Inflammatory Bowel Disease in Pediatrics

Jason M. Shapiro, MD, David Kawatu, MD, Barbara Bancroft, MS, RN, and Neal LeLeiko, MD, PhD

Crohn's disease (CD) and ulcerative colitis (UC) are chronic diseases characterized by unpredictable periods of disease activity and quiescence. Some patients suffer from almost continuous symptoms, others, only rare flares of disease activity. In addition to affecting the daily lives of patients, these diseases can dramatically alter family functioning and the patient's opportunity for becoming a productive adult. As difficult as it may be to manage adults with the disease, the problem of managing childhood disease is made more challenging by children's growth, their emotional and social development, and the knowledge that even after 30 years of complications of the disease and therapies, pediatric patients may just be entering the prime of their productive years. The difficult task of eventually transitioning the adolescent to adult health care providers presents additional challenges.

Current management practices are based on the use of old and new medications neither rigorously tested nor approved for use in children. In an effort to better define the contemporary natural history of IBD in children and augment current management practices, the Pediatric Inflammatory Bowel Disease Research Registry was established in 2002. Initially a collaboration of 21 centers in the US and Canada, this registry has produced several important advances in our understanding of IBD in children. Much of that research is reported in this review. The focus of this paper is to review current advances in pediatric IBD and to emphasize the need for more prospective research.

IBD in the Pediatric Patient

CD is diagnosed most frequently in patients in their 20s and UC more commonly presents in patients in their 30s. Approximately 10% to 25% of IBD cases are diagnosed before adulthood.[1] Data suggest that presentation in childhood confers a risk of more extensive disease. In a study comparing phenotypic expression of disease, younger children (less than 5) tended to present with isolated colonic disease while those ages 6-17 demonstrated a statistically significant increase in small bowel involvement, predominantly ileocolonic in nature. Furthermore, older children had a more complicated disease course with increased risk for the development of an abscess, fistula, or stricture. While medical management of IBD is preferred, children with extensive disease are at risk for surgical interventions such as intestinal resection. In a retrospective study using data from six IBD centers, Gupta et al. observed surgical rates of 5.7% at one year, 17% at five years and 28.4 % at ten years in pediatric CD.[2] Prospective data from the Pediatric IBD Registry showed a 5% rate of Crohn's related surgery at 1 year and 13% at 4 years.[3] Thus, although treatment of CD primarily is medical, many patients will require surgery at some point.

Communication with the child's school can be as important an intervention as providing medication.

Clinical Presentation

The clinical presentation of IBD typically involves chronic abdominal pain accompanied by some combination of weight loss, diarrhea, or hematochezia. (Table 1) Additionally, some patients may present with (or later develop) extra-intestinal manifestations. (Table 2) In the pediatric population, malnutrition, growth failure, and pubertal delay can be a significant component of disease presentation and morbidity. Between 25-80% of children newly diagnosed with CD will present with some degree of linear growth impairment. This may be attributed to sub-optimal oral intake, chronic inflammation and protein-losing enteropathy. The effects of corticosteroid treatment and chronically elevated inflammatory cytokines may further impair growth. Population trends towards a higher body mass index in children can complicate or delay the diagnosis of IBD in children. Registry data examining BMI in children with newly diagnosed IBD show that 10% of children with newly diagnosed CD and 30% with UC were categorized as overweight.[4]

Laboratory Assessment

Laboratory evaluation of a patient with suspected IBD tends to focus on signs of chronic disease; e.g., microcytic anemia or hypoalbuminemia, as well as acute phase reactants such as ESR, **C-reactive protein (CRP)**, and thrombocytosis. These tests can establish the presence of an inflammatory illness. Recent IBD consortium data show that among children presenting with mild (more diagnostically challenging) disease, normal laboratory values (hemoglobin, platelet count, albumin,and ESR) were present in 21% of patients with mild CD and 54% with mild UC.[5] This suggests that the diagnosis of IBD should still be pursued in the patient with a clinical presentation consistent with IBD but with normal laboratory values.

