Pediatric Aspects of Inflammatory Bowel Disease

58

Brendan Boyle and Jeffrey S. Hyams

Introduction

A significant percentage of newly diagnosed individuals with inflammatory bowel disease (IBD) fall within the pediatric age range (≤16 years old). These patients often present a set of issues that differ from adults with IBD and require a good understanding of how the effects of disease and therapy on growth and development must influence care. This chapter will highlight important differences between pediatric and adult IBD. A description of risks and benefits of available therapies will also be reviewed, especially with regard to risks of toxicity with thiopurines as monotherapy or in combination with anti-TNF given the association with lymphoma and HSTCL in younger patients with IBD.

Pediatric Aspects of IBD

Demographics

The Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry, a natural history study started in 2002 enrolled 1928 subjects diagnosed with IBD before their 16th birthday. The age distribution of the cohort at diagnosis was 6 % <5 years, 28 % from 5–9 years, and 66 % from 10–16 years with a slight predominance of males over females (57 % vs. 43 %) [1]. In a population-based state-wide US epidemiologic study, the incidence of IBD in the pediatric population was 7.5 per 100,000 with that of Crohn's disease (4.6 per 100,000) being twice that of ulcerative colitis (2.1 per 100,000). Eighty-nine percent of new cases were nonfamilial [2].

Disease Location

The location or extent of disease differs according to age of disease onset in children newly diagnosed with Crohn's disease. Children under the age of 10 years, and in particular children under the age of 5 years, characteristically present with isolated colitis, whereas ileal disease (with or without accompanying colitis) begins to occur more often in children whose disease is diagnosed after the age of 9–10 years [3, 4]. Upper tract involvement (proximal to the ligament of Treitz) is present most commonly in those children with ileocolonic disease (up to 50–60 %), with esophageal involvement seen in 27 % (macroscopic in 18 %), and gastroduodenal involvement in 56 % (macroscopic 42 %). Isolated UGI involvement is rare [5]. Pediatric onset ulcerative colitis is characterized by extensive colitis or pancolitis in the majority of cases and isolated proctitis is less common than in adult populations [6, 7].

Serology

As in adults antibodies to a variety of microbial antigens have been found in children with Crohn's disease. However, in children there appears to be an age-related expression of these antibodies. In a cohort of 705 children from three prospectively characterized cohorts in North America, the rate of ASCA (both IgG and IgA) positivity was <20 % for children <7years of age compared to 40 % for those 8–15 years of age, likely representing the preponderance of isolated colonic disease in young children. Anti-CBIR1 was detected in 66 % and 54 %, respectively, from the two age groups [8].

B. Boyle, M.D., M.P.H.
Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Nationwide Children's Hospital, The Ohio State University College of Medicine and Public Health, 700 Children's Drive, Columbus, OH 43205, USA
e-mail: brendan.boyle@nationwidechildrens.org

J.S. Hyams, M.D. (✉)
Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106, USA

University of Connecticut School of Medicine, 282 Washington Street, Hartford, CT 06106, USA
e-mail: jhyams@connecticutchildrens.org

D.C. Baumgart (ed.), *Crohn's Disease and Ulcerative Colitis*, DOI 10.1007/978-3-319-33703-6_58

Clinical Behavior at Diagnosis

In French and North American population-based pediatric studies, disease behavior at diagnosis was inflammatory (B1) in 70–72 % and stricturing (B2) or penetrating (B3) in 22–30 % [9, 10]. A French population-based study of children with ulcerative colitis found 26 % had proctitis, 35 % left-sided disease, and 37 % extensive colitis at diagnosis [7]. This disease distribution is quite different than reported previously from North America where extensive disease at diagnosis has been observed in up to 80 % of children at presentation [2, 11]. More recent studies propose further subdividing children by age of diagnosis, with those diagnosed at age <10 years consider early onset IBD (EOIBD), and those diagnosed age <6 years as very early onset IBD (VEOIBD). Patients in the VEOIBD group are more likely to have monogenic IBD, with increased risk of primary immunodeficiency, autoimmune enteropathy, and primarily colonic disease distribution. These findings are distinct from patients diagnosed after age 7 years that more commonly have conventional, polygenic IBD [12–14]. The discovery of mutations in the genes coding for one of the two IL10 receptors causing loss of function in IL10 signaling has prompted increasing work looking for genetic polymorphisms that produce a severe IBD-like phenotype [15].

