



LEADING ARTICLE

Differences in the management of pediatric and adult onset ulcerative colitis — lessons from the joint ECCO and ESPGHAN consensus guidelines for the management of pediatric ulcerative colitis



Frank M. Ruemmele^{a,b,*}, Dan Turner^c

^a Université Sorbonne Paris Cité, Paris Descartes, Paris, France

^b APHP, Hôpital Necker Enfants Malades, Service de Gastroentérologie, Pediatric IBD Program, Paris, France

^c Pediatric Gastroenterology Unit, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel

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Abstract

An expert panel of the European Crohn's and Colitis Organisation (ECCO) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) initiated a consensus process to produce the first pediatric specific ulcerative colitis (UC) guidelines based on a systematic literature review. Treatment strategies must reflect that pediatric-onset UC has a slightly different phenotype than adult-onset disease with more often extensive (pancolitis) and more aggressive disease course. Other pediatric-specific aspects include growth, puberty, bone density accrual and emotional development and body image acquisition. These differences and others influenced the development of pediatric treatment algorithms. It is recommended that virtually all children with UC must be treated with some maintenance therapy and 5-ASA requirement and dosing are often higher in children. A larger number of children are at risk for steroid-dependency, and this should not be tolerated; steroid sparing strategies with early use of immunosuppressors are recommended in high-risk patients. On the other hand, the safety profile of immunosuppressive therapy in children includes the rare forms of lymphomas and many future treatment years. Colectomy and pouch formation should be balanced in the treatment algorithms against the higher rate of future infertility in girls. The acute and on-going management of pediatric UC should be guided by evidence- and consensus-based balanced decisions, reflecting a vision of long-term treatment goals.

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* Corresponding author at: Pediatric Gastroenterology, Hôpital Necker-Enfants Malades, Université Paris Descartes, INSERM U989, 149 Rue de Sèvres, 75015 Paris, France.

E-mail address: frank.ruemmele@nck.aphp.fr (F.M. Ruemmele).

1. Introduction

Multiple studies show that onset of ulcerative colitis (UC) during childhood has a different disease pattern and more aggressive evolution compared to adult onset. The most striking differences are disease extent and severity; the recent multicenter EUROKIDS data on 670 children with UC [1] is in keeping with previous studies showing that 60–80% of pediatric-onset UC presents as pancolitis, compared with only 20–30% of adult-onset UC [2,3]. Extent of disease has been consistently associated with a more severe and aggressive disease course. Within five years from diagnosis a significantly higher percentage of patients with childhood onset UC are admitted to emergency units for acute severe colitis, compared to adult-onset disease [2,4,5]. More children fail intravenous steroids during an acute severe episode [6,7]. Consequently, this translates into higher colectomy rates in children compared to adult UC populations. In the series of Van Limbergen et al. [3] colectomy rate within ten years from diagnosis was over 40% in pediatric onset UC compared to less than 20% in adult onset UC. More recent studies show lower colectomy rates of 25% in 6 years [8] and 15% in 10 years [9]. Rectal sparing was reported to be more common in children (10–30%) [10–12]. In addition, lack of histological chronicity is common upon presentation in children, markedly more than in adults. Thus, diagnostic procedures have to be adapted and monitoring of disease evolution by limited sigmoidoscopy may not be sufficient in some cases. On the other hand, endoscopic evaluation, which requires complete anesthesia in pediatrics, is very stressful for children and their caregivers, thereby, limiting the feasibility of repeated tests and relying more on clinical assessments than in practice by adult gastroenterologists.

The pediatric age group also raises several age-specific considerations related to growth, pubertal development and the acquirement towards adulthood of autonomy, body image, and self-confidence. Care of these patients requires particular skills in adolescence medicine. LeLeiko et al. [13] showed that up to 75% of adolescent patients do not completely adhere to treatment strategies, further complicating disease control. Growth and pubertal development significantly influence treatment strategies, although this is more a Crohn's disease-specific issue. Maximal bone density, impaired in 20–50% of pediatric IBD patients, is reached by end of childhood thereby impacting future risk for osteoporosis and fractures. Apart from the direct effect of the inflammatory process, steroids further impair growth and bone mineral density, and thus steroid-sparing strategies are of most importance in children.

Evidence-based consensus guidelines must incorporate these pediatric specific aspects. An international pediatric IBD expert panel among members of ECCO (European Crohn's and Colitis Organisation) and ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) was formed after an open call. A systematic review of the literature and a consensus process were performed focusing on pediatric specific considerations related to the diagnosis and care of children and adolescents with UC. Diagnostic and treatment strategies for pediatric UC (excluding acute severe colitis) were summarized in 40 formal recommendations and 68 practice points, each with a support of at least 80% of the participants [14].