Measurement of Disease Activity

Pediatric gastroenterologists have used the subjective **Physicians Global Assessment (PGA)** for many years. For both clinical application and research purposes, objective quantitative tools to measure disease activity are crucial. Objective assessment of disease activity in children with CD now includes evaluation of pubertal status and the **Pediatric Crohn's Disease Activity Index (PCDAI)**. Assessment of pubertal status is performed clinically by assessing the appearance of secondary sex characteristics. The standard measurement used by pediatricians is the Tanner Stage, based on physical exam findings that focus on gender-specific changes that occur during breast, gonadal, and pubic hair development. A consensus of pediatric IBD experts developed the PCDAI in 1990; it was subsequently validated at 12 North American institutions. In comparison to the (adult) CDAI, the PCDAI decreases the importance given to subjective historical items adding instead height velocity, and adds ESR and albumin to the laboratory measurements. The PCDAI score can range from 0-100: a score

Table 1 Symptoms at the time of diagnosis of IBD in Children < 18

Sign/Symptom	Crohn's Disease	Ulcerative Colitis
Abdominal Pain	72-86%	~60%
Diarrhea	56-80%	~87%
Rectal Bleeding	22-49%	~92%
Growth failure*	25-88%	15-25%
Weight Loss	22-59%	~46%
Fever	~44%	~30%
Perianal skin tags[17]	5%	N/A
Perianal disease (fistula, fissures)[17]	10%	N/A
Arthralgia	8-17%	~8%
Skin or eye complaints	1-8%%	~4%

(adapted from numerous sources)

of <10 distinguishes inactive vs. active disease; 10-30 = mild disease; > 30 = moderate-severe disease. A decrease of 12.5 points is taken as evidence of improvement.

The PCDAI has been further validated along with the **physician global assessment (PGA)** in multi-center trials.[6] The study concluded that the PCDAI accurately reflects disease activity and is an appropriate tool for intervention trials in CD in children. The PCDAI is able to show short term (3 month) changes in patient condition, even though the growth velocity is unlikely to change over 3 months. In long-term trials, changes in growth parameters would be reflected in the PCDAI rather than the CDAI. The PCDAI has become the standard for quantifying pediatric CD activity.

The recently validated **Pediatric Ulcerative Colitis Activity Index (PUCAI)** is used to quantify changes in disease activity in children with UC.[7] The PUCAI assesses bowel frequency, consistency, presence of blood, nighttime diarrhea and limitation of normal activities. It does not rely on any laboratory findings

Psychosocial Aspects of Disease

Symptomatic disease can result in frequent, sometimes prolonged hospitalizations requiring school absence. Some children face frequency and urgency to move their bowels, an embarrassing situation if they are unable to access a private restroom at school. Communication with the child's school can be as important an intervention as providing medication.

Furthermore, recent data suggest that adolescents may have less than 50% adherence to IBD drug regimens.[8] While the younger child may focus on symptomatic complaints, teenagers often struggle with regimented medication schedules and the social implications of chronic steroid exposure (i.e. cushingoid features and facial acne). A diagnosis of IBD in the pediatric patient has the potential to have devastating effects on quality of life.

In evaluating **health-related quality of life (HRQOL)** in the first year after diagnosis, the pediatric IBD registry administered a validated questionnaire (IMPACT II) to 218 patients over the age of nine. Initial assessment demonstrated expected significant differences between those presenting with mild, moderate and severe disease phenotypes. However, re-evaluation at 6 months and again at 1 year demonstrated statistically significant improvements in HRQOL overall.[9] These data stressed the importance of successful induction and maintenance of remission. The challenge is finding the balance between aggressive disease management and acceptable risk to the patient.