Measuring Disease Activity

While measuring the severity of gastrointestinal symptoms and laboratory abnormalities is similar in children and adults, the profound effect of IBD on linear growth is clearly a pediatric-only problem. Growth abnormalities are quite common in pediatric Crohn's disease and may be the major clinical manifestation. Thus, growth data have been incorporated into the most widely used instrument to measure disease activity in children with Crohn's disease, the Pediatric Crohn's Disease Activity Index (PCDAI) [16]. As measuring changes in growth velocity can only be done accurately over periods of 6 months or more, this has led to concerns that the PCDAI might not be sensitive enough to discern changes in clinical activity over the short-term (e.g., 3 months or less); however, this has not been borne out by additional studies [17]. The PCDAI can range in score from 0 to 100 with <10 denoting remission, 10–30 mild disease, and >30 moderate to severe disease. Given the limitations in calculating the complete PCDAI at each visit, more recently the weighted PCDAI (wPCDAI) has also been proposed as a more feasible instrument [18]. Additionally, the short PCDAI, a simplified disease assessment tool excluding need for laboratory and perianal assessment, has been developed and validated against the full and abbreviated PCDAI has been proposed to be utilized in observational and quality improvement research [19].

The Pediatric Ulcerative Colitis Activity Index (PUCAI) has been developed and validated to measure the activity of pediatric ulcerative colitis [20]. It ranges from 0 to 85 points with <10 signifying inactive disease, 10–34 mild disease, 35–64 moderate disease, and 65 or greater severe disease. Debate regarding how to most fully assess clinical remission in IBD exists. Variable definitions of remission in IBD including clinical, serologic, endoscopic, and histologic remission have been proposed and have resulted in the concept of "treat to target", with some centers suggesting histologic remission should be the ultimately therapeutic goal [21].

An expanding body of literature has evaluated the use of biomarkers including fecal calprotectin as an indirect assessment of luminal activity. Recent studies have found that many patients in clinical or even endoscopic remission continue to have histologically active disease. Fecal calprotectin was found to be significantly higher in those with active histologic disease compared to those with histologic healing (median 278 μg/g vs. 68 μg/g ($p=0.002$)), suggesting calprotectin may be a more reliable marker of histologic disease activity [22]. Additional studies have suggested cut off calprotectin values of approximately <200 μg/g correlate well with endoscopic and histologic healing. Use of the calprotectin therefore may reduce the need for repeat endoscopic evaluation [23]. Application of calprotectin as a reliable marker of remission in the pediatric population requires further investigation.

Growth

The effect of disease activity on linear growth is unique to pediatrics. It has been estimated that up to 88 % of children with Crohn's disease have abnormal growth velocity at the time of diagnosis while in pediatric ulcerative colitis this number is <10 % [24]. In our experience the numbers for patients with Crohn's disease are not quite so stark, but certainly still involves well over 30–40 % of newly diagnosed patients. Two excellent review articles on this topic have been published and should be consulted for further detail [25, 26].

Many mechanisms of disturbed growth have been suggested for pediatric IBD. Poor growth appears to relate to a combination of factors including chronic caloric deprivation largely secondary to poor intake [27]. However, the inflammatory process itself leads to the production of cytokines that result in IGF-1 dysregulation by decreasing responsiveness of the growth hormone receptor in the liver to growth hormone diminishing IGF-1 production. Moreover, there is a direct effect of the cytokines on growing bone [28] and decreasing responsiveness to testosterone [29]. Use of corticosteroids even in small daily doses of prednisone (5 mg/m^2) can also impair growth

[30, 31]. The crucial factor in the effect of corticosteroids on growth appears not to be the dose used short-term, but rather whether they are used long-term [32].

Diagnosis of Pediatric IBD

The diagnosis of IBD in children is usually straightforward and the techniques employed are similar to those used in adults including upper and lower endoscopy and small bowel assessment usually performed with radiographic imaging. Ionizing radiation exposure when imaging the small bowel is of special concern given its association with DNA damage. The potential increased likelihood of malignancy following recurrent exposure to ionizing radiation emphasizes the importance of minimizing radiation exposure in the pediatric population [33–35]. Magnetic resonance enterography (MRE) is replacing barium imaging and CT scans in many institutions. A 2013 systematic review of 11 studies evaluated the use of MRE to assess the small bowel in a total of 496 pediatric patients with CD. It was concluded that in centers with expertise in MRE, this is the preferred imaging technique over those involving radiation. Rates of detecting small bowel abnormalities were similar while minimizing radiation exposure [36].

Management of Pediatric IBD

There are few controlled trials of medications in the treatment of pediatric IBD; most experience is extrapolated from adult studies though several recent trials have demonstrated the efficacy of biologic therapies with anti-TNF in treating both pediatric CD and UC.

Aminosalicylates

Though data to support the use of aminosalicylates for the treatment of pediatric Crohn's disease or ulcerative colitis are scant, they are commonly used for both. Specific dosing guidelines for children have not been established and therefore in practice there is large variation. The most common dose used is 50 mg/kg/day of mesalamine though anecdotally some clinicians use up to 100 mg/kg/day (maximum 4 g). No pediatric-specific side effects have been identified.