2. Differences in treatment strategies between adult UC and pediatric UC

While in adult-onset UC the choice of induction and maintenance treatment is determined by both disease extent and severity, in children disease activity dominates treatment strategies. Since limited disease is less common, disease extent is not a very useful parameter in managing childhood UC. Despite the generally accepted step-up approach in pediatric UC, more children will require rapid treatment escalation both for induction and maintenance of remission, due to a more severe disease presentation. Children with a refractory disease or those with frequent flares must be carefully evaluated for adherence to treatment using published strategies. Lastly, all children should be offered support programs that teach coping skills with this deliberating chronic disease. Although this is also true in adult medicine, the importance of such programs is higher in the vulnerable pediatric age group.

2.1. Induction therapy

Similar to adult recommendations, oral 5-ASA regimens are recommended as the first line induction therapy for mild to moderate UC. However, high 5-ASA doses are particularly useful in extensive and more severe disease [15–17] as commonly seen in children. Therefore higher 5-ASA doses and combination with rectal therapy are required more often in children than in adults [14]. Furthermore, the use of topical 5-ASA as monotherapy is less indicated in children compared to adult patients since isolated proctitis is an infrequent phenotype in children.

About half of the children with UC will become steroid-refractory or dependent by 1 year as documented in real life cohorts, despite the increasing use of immunomodulators and infliximab [9,18]. While glucocorticosteroids are initially effective in 70–90% of children with UC, steroid dependency may be seen in up to 50% of children and this should not be tolerated, given their detrimental effect on growth, body image and bone mineral accrual. The consensus panel developed a detailed tapering strategy allowing harmonizing the use of glucocorticosteroid when treating pediatric UC (Table 1).

In contrast to adult-onset UC where the use of *Escherichia coli* Nissle was shown to be an effective alternative to 5-ASA for maintenance therapy, there is insufficient evidence to recommend routine probiotic or antibiotic therapy in pediatric UC for induction or maintenance of remission. However, when extrapolating adult data, probiotics 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.

2.2. Maintenance therapy

Maintenance therapy is recommended for all patients with pediatric onset UC, in keeping with the recent update of the ECCO consensus on adult-onset UC [19], while previous adult recommendations stipulated that some patients do not require maintenance therapy [20].

Table 1 Consensus-based steroid tapering algorithm for pediatric UC.

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

Start initial steroid medication at 1 mg/kg prednisolone equivalent (up to 40 mg once daily, in acute severe colitis doses up to 60 mg/day might be used). If treatment response is a drop in the PUCAI < 15 consider decrease according to the table, if PUCAI = 15–30 prolong stable dose for another week, and if PUCAI > 35 increase steroid dose to previous 1–2 steps for at least one week before considering weaning.

Oral 5-ASA regimens are recommended as the first line maintenance therapy, in analogy to adult patients. However, pediatric onset UC more frequently requires maintenance therapy with immunosuppressive agents. In a recent Italian inception cohort study of 110 children with UC diagnosed during 2006–2011, 40% were treated with immunomodulators by 1 year and 15% with infliximab [18]. Thiopurines (azathioprine or mercaptopurine), which are considered more effective than 5-ASA [21,22] 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. In addition, top-down treatment with thiopurines should be considered upon diagnosis if the presenting phenotype is acute severe colitis, which is more commonly seen in children and poses a significant predictive factor for early colectomy. The North American registry data of 133 children with UC reported a 1-year steroid-free remission rate of 49% on thiopurines [23]. It is not clear if combining 5-ASA with thiopurine or even infliximab is beneficial but it is not unreasonable to do so given the severity of pediatric onset UC and high safety profile of 5-ASA.

The use of anti-TNF agents should be limited to patients with active or steroid dependent disease despite optimized 5-ASA and thiopurine medications, or those with steroid-refractory acute severe colitis. In thiopurine-naïve patients, stepping down from anti-TNF may be considered after 6–12 months after verifying that deep and sustained remission has been achieved.

Combination therapy with thiopurines and infliximab poses an increased risk for hepatosplenic T cell lymphoma, particularly in young males, and a general increase of lymphoma risk [24–26]. On the other hand, there is no firm evidence to show that the clinical benefit of combined therapy in thiopurine-failure patients is significant and outweigh the risk in children. Following the precautionary principal, it is recommended to consider stopping thiopurine after 3–6 months of combined therapy, especially in thiopurine-failure children. Treatment individualization is required based on careful risk–benefit stratification.

Colectomy is always a viable option to discuss. The many future disease and treatment affected years must be factored in the decision whether to perform colectomy, as this impacts on body image and quality of life. The

discussion of colectomy should particularly include reduced fertility in females undergoing pouch procedure.

3. Concluding remarks

Although pathogenesis and most disease-specific parameters in children are not very different than in adults, still many disease specific important differences mandate changes in pediatric treatment algorithms. In general, escalation to immunomodulators and anti-TNF is more often indicated in children as compared with adults, but nonetheless colectomy rate remains higher. Timely introduction and escalation to appropriate therapy while ensuring complete remission could ensure long-term sustained remission and may reduce malignancy risk given the many future colitis years in children. On the other hand, children with UC have many future medication years with multiple associated adverse events. Both sides should be carefully factored in the complex decision-making process, especially in children.

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