IBD Management in the Pediatric Patient

While generally the goals of managing IBD in children and adults are similar, there are important differences, based on the developmental stages of the patient. Therapeutic goals focus on achieving symptomatic control and mucosal healing; however, the ultimate challenge and underlying responsibility of the pediatric practitioner is ensuring that the child live as normal a life as possible and eventually become a productive member of adult society. Medications used for medical management are summarized in Table 3 (medications discussed in detail in previous issue by Harris et al).

Mild disease is generally treated with 5-aminosalicylate compounds. Antibiotics may also be employed. While these medications are considered less potent and often well tolerated, they are not without side effects. Clearly the child on chronic antibiotics is at risk for development of resistant organisms and infection with toxigenic strains of *Clostridium difficile* as well as fungal infections. For distal disease (proctitis) topical therapy is available in the form of steroid enemas and mesalamine enemas, foams and suppositories. Despite effectiveness in some

Table 2 Extraintestinal Manifestations of Inflammatory Bowel Disease

Site	Manifestation
Skin	Erythema nodosum, pyoderma gangrenosum, metastatic Crohn's disease (especially around mucous membranes)
Liver	Steatosis, nonspecific transaminitis, chronic hepatitis, sclerosing cholangitis, cholelithiasis, acalculous cholecystitis, Budd-Chiari syndrome
Bone	Osteopenia, aseptic necrosis
Joint	Arthralgias, arthritis, ankylosing spondylitis, sacroiliitis
Eye	Uveitis, episcleritis, keratitis,glaucoma (2° to steroids)
Uro-gynecologic	Nephrolithiasis, obstructive hydronephrosis, enterovesical fistula, recto-vaginal fistula, nephritis, amyloidosis
Hematologic	Anemia (iron, folate, B12, autoimmune hemolytic), thrombocytosis, thrombocytopenia
Vascular	Hypercoagulability (thrombosis, thrombophlebitis, portal vein thrombosis, sinus vein thrombosis)
Pancreas	Pancreatitis
Other	Growth delay/failure, pubertal delay, menstrual irregularities, increased risk of colonic malignancy with chronic inflammation,(lymphoma 2° to meds)

Table 3 Commonly used Pharmacologic Therapy of Inflammatory Bowel Disease in Children (note * denotes not an approved use for children)

Medications	Indications	Complications
Aminosalicylates (*mesalamine)	Mild-to-moderate UC, mild Crohn's colitis, or mild distal small bowel disease	Rash, headache, vomiting, dyspepsia, bloody stools, pancreatitis, alopecia
Corticosteroids (*prednisone, *budesonide)	Budesonide: Mild-to-moderate distal small bowel and proximal colon (CD); Prednisone: moderate-to-severe UC or CD	Cushingoid facies, growth suppression, osteopenia, hypertension, acne, potential adrenal crisis if not appropriately weaned
Antibiotics (*metronidazole, *ciprofloxacin, *cephalexin)	Perirectal fistula, abscess pouchitis (CD), bacterial overgrowth	Diarrhea, c. difficile, development of resistant organisms
Immunomodulators (*6-mercaptopurine, *azathioprine, *methotrexate)	Severe small or large bowel disease, steroid-dependent or refractory disease, severe fistula, growth failure (CD or UC)	Bone marrow suppression, pancreatitis, hepatitis, infection
Biologic therapy (*infliximab, *adalumimab *certolizumab pegol)	Steroid-dependent or refractory CD, perirectal fistulae, maintenance of remission	Hypersensitivity reactions, infection, autoimmune disease

*= FDA approved for children > 6

situations, young children and teens may resist rectally instilled medications.