Corticosteroids

Corticosteroids have been the historical mainstay of the treatment of moderate to severe Crohn's disease and ulcerative colitis though no placebo-controlled randomized trials have been published. Nonetheless the ability of corticosteroids to induce remission in most children has been well established [37, 38]. A natural history study of the effect of corticosteroids in pediatric Crohn's disease found that at 1 year, 61 % of patients were corticosteroid responsive, 31 % corticosteroid dependent, and 8 % had gone on to surgery [37]. A similar study published on the use of corticosteroids in newly diagnosed ulcerative colitis disease in children found that by 1 year 45 % of children were corticosteroid dependent and 5 % of the corticosteroid-treated patients had come to colectomy [38]. In both reports the use of immunomodulators (50–75 % of patients) and infliximab (17–25 %) was common in patients with corticosteroid dependence. Two studies have compared budesonide with prednisolone in the treatment of Crohn's disease in children and shown similar efficacy [39, 40], though bias in patient selection (i.e., milder patients) may have influenced the results. Pediatric-specific side effects of corticosteroids are common and effects on growth, bone metabolism, and the cosmetic issues such as Cushingoid appearance and acne are of particular concern.

Immunomodulators

Multiple publications have looked at the use of immunomodulators in the treatment of pediatric Crohn's disease though only one randomized placebo-controlled study has been performed [41]. In this study of 55 newly diagnosed children with moderate to severe CD who all received an initial course of prednisone and then either 6-mercaptopurine or placebo, initial remission rates at 3 months were similar, but by 1 year the 6-mercaptopurine-treated group had received significantly less corticosteroid and had a much lower relapse rate. Largely based on this study, thiopurines became standard of care in the treatment of moderate to severe CD in children and are customarily introduced quite soon after diagnosis. However, several follow-up observational or retrospective studies have found rates of sustained remission to be decreased compared to the original RCT [42–44]. Two recent studies looking at the effect of early introduction of thiopurines in adults with Crohn's disease have shown no beneficial effect [45, 46]. The potential of thiopurines to contribute to lymphoma, skin cancer, as well as hemophagocytic lymphohistiocytosis (HLH) has caused some clinicians to limit their use (see below).

Increased interest has focused on methotrexate as an alternative immunomodulator. Two pediatric studies found that 45–50 % of patients intolerant of thiopurines were in steroid-free remission at 12 months after change from thiopurines to MTX [47, 48]. Furthermore, a recent study evaluating data from a large prospective IBD registry found that the use of MTX as maintenance therapy has been increasing, with 14 %

of patients treated with MTX as first-line immunomodulator therapy in 2002 and expanding to 60 % in 2010 [49]. A 2014 multicenter retrospective cohort study comparing outcomes for patients treated with subcutaneous versus oral MTX found rates of overall steroid free remission to be similar. However, oral MTX use was associated with a longer time to remission, less improvement in linear growth and a trend toward reduced sustained SFR. The authors therefore suggested the subcutaneous route is initially preferred [50]. No head-to-head comparisons of outcomes with thiopurines and methotrexate in pediatric CD have been published.

Biological Therapy

The REACH clinical trial included 112 initial study subjects with moderate/severe disease despite therapy with corticosteroids and immunomodulators who were treated with 5 mg/kg at 0, 2, and 6 weeks. Eighty-eight percent were in response and 59 % in remission at 10 weeks. Patients in response or remission at 10 weeks were then randomized to receive either 5 mg/kg every 8 weeks or every 12 weeks, with an opportunity to step up dose to 10 mg/kg or decrease interval (for those in the 12 week group) in case of loss of response. At week 54, 33 of 52 (64 %) and 29 of 52 (56 %) patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 17 of 51 (33 %) and 12 of 51 (24 %) patients receiving treatment every 12 weeks ($p = .002$ and $p < .001$, respectively) [51].

Longer-term follow-up following infliximab therapy in children has also been examined. A multicenter study involving 66 patients in the Netherlands had a mean follow-up of 41 months with 15 % having a prolonged response following episodic therapy, 56 % were infliximab dependent (requiring repeated infusions to maintain efficacy), and 29 % lost response [52]. A second multicenter study examined the long-term course of 202 children with follow-up periods ranging up to 3 years. One hundred twenty-eight of the study cohort were treated with maintenance therapy and had follow-up of ≥1 year. The likelihood of continuing infliximab was 93 %, 78 %, and 67 % at 1, 2, and 3 years respectively (Kaplan Meier analysis). A step-up in therapy (either increased dose or decreased interval) was needed in about half the patients. Corticosteroid-free clinical remission for the periods from 0–1, 1–2, and 2–3 years after starting infliximab was 26 %, 44 %, and 33 % [53].

