhal RM, Bishop WP. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2008;14:1678–82.
156. Oren R, Arber N, Odes S, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996;110:1416–21.
157. Onuk MD, Kaymakoglu S, Demir K, et al. Low-dose weekly methotrexate therapy in remission maintenance in ulcerative colitis. *Gut* 1996;39:A75.
158. Aloï 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.
159. Turner D, Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. *Inflamm Bowel Dis* 2011;17:440–9.
160. 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.
161. Yamamoto S, Nakase H, Matsuura M, et al. Tacrolimus therapy as an alternative to thiopurines for maintaining remission in patients with refractory ulcerative colitis. *J Clin Gastroenterol* 2011;45:526–30.
162. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2006;CD005112
163. 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.
164. 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;10:391–9.
165. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 2010; 105:1430–6.
166. 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.
167. 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;142:257–65.
168. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; 362:1383–95.
169. Panaccione R, Ghosh S, Middleton S, et al. Infliximab, azathioprine or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis. The UC SUCCESS trial. *J Crohns Colitis* 2011;5:13.
170. Lichtenstein GR, Diamond RH, Wagner CL, et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. *Aliment Pharmacol Ther* 2009;30:210–26.
171. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008; 134:1861–8.
172. Fanjiang G, Russell GH, Katz AJ. Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2007;44:312–7.
173. Chaparro M, Guerra I, Munoz-Linares P, et al. Systematic review: antibodies and anti-TNF-alpha levels in inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;35:971–86.
174. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;105:1133–9.
175. Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther* 2009;29:286–97.
176. Thanaraj S, Hamlin PJ, Ford AC. Granulocyte/monocyte adsorptive apheresis for ulcerative colitis. *Aliment Pharmacol Ther* 2010; 32:1297–306.
177. Sands BE, Sandborn WJ, Feagan B, et al. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis. *Gastroenterology* 2008;135:400–9.
178. Tomomasa T, Kobayashi A, Kaneko H, et al. Granulocyte adsorptive apheresis for pediatric patients with ulcerative colitis. *Dig Dis Sci* 2003;48:750–4.
179. Kumagai M, Yamato Y, Maeda K, et al. Extracorporeal leukocyte removal therapy for patients with ulcerative colitis. *Pediatr Int* 2007; 49:431–6.
180. 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.
181. 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.
182. 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.
183. Tomomasa T, Tajiri H, Kagimoto S, et al. Leukocytapheresis in pediatric patients with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2011;53:34–9.
184. Emmrich J, Petermann S, Nowak D, et al. Leukocytapheresis (LCAP) in the management of chronic active ulcerative colitis—results of a randomized pilot trial. *Dig Dis Sci* 2007;52:2044–53.
185. Sakata Y, Iwakiri R, Amemori S, et al. Comparison of the efficacy of granulocyte and monocyte/macrophage adsorptive apheresis and leukocytapheresis in active ulcerative colitis patients: a prospective randomized study. *Eur J Gastroenterol Hepatol* 2008;20:629–33.
186. Dr. David M. Kaufman - USA, et al. Intravenous immunoglobulin therapy for active, extensive, and medically refractory idiopathic ulcerative or Crohn's colitis. *Am J Gastroenterol* 1992;87:91–100.
187. Buning J, Homann N, von Smolinski D, et al. Helminths as governors of inflammatory bowel disease. *Gut* 2008;57:1182–3.
188. Summers RW, Elliott DE, Qadir K, et al. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2003;98:2034–41.
189. Summers RW, Elliott DE, Urban JF Jr et al. *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005;128:825–32.

190. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2007;CD006443
191. Bernstein CN, Fried M, Krabshuis JH, et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis* 2010;16:112–24.
192. 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.
193. Seetharamaiah R, West BT, Ignash SJ, et al. Outcomes in pediatric patients undergoing straight vs J pouch ileoanal anastomosis: a multi-center analysis. *J Pediatr Surg* 2009;44:1410–7.
194. Pakarinen MP, Natunen J, Ashorn M, et al. Long-term outcomes of restorative proctocolectomy in children with ulcerative colitis. *Pediatrics* 2009;123:1377–82.
195. Weston-Petrides GK, Lovegrove RE, Tilney HS, et al. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. *Arch Surg* 2008;143:406–12.
196. Tjandra JJ, Fazio VW, Milsom JW, et al. Omission of temporary diversion in restorative proctocolectomy—is it safe? *Dis Colon Rectum* 1993;36:1007–14.
197. Ahmed Ali U, Keus F, Heikens JT, et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. *Cochrane Database Syst Rev*. 2009;CD006267
198. Wu XJ, He XS, Zhou XY, et al. The role of laparoscopic surgery for ulcerative colitis: systematic review with meta-analysis. *Int J Colorectal Dis* 2010;25:949–57.
199. Fraser JD, Garey CL, Laituri CA, et al. Outcomes of laparoscopic and open total colectomy in the pediatric population. *J Laparoendosc Adv Surg Tech A* 2010;20:659–60.
200. Mattioli G, Pini-Prato A, Barabino A, et al. Laparoscopic approach for children with inflammatory bowel diseases. *Pediatr Surg Int* 2011; 27:839–46.
201. da Luz Moreira A, Kiran RP, Lavery I. Clinical outcomes of ileorectal anastomosis for ulcerative colitis. *Br J Surg* 2010;97:65–9.
202. Cornish JA, Tan E, Teare J, et al. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007;50:1128–38.
203. Waljee A, Waljee J, Morris AM, et al. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006;55:1575–80.
204. Mortier PE, Gambiez L, Karoui M, et al. Colectomy with ileorectal anastomosis preserves female fertility in ulcerative colitis. *Gastroenterol Clin Biol* 2006;30:594–7.
205. 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.
206. Randall J, Singh B, Warren BF, et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg*. 2010;97:404–9.
207. Yang Z, Wu Q, Wu K, et al. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2010;31:486–92.
208. Kappelman M, Horvath-Puho E, Sandler RS, et al. The association between IBD and venous thromboembolism in Danish children and adults: A population-based case-control study. *Gastroenterology* 2010;138:S-105–6
209. Rintala RJ, Lindahl HG. Proctocolectomy and J-pouch ileo-anal anastomosis in children. *J Pediatr Surg* 2002;37:66–70.
210. Alexander F, Sarigol S, DiFiore J, et al. Fate of the pouch in 151 pediatric patients after ileal pouch anal anastomosis. *J Pediatr Surg* 2003;38:78–82.
211. Stavlo PL, Libsch KD, Rodeberg DA, et al. Pediatric ileal pouch-anal anastomosis: functional outcomes and quality of life. *J Pediatr Surg* 2003;38:935–9.
212. Robb BW, Gang GI, Hershko DD, et al. Restorative proctocolectomy with ileal pouch-anal anastomosis in very young patients with refractory ulcerative colitis. *J Pediatr Surg* 2003;38:863–7.
213. Perrault J. Pouchitis in children: therapeutic options. *Curr Treat Options Gastroenterol* 2002;5:389–97.
214. Shen B, Lashner BA, Bennett AE, et al. Treatment of rectal cuff inflammation (cuffitis) in patients with ulcerative colitis following restorative proctocolectomy and ileal pouch-anal anastomosis. *Am J Gastroenterol* 2004;99:1527–31.
215. Slatter C, Girgis S, Huynh H, et al. Pre-pouch ileitis after colectomy in paediatric ulcerative colitis. *Acta Paediatr* 2008;97:381–3.
216. 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.
217. Biancone L, Michetti P, Travis SP, et al. European evidence based consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis* 2008;2:63–92.
218. Kaditis AG, Perrault J, Sandborn WJ, et al. Antineutrophil cytoplasmic antibody subtypes in children and adolescents after ileal pouch-anal anastomosis for ulcerative colitis. *J Pediatr Gastroenterol Nutr* 1998;26:386–92.
219. Holubar SD, Cima RR, Sandborn WJ, et al. Treatment and prevention of pouchitis after ileal-pouch anal anastomosis for ulcerative colitis. *Cochrane Database Syst Rev*. 2010;CD001176.
220. 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.
221. 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.
222. 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.
223. Aloï M, Cucchiara S. Extradigestive manifestations of IBD in pediatrics. *Eur Rev Med Pharmacol Sci* 2009;13(suppl 1):23–32.
224. 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.
225. 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.
226. Hyams JS. Extraintestinal manifestations of inflammatory bowel disease in children. *J Pediatr Gastroenterol Nutr* 1994;19:7–21.
227. Hyams JS. Crohn's disease in children. *Pediatr Clin North Am* 1996;43:255–77.
228. Winesett M. Inflammatory bowel disease in children and adolescents. *Pediatr Ann* 1997;26:227–34.
229. Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin North Am* 2003;32:967–95.
230. 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.
231. 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; 2010:553–61.
232. Charatcharoenwittaya P, Lindor KD. Primary sclerosing cholangitis: diagnosis and management. *Curr Gastroenterol Rep* 2006;8:75–82.
233. Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995;22:1404–8.
234. Fevery J, Henckaerts L, Van Oirbeek R, et al. Malignancies and mortality in 200 patients with primary sclerosing cholangitis: a long-term single-centre study. *Liver Int* 2012;32:214–22.
235. Cullen SN, Chapman RW. The medical management of primary sclerosing cholangitis. *Semin Liver Dis* 2006;26:52–61.
236. 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.
237. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009;50:808–14.