The next line of therapy typically involves systemic steroids. Pediatric IBD Registry data show that in children with CD 84% have a complete or partial response to steroids, but even with the addition of immunomodulators, at one year 31% were corticosteroid-dependent and 8% had required surgery.[10] In children with UC treated with corticosteroids, disease activity at three months was inactive or mild-moderate in 87%. At one year 50% were considered steroid-responsive; however, 45% were corticosteroid dependent and 5% had colectomies.[11]

Prolonged exposure to steroids is unacceptable in children. Use of immunomodulators such as 6-MP are well studied and effective as maintenance therapy, but also present a set of risks and disadvantages. As the onset of action is typically 4-6 months, the patient with moderate-to-severe disease often requires additional therapies while awaiting clinical response. In addition, monitoring is required as 6-MP metabolites can result in hepatoxicity, pancreatitis and bone marrow suppression. Prior to initiating therapy, TPMT (Thiopurine s-methyltransferase) genetic profiles are obtained to assess the activity of the enzyme responsible for 6-MP metabolism. A study in 2000 demonstrated a statistically significant response to early introduction of 6-mercaptopurine versus placebo in 55 pediatric patients recently diagnosed with CD. Specifically, researchers concluded that early introduction of 6-MP therapy achieved and maintained a much higher rate of steroid-free remission.[12] A recent follow-up study from the Pediatric IBD registry demonstrated a decrease in both steroid use and number of hospitalizations in patients with moderate to severe CD started on immunomodulators within the first year of diagnosis.[13]

Prolonged exposure to steroids is unacceptable in children.

The "biological" therapies represent the next level of medical management of IBD. The principle biological agents are monoclonal antibodies against the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha). These medications offer much potential benefit to the steroid-dependent or refractory patient.[14] The major concern is immunosuppression and risk of secondary infections. The appropriate role of biological agents (infliximab, adalimumab as well as newer agents) is the subject of active and ongoing study. Of concern, however, are reports of lymphoproliferative disease such as the highly fatal hepatosplenic T-cell lymphoma associated with infliximab exposure. The majority of the reported cases involved patients who were receiving concomitant therapy with immunomodulators such as 6-MP or systemic steroids. Thus, the true long-term risks of lymphoma and other malignancies in children receiving TNF inhibitors are unknown (but are generally estimated at about 1:1000 medication recipients).

With no definitive way to manage the child with IBD, there is marked variability among centers. Kappelman et al. demonstrated statistically significant inter-center variation in utilization of the five classes of medications most commonly used to manage pediatric CD (immunomodulators, steroids, antibiotics, 5-ASA compounds, and biologics such as infliximab).[15] An underlying theme in these management strategies is minimizing exposure to corticosteroids. While treatment must be individualized, so far differences in outcome have not been associated with the different approaches.

Ongoing Research

Today, optimal care for children with IBD requires a multi-disciplinary team of physicians, nurses, clinical nutritionists, social workers, and child psychologists. Current research efforts are trying to address the lack of understanding of the natural history of IBD in the child as well as the role of the newest therapies (as well as many of the old standby therapies). This can be especially challenging since most therapies have never been specifically approved for use in the pediatric age group. The pediatric IBD registry follows over 1000 children with IBD. In the first 5 years since its inception in 2002, this consortium has been responsible for several major research papers[3-5, 9-11, 13, 15-17] describing aspects of the natural history of IBD. The division of Pediatric Gastroenterology at Hasbro Children's Hospital has enrolled over 90 patients and is the second largest contributor to the registry. Most recently the Ocean State Crohn's

and Colitis Area Registry study has been launched in Rhode Island (OSCCAR). OSCCAR is a prospective study of an inception cohort of newly diagnosed adult and pediatric patients in Rhode Island (see previous issue, "introduction to OSCCAR"). OSCCAR promises to provide a wealth of new and exciting information into the natural history of IBD. Taken together, OSCCAR and the Pediatric Collaborative Research Consortium will provide new insights into IBD epidemiology, genomics, metabolomics, microbiology, pathophysiology and environmental determinants of disease susceptibility.