Recent adult studies have identified the relationship between sustained remission and infliximab trough and antibody to infliximab levels (ATI) [54]. Similar associations are found in pediatric IBD. A prospective cohort study of pediatric patients with IBD found that higher infliximab levels and lower CRP at week 14 were associated with week 54 efficacy and rates of remission [55]. A retrospective pediatric study of 134 patients with IBD found similar associations. ATI ≥ 5 was associated with lower infliximab trough levels than those with ATI < 5 ($p < 0.001$). Additionally, ATI ≥ 12 was associated with need for surgical resection compared to those with ATI < 12 ($p = 0.01$) [56].

The use of adalimumab in pediatric Crohn's disease was initially reported in multiple small single center series and one larger retrospective report of 115 patients. Nearly all patients had previously been treated with infliximab. The majority of children received induction dosing of 80 and 40 mg separated by 2 weeks followed by 40 mg every other week . Corticosteroid-free remission was noted in 22 %, 33 %, and 42 % of patients at 3, 6, and 12 months, respectively [57]. More recently, the open-label IMAgINE 1 study evaluated the efficacy of adalimumab with moderate to severe Crohn's disease. Study design evaluated outcomes for groups treated with high- or low-dosage after 26 weeks. In total, adalimumab was found to induce and maintain remission in 33 % of patients at 26 weeks. In patients that were infliximab naïve at the initiation of the trial, clinical remission rates at 26 weeks were significantly increased in the high dose versus low dose groups (57 % vs. 35 % $p = 0.026$) [58].

Outcomes with the use of infliximab in children with ulcerative colitis from a large multicenter pediatric IBD Registry have been reported. Corticosteroid-free inactive disease by physician global assessment was noted in 12/44 at 6 months (27 %), 15/39 at 12 months (38 %), and 6/28 (21 %) at 24 months. Kaplan-Meier analysis showed the likelihood of remaining colectomy-free following infliximab was 75 % at 6 months, 72 % at 12 months, and 61 % at 2 years [59]. In a more recent prospective pediatric UC trial including patients with moderate to severe UC, 73 % of patients responded to infliximab by week 8 after induction dosing of 5 mg/kg at weeks 0, 2, and 6. At week 54, 38 % of responders that continued to receive standard dosing maintenance infliximab therapy remained in remission [60].

The landmark SONIC study included adults with Crohn's disease and demonstrated significantly improved corticosteroid-free remission rates in anti-TNFα naive patients treated with azathioprine plus infliximab versus infliximab alone or azathioprine alone, and therefore use of dual therapy in this population greatly increased [61]. However, there are also convincing data that adult patients who have failed thiopurines and move on to infliximab do not have additional success by maintaining the thiopurine [62]. Moreover, the recently published COMMIT study in adults with Crohn's disease showed no added efficacy when comparing infliximab alone to infliximab plus methotrexate with both groups having clinical remission rates near 70 % at week 50. However, antibodies to infliximab were higher in the monotherapy group compared to combination (20 % vs. 4 % $p = 0.01$) [63].

The impressive remission rates and potential promise of mucosal healing have prompted early consideration for biological therapy in treating IBD. For pediatric patients in particular, establishing corticosteroid-free remission prior to or during the years of rapid linear growth and sexual development is very important. The use of an anti-TNFα agent as primary therapy in the setting of extensive disease, complicated early disease, severe fistula, or disease onset in an adolescent with growth failure already showing signs of puberty in whom the window for growth is short has become increasingly common. Data have also suggested that antibody titers to specific microbial antigens measured at the time of diagnosis may predict the development of complicated disease requiring surgery (obstruction, perforation) and may play a role in helping identify subjects more likely to benefit from biological therapy at the time of diagnosis [64].

The striking impact of early anti-TNF use upon growth in inflammatory CD was recently demonstrated using data from a large observational cohort study, which included patients newly diagnosed with Crohn's disease at age <17. Twelve month outcomes for 3 groups of propensity-matched patients were compared: early infliximab, early immunomodulator therapy (IM), or no IM or infliximab therapy in the first 3 months. Clinical and growth outcomes were both found to be superior in those treated with early infliximab therapy compared to those with early IM or no early IM or infliximab therapy. In patients treated with early infliximab, 85 % were in remission at month 12 compared to 60 % in the early IM and 54 % in the no early IM or infliximab groups ($p = 0.0003$). Normalization of C-reactive protein was most frequent in the early infliximab group. Further data are needed to determine which patients should be considered for anti-TNF therapy at the time of diagnosis [65].