238. 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.
239. 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.
240. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;88:995–1000.
241. Markowitz J, Grancher K, Rosa J, et al. Growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1993;16:373–80.
242. 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.
243. Gonzalez-Huix F, Fernandez-Banares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;88:227–32.
244. McIntyre PB, Powell-Tuck J, Wood SR, et al. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986;27:481–5.
245. Dickinson RJ, Ashton MG, Axon AT, et al. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 1980;79:1199–204.
246. Barabino A, Tegaldo L, Castellano E, et al. Severe attack of ulcerative colitis in children: retrospective clinical survey. *Dig Liver Dis* 2002;34:44–9.
247. Bechtold S, Alberer M, Arenz T, et al. Reduced muscle mass and bone size in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16:216–25.
248. 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.
249. Gokhale R, Favus MJ, Karrison T, et al. Bone mineral density assessment in children with inflammatory bowel disease. *Gastroenterology* 1998;114:902–11.
250. 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.
251. 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.
252. 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.
253. 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.
254. Greenley RN, Stephens M, Doughty A, et al. Barriers to adherence among adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16:36–41.
255. 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.
256. Timmer A, Preiss JC, Motschall E, et al. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev*. 2011:CD006913-CD006913.
257. 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.
258. Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. *Am J Gastroenterol* 2005;100:1386–92.
259. Vaisto T, Aronen ET, Simola P, et al. Psychosocial symptoms and competence among adolescents with inflammatory bowel disease and their peers. *Inflamm Bowel Dis* 2010;16:27–35.
260. 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.
261. Hommel KA, Baldassano RN. Barriers to treatment adherence in pediatric inflammatory bowel disease. *J Pediatr Psychol* 2010;35:1005–10.
262. 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.
263. Goodhand J, Hedin CR, Croft NM, et al. Adolescents with IBD: the importance of structured transition care. *J Crohns Colitis* 2011;5:509–19.
264. Crowley R, Wolfe I, Lock K, et al. Improving the transition between paediatric and adult healthcare: a systematic review. *Arch Dis Child* 2011;96:548–53.
265. 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.
266. Actis GC, Fadda M, Pellicano R, et al. The 17-year single-center experience with the use of azathioprine to maintain remission in ulcerative colitis. *Biomed Pharmacother* 2009;63:362–5.
267. Turner D, Otley AR, Mack D, et al. Development and evaluation of a Pediatric Ulcerative Colitis Activity Index (PUCAI): a prospective multicenter study. *Gastroenterology* 2007;133:423–32.

**Appendix 1: Predefined questions that the subgroups addressed**

**Evaluation**

1. The diagnosis of UC in children
2. The required investigations at baseline and differential diagnosis
3. Monitoring disease activity and remission in children
4. Predictors of severe disease course

**Medical management**

5. The role of antibiotics in pediatric UC (excluding pouchitis)
6. 5-ASA in pediatric UC
7. Thiopurines in pediatric UC
8. Methotrexate in pediatric UC
9. Corticosteroids in pediatric UC
10. Defining and managing steroid dependence
11. Defining and managing steroid refractoriness
12. Enemas in pediatric UC
13. Biologics in pediatric UC
14. Maintenance of remission: timing of choice of each medication
15. Probiotics in pediatric UC
16. Other investigational interventions

**Surgical considerations**

17. The preferred elective surgery in pediatric UC and indications
18. Ways to minimize surgical complications
19. Pouchitis in children

**General considerations**

20. Nutrition, growth, and bone health
21. Psychosocial support to the child and the family and transitional care
22. EIMs
23. Risks and adverse events

**Appendix 3: The Pediatric Ulcerative Colitis Activity Index**

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

For user's guide and cutoff values for response, remission, mild, moderate, and severe disease activity, refer to the original study (267).

**Appendix 2: Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence-based Medicine**

Level	Diagnostic study	Therapeutic study
1a	SR with homogeneity of level 1 diagnostic studies	SR with homogeneity of RCTs
1b	Validating cohort study with good reference standard	Individual RCT (with narrow CI)
1c	Specificity or sensitivity is so high that a positive or a negative result rules out the diagnosis	All or none
2a	SR with homogeneity of level >2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low-quality RCT; eg, <80% follow-up)
2c		“Outcomes” research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case-control studies
3b	Nonconsecutive study; or without consistently applied reference standards	Individual case-control study
4	Case-control study, poor or nonindependent reference standard	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

**Grading of recommendation**

- A** Consistent level 1 studies
- B** Consistent level 2 or 3 studies or extrapolations from level 1 studies
- C** Level 4 studies or extrapolations from level 2 or 3 studies
- D** Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

For details, see [http://www.cebm.net/levels\\_of\\_evidence.asp#refs](http://www.cebm.net/levels_of_evidence.asp#refs).