Future Directions

A consortium of pediatric IBD centers, including members of the IBD registry, recently reported that the rate of complicated CD increases in children as the number and magnitude of immune reactivity assays increase. Disease progression is significantly faster in children expressing immune reactivity.[16] Whether these results will have practical consequences remains to be seen. However, this could be a powerful indicator of one's future clinical course. As can be appreciated from this review, much of the newest data emphasize the role of studies such as the Pediatric IBD registry and OSCCAR. While both these studies are based on the biological determinants of disease, they lack focus on the equally important psychological components. Establishment of a prospective behavioral health registry that will provide knowledge from an integrated biopsychosocial model perspective is anticipated in the near future. Thus, the ongoing analysis of prospectively acquired data promises to provide much insight into the natural history of IBD and inform us about the most effective therapeutic strategies.

References

1. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Practice & Res Clin Gastroenterol* 2002;18:509-23.
2. Gupta N, Cohen SA, et al. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterol* 2006; 130:1069-77.
3. Schaefer ME, Hyams J, et al. Surgery in a prospectively followed cohort of pediatric patients with Crohn's Disease. *Gastroenterol* 2008;134, Supplement 1: A-498.
4. Kugathasan S, Nebel J, et al. Body mass index in children with newly diagnosed inflammatory bowel disease. *J Pediatr* 2007; 115:523-7.
5. Mack DR, Langton C, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. *Pediatrics* 2007; 119:1113-9.
6. Hyams J, Markowitz J, , et al. Evaluation of the pediatric crohn disease activity index. *J Pediatr Gastroenterol Nutr* 2005; 41:416-21.
7. Turner D, Otley AR, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index. *Gastroenterol* 2007; 133:423-32.
8. Mackner LM, Crandall WV. Oral medication adherence in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:1006-12.
9. Otley AR, Griffiths AM, et al. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2006;12:684-91.
10. Markowitz J, Hyams J. Corticosteroid therapy in the age of infliximab. *Clin Gastroenterol Hepatol* 2006;4:1094-6.
11. Hyams J, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol* 2006;4:1118-23.
12. Markowitz J, Grancher K, et al. A multicenter trial of 6-mercaptopurine with prednisone in children with newly diagnosed Crohn's disease. *Gastroenterol* 2000;119:895-902.
13. Punati J, Markowitz J, et al. Effect of early immunomodulator use in moderate to severe Crohn disease. *Inflamm Bowel Dis* 2008;14:949-54.
14. Hyams J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterol* 2007;132:1167-70.
15. Kappelman MD, Bousvaros A, et al. Intercenter variation in initial management of children with Crohn's disease. *Inflamm Bowel Dis* 2007; 13:890-5.
16. Dubinsky MC, Kugathasan S, et al. Western Regional Pediatric IBD Research Alliance; Pediatric IBD Collaborative Research Group; Wisconsin Pediatric IBD Alliance. *Clin Gastroenterol Hepatol.* 2008;6:1105-11. Epub 2008 Jul 10
17. Keljo DJ, Markowitz J, et al. Pediatric Inflammatory Bowel Disease Collaborative Research Group. *Inflamm Bowel Dis*.2008 Nov 20. [Epub ahead of print]

Jason M. Shapiro, MD, is a Fellow, Pediatric Gastroenterology, Nutrition and Liver Disease, Hasbro Children's Hospital/ Rhode Island Hospital.

David Kawatu, MD, is Assistant Professor, The Warren Alpert Medical School of Brown University, and Director, Pediatric GI Fellowship Training Program, Hasbro Children's Hospital/Rhode Island Hospital.

Barbara Bancroft, MSRN, is a Research Nurse Coordinator, Pediatric Gastroenterology, Nutrition & Liver Disease, Hasbro Children's Hospital/Rhode Island Hospital.

Neal S. LeLeiko MD, PhD, is Professor of Pediatrics, The Warren Alpert School Medical School of Brown University, and Director, Division of Pediatric Gastroenterology, Hasbro Children's Hospital/Rhode Island Hospital.

Disclosure of Financial Interests

The authors have no financial interests to disclose.

Correspondence

Jason M. Shapiro, MD
Hasbro Children's Hospital
593 Eddy Street
Providence, RI 02903
Phone: (401) 444-8306
e-mail:jshapiro@lifespan.org