Pediatric trials evaluating combination versus monotherapy with anti-TNF have not been performed. However, recently published observational data evaluated durability of infliximab therapy in 502 patients with Crohn's disease. In total, approximately 60 % of patients remained on infliximab 5 years after its initiation. The probability ± standard error that patients remained on infliximab 5 years after initiating treatment was significantly higher for those receiving concomitant therapy for >6 months compared to both anti-TNF monotherapy or those treated with combination therapy for <6 months (0.7 ± 0.04 vs. 0.48 ± 0.08 vs. 0.55 ± 0.06 ($p < 0.001$)). Importantly, the durability of infliximab therapy in males treated for >6 months with combination therapy was greater in those treated with infliximab/MTX than those treated with infliximab/thiopurines (0.97 ± 0.03 vs. 0.58 ± 0.08 $p < 0.01$) [66].

Clinical experience with anti-integrin therapy including natalizumab and more recently vedolizumab is emerging. There is a single report on the use of natalizumab in adolescents with moderate to severe Crohn's disease. Using an open-label dosing schedule of 3 mg/kg at weeks 0, 4, and 8 weeks in 31 subjects, 55 % had a clinical response and 29 % were in remission at 10 weeks [67]. Natalizumab targets both alpha4beta1 and alpha4beta7 integrin therefore modulating both brain and gut lymphocyte migration. Its use has been associated with progressive multifocal leukoencephalopathy (PML) caused by reactivation of latent JC virus. In contrast to natalizumab, vedolizumab targets only alpha4beta7 integrin and thus acts only upon gut, not brain lymphocytes and should therefore have reduced risk of PML. The adult 2013 RCTs in both CD and UC found vedolizumab to be effective toward inducing remission and has been recently approved for treatment of both UC and CD in adults [68, 69]. Currently, pediatric data with the use of vedolizumab is limited to abstract presentations.

Toxicity and Risk

It is known that both immunomodulators and anti-TNF therapies have potential risks of toxicity and these are of particular concern in pediatric patients. The risks of chronic thiopurine toxicity are being increasingly recognized. Bone marrow suppression, hepatotoxicity, and infectious risks including viral, bacterial, and opportunistic have been previously well described [70]. More recent publications have described the risk of hemophagocytic lymphohistiocytosis (HLH) and EBV associated lymphoproliferative disorders, especially in association with primary EBV infection in patients treated with thiopurines [71, 72]. Lymphoma risk with thiopurines is also greatest in patients <30 years having a standardized incidence ratio of 6.99 (95 % CI 2.99–16.4). The risk in males appears greater than females [73].

Of particular concern in pediatrics, especially in males, is the decision regarding whether combination therapy with anti-TNF and thiopurines is contraindicated. This dilemma stems from the association of hepatosplenic T cell lymphoma (HSTCL) occurring in young patients (primarily males) treated with concomitant therapy [74]. No cases of HSTCL have been noted in adult or pediatric patients treated with infliximab monotherapy, however, in nearly all cases of HSTCL, the unifying drug exposure has been thiopurines.

Given the predilection of this invariably fatal lymphoma for young males, most pediatric gastroenterologists do not use combined anti-TNF/thiopurine therapy in young male patients. If there is a need to use combined therapy, methotrexate has become the immunomodulator of choice in low dosage to decrease anti-infliximab antibody production. No consensus exists as to whether young females can or cannot be treated with combined therapy with thiopurines and anti-TNFα agents as HSTCL has rarely been reported in females as well [74] . The recently described improved durability of infliximab when used in combination with MTX

provides a promising alternative to combination therapy with thiopurines or treatment with anti-TNF monotherapy [66].

Enteral Nutritional Support

There is considerable variation in the frequency with which primary enteral nutrition is used as an induction strategy in children newly diagnosed with Crohn's disease. While commonly used in Europe, it is utilized much less frequently in most of North America despite its favorable side effect profile, positive impact upon growth/nutritional deficiencies and lack of toxicity risk. There are several older published trials comparing the relative efficacy of enteral nutrition versus corticosteroids and in whole there is fairly equivalent efficacy [75–77]. A recent prospective study compared 8 week outcomes in three groups of pediatric patients with active disease: anti-TNF therapy, exclusive enteral nutrition (EEN) or partial enteral nutrition (PEN). Improvement in mucosal inflammation was found to be superior for both the EEN and anti-TNF groups compared to PEN, thus adding further support for expanded use of this treatment approach [78].

There are situations in which enteral nutrition should be the initial intervention of choice including patients with primarily small bowel disease and growth failure. In these patients, primary enteral nutritional therapy can both induce remission and also reverse nutritional deficiencies and promote improved linear growth. A challenge unique to treatment with exclusive enteral therapy is to successfully motivate the child and family to maintain treatment by drinking the formula or using a nasogastric tube. In some patients enteral therapy has been used for several months initially to then be followed by scheduled periods of re-administration after allowing a regular diet [79]. For many patients who start primary enteral nutrition therapy, an immunomodulator is concomitantly initiated as the long-term maintenance strategy.

Severe/Fulminant Ulcerative Colitis

The management of fulminant colitis in children presents a particular challenge. Frequently these are children at or shortly following diagnosis when understanding of the disease itself may be limited, and a willingness to proceed to colectomy if necessary has not been established. A prospective study of children with fulminant ulcerative colitis has given additional insight into disease management in this situation. In this study, 126 children hospitalized with severe ulcerative colitis were followed for up to 1 year. Approximately one third failed therapy with intravenous steroids and required rescue with either infliximab, cyclosporine, or colectomy. The most sensitive predictor of the failure of intravenous corticosteroids was a PUCAI score of 45 or higher on day 3 of hospitalization. Overall 9 % and 19 % of children hospitalized with severe/fulminant colitis required colectomy by initial discharge or 1 year, respectively [80]. More recent studies have focused upon dose optimization with infliximab in treating acute severe UC (ASUC). A recent adult and pediatric review concluded that standard weight-base infliximab dosing may not be equally effective for ASUC. Potential contributors to the need for dose optimization in this population include high TNF burden, highly active reticuloendothelial system, and marked infliximab stool losses related to protein losing enteropathy [81]. Prospective studies will be needed to better understand targeted management with infliximab in pediatric ASUC.

Most pediatric gastroenterologists will use infliximab as their preferred rescue medication for corticosteroid failures, though some still prefer calcineurin inhibitors. Small case series have been published on the use of cyclosporine and tacrolimus for severe colitis in children [82, 83]. Though the results of these studies have suggested a delay in the need for colectomy following calcineurin inhibitor treatment, the overall long-term prognosis for avoiding colectomy is low. Failure of one of these agents should not lead to use of the other because of concerns of increased risk of serious infection. In the authors' view saving a life is more important than saving a colon. Results of colectomy and ileal pouch anal anastomosis (IPAA) in children are similar to those of adults. The issue of possible impaired fecundity later in life for adolescent girls who may be subject to IPAA should be raised before this procedure is done.

Summary

It is crucial that clinicians caring for children and adolescents with IBD be fully informed about the relationship of disease activity and therapy to growth and development, each of which need to be considered when planning various medical and surgical therapies. The balance between risks and benefits of therapies, especially regarding potential toxicities with thiopurine monotherapy and in combination with anti-TNF therapy is increasingly recognized.

References

1. Oliva-Hemker M, Hutfless S, Al Kazzi ES, Lerer T, Mack D, LeLeiko N, et al. Clinical presentation and five-year therapeutic management of very early-onset inflammatory bowel disease in a large north American cohort. J Pediatr. 2015.doi:10.1016/s0022-3476-00429-1.
2. Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr. 2003;143:525–31.

3. Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr. 2005;146:35–40.
4. Meinzer U, Ideström M, Alberti C, Peuchmaur M, Belarbi N, Bellaïche M, et al. Ileal involvement is age dependent in pediatric Crohn's disease. Inflamm Bowel Dis. 2005;11:639–44.
5. Mack D, Markowitz J, Lerer T, Griffiths A, Evans J, Otley A, et al. S1189 Upper gastrointestinal involvement in pediatric Crohn's disease: experience of a large multicenter inception cohort. Gastroenterology. 2010;138(5):S-200.
6. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114–22.
7. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, Tilloy E, Brazier F, Merle V, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104:2080–8.
8. Markowitz J, Kugathasan S, Dubinsky M, Mei L, Crandall W, Leleiko N, et al. Age of diagnosis influences serologic responses in children with Crohn's disease: a possible clue to etiology? Inflamm Bowel Dis. 2009;15:714–9.
9. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135:1106–13.
10. Dubinsky MC, Lin YC, Dutridge D, Picornell Y, Landers CJ, Farrior S, et al. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. Am J Gastroenterol. 2006;101:360–7.
11. Hyams JS, Davis P, Grancher K, Lerer T, Justinich CJ, Markowitz J. Clinical outcome of ulcerative colitis in children. J Pediatr. 1996;129:81–8.
12. Ruemmele FM, El Khoury MG, Talbotec C, Maurage C, Mougenot JF, Schmitz J, et al. Characteristics of inflammatory bowel disease with onset during the first year of life. J Pediatr Gastroenterol Nutr. 2006;43:603–9.
13. Benchimol E, Mack DR, Nguyen GC, Snapper SB, Li W, Mojaverian N, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. Gastroenterology. 2014;147:803–13.
14. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147:990–1007.
15. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361:2033–45.
16. Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12:439–47.
17. Hyams J, Markowitz J, Otley A, Rosh J, Mack D, Bousvaros A, et al. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. J Pediatr Gastroenterol Nutr. 2005;41:416–21.
18. Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflamm Bowel Dis. 2012;18:55–62.
19. Kappelman MD, Crandall WV, Colletti RB, Goudie A, Leibowitz IH, Duffy L, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. Inflamm Bowel Dis. 2011;17:112–7.
20. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133:423–32.
21. Bryant RV, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut. 2015. doi:10.1136/gutjnl-2015-309598.
22. Guardiola J, Lobatón T, Rodríguez-Alonso L, Ruiz-Cerulla A, Arajol C, Loayza C, et al. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. Clin Gastroenterol Hepatol. 2014;12:1865–70.
23. Theede K, Holck S, Ibsen P, Ladelund S, Nordgaard-Lassen I, Mertz Nielsen A. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing of ulcerative colitis. Clin Gastroenterol Hepatol. 2015. doi:10.1016/s1542-3565-00773-9.
24. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology. 1988;95:1523–7.
25. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. Nat Rev Gastroenterol Hepatol. 2009;6:513–23.
26. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis. 2008;14:839–49.
27. Motil KJ, Grand RJ. Nutritional management of inflammatory bowel disease. Pediatr Clin North Am. 1985;32:447–69.
28. Varghese S, Wyzga N, Griffiths AM, Sylvester FA. Effects of serum from children with newly diagnosed Crohn disease on primary cultures of rat osteoblasts. J Pediatr Gastroenterol Nutr. 2002;35:641–8.
29. Mauras N. Growth hormone therapy in the glucocorticosteroid-dependent child: metabolic and linear growth effects. Horm Res. 2001;56 Suppl 1:13–8.
30. Hyams JS, Moore RE, Leichtner AM, Carey DE, Goldberg BD. Relationship of type I procollagen to corticosteroid therapy in children with inflammatory bowel disease. J Pediatr. 1988;112:893–8.
31. Allen DB. Influence of inhaled corticosteroids on growth: a pediatric endocrinologist's perspective. Acta Paediatr. 1998;87:123–9.
32. Pfefferkorn M, Burke G, Griffiths A, Markowitz J, Rosh J, Mack D, et al. Growth abnormalities persist in newly diagnosed children with Crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr. 2009;48:168–74.
33. Brody AS, Frush DP, Huda W, Brent RL. Radiation risk to children from computed tomography. Pediatrics. 2007;120:677–82.
34. Brenner DJ, Sachs RK. Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach. Radiat Environ Biophys. 2006;44:253–6.
35. Mazrani W, McHugh K, Marsden PJ. The radiation burden of radiological investigations. Arch Dis Child. 2007;92:1127–31.
36. Giles E, Barclay AR, Wilson DC, Chippington S. Systematic review: MRI enterography for assessment of small bowel involvement in paediatric Crohn's disease. Aliment Pharmacol Ther. 2013;37:1121–31.
37. Markowitz J, Hyams J, Mack D, Leleiko N, Evans J, Kugathasan S, et al. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol. 2006;4:1124–9.
38. Hyams J, Markowitz J, Lerer T, Griffiths A, Mack D, Bousvaros A, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. Clin Gastroenterol Hepatol. 2006;4:1118–23.
39. Levine A, Weizman Z, Broide E, Shamir R, Shaoul R, Pacht A, et al. A comparison of budesonide and prednisone for the treatment of

active pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2003;36:248–52.
40. Escher JC. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. Eur J Gastroenterol Hepatol. 2004;16:47–54.
41. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology. 2000;119:895–902.
42. Boyle BM, Kappelman MD, Colletti RB, Baldassano RN, Milov DE, Crandall WV. Routine use of thiopurines in maintaining remission in pediatric Crohn's disease. World J Gastroenterol. 2014;20:9185–90.
43. Riello L, Talbotec C, Garnier-Lengliné H, Pigneur B, Svahn J, Canioni D, et al. Tolerance and efficacy of azathioprine in pediatric Crohn's disease. Inflamm Bowel Dis. 2011;17:2138–43.
44. Goodhand JR, Tshuma N, Rao A, Kotta S, Wahed M, Croft NM, et al. Do children with IBD really respond better than adults to thiopurines? J Pediatr Gastroenterol Nutr. 2011;52:702–7.
45. Panés J, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, Torres Y, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology. 2013;145:766–74.
46. Cosnes J, Bourrier A, Laharie D, Nahon S, Bouhnik Y, Carbonnel F, et al. Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. Gastroenterology. 2013;145:758–65.
47. Turner D, Grossman AB, Rosh J, Kugathasan S, Gilman AR, Baldassano R, et al. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol. 2007;102:2804–12.
48. Uhlen S, Belbouab R, Narebski K, Goulet O, Schmitz J, Cézard JP, et al. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. Inflamm Bowel Dis. 2006;12:1053–7.
49. Sunseri W, Hyams JS, Lerer T, Mack DR, Griffiths AM, Otley AR, et al. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. Inflamm Bowel Dis. 2014;20:1341–5.
50. Turner D, Doveh E, Cohen A, Wilson ML, Grossman AB, Rosh JR, et al. Efficacy of oral methotrexate in paediatric Crohn's disease: a multicentre propensity score study. Gut. 2014. doi:10.1136/gutjnl-2014-307964.
51. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132:863–73.
52. de Ridder L, Rings EH, Damen GM, Kneepkens CM, Schweizer JJ, Kokke FT, et al. Infliximab dependency in pediatric Crohn's disease: long-term follow-up of an unselected cohort. Inflamm Bowel Dis. 2008;14:353–8.
53. Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Kugathasan S, Evans J, et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. Inflamm Bowel Dis. 2009;15:816–22.
54. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320–9.
55. Singh N, Rosenthal CJ, Melmed GY, Mirocha J, Farrior S, Callejas S, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2014;20:1708–13.
56. Zitomersky NL, Atkinson BJ, Fournier K, Mitchell PD, Stern JB, Butler MC, et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. Inflamm Bowel Dis. 2015;21:307–14.
57. Rosh JR, Lerer T, Markowitz J, Goli SR, Mamula P, Noe JD, et al. Retrospective evaluation of the safety and effect of adalimumab therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol. 2009;104:3042–9.
58. Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion Jr WA, Colletti RB, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012;143:365–74.
59. Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Stephens M, Evans J, et al. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol. 2010;105:1430–6.
60. Hyams J, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391–9.
61. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–95.
62. Lichtenstein GR, Diamond RH, Wagner CL, Fasanmade AA, Olson AD, Marano CW, 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.
63. Feagan BG, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology. 2014;146:681–8.
64. Dubinsky MC, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, et al. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. Clin Gastroenterol Hepatol. 2008;6:1105–11.
65. Walters TD, Kim MO, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. Gastroenterology. 2014;146:383–91.
66. Grossi V, Lerer T, Griffiths A, LeLeiko N, Cabrera J, Otley A, et al. Concomitant use of immunomodulators affects the durability of infliximab therapy in children with Crohn's disease. Clin Gastroenterol Hepatol. 2015. doi:10.1016/s.1542-3565-00412-7.
67. Hyams JS, Wilson DC, Thomas A, Heuschkel R, Mitton S, Mitchell B, et al. Natalizumab therapy for moderate to severe Crohn disease in adolescents. J Pediatr Gastroenterol Nutr. 2007;44:185–91.
68. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
69. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
70. Warman JI, Korelitz BI, Fleisher MR, Janardhanam R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. J Clin Gastroenterol. 2003;37:220–5.
71. James DG, Stone CD, Wang HL, Stenson WF. Reactive hemophagocytic syndrome complicating the treatment of inflammatory bowel disease. Inflamm Bowel Dis. 2006;12:573–80.
72. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374:1617–25.
73. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13:847–58.
74. Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, 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.

75. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr. 2000;31:8–15.
76. Sanderson IR, Udeen S, Davies PS, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. Arch Dis Child. 1987;62:123–7.
77. Ruuska T, Savilahti E, Maki M, Ormala T, Visakorpi JK. Exclusive whole protein enteral diet versus prednisolone in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr. 1994;19:175–80.
78. Lee D, Baldassano RN, Otley AR, Albenberg L, Griffiths AM, Compher C, et al. Comparative effectiveness of nutritional and biological therapy in North American children with active Crohn's disease. Inflamm Bowel Dis. 2015;21:1786–93.
79. Belli DC, Seidman E, Bouthillier L, Weber AM, Roy CC, Pletincx M, et al. Chronic intermittent elemental diet improves growth failure in children with Crohn's disease. Gastroenterology. 1988;94:603–10.
80. Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology. 2010;138:2282–91.
81. Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. Aliment Pharmacol Ther. 2015;41:1094–103.
82. Treem WR, Cohen J, Davis PM, Justinich CJ, Hyams JS. Cyclosporine for the treatment of fulminant ulcerative colitis in children. Immediate response, long-term results, and impact on surgery. Dis Colon Rectum. 1995;38:474–9.
83. Bousvaros A, Kirschner BS, Werlin SL, Parker-Hartigan L, Daum F, Freeman KB, et al. Oral tacrolimus treatment of severe colitis in children. J Pediatr. 2000;137:794–9.