Inflammatory bowel disease in early childhood and adolescence: special considerations

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The similarities between adult and pediatric patients diagnosed with inflammatory bowel disease (IBD) are obvious and numerous. In this article the authors describe some of the IBD features unique to the pediatric population. These features could potentially have significant impact both in research as well as clinical management of patients with IBD.

Epidemiologic data derived from studies in the pediatric population have a potential to enable us to develop better understanding of IBD etiology, especially environmental factors, as well as clinical features, which then may allow for prediction of natural disease course. The diagnosis of IBD in children comes often at a vulnerable time of growth and development. Despite the increased nutritional needs related to the rapid periods of growth during childhood and adolescence, many pediatric patients afflicted with IBD will paradoxically demonstrate decreased appetite, increased metabolism, and decreased absorptive capacity. Clinical presentation is often uncharacteristic, and environmental and genetic factors have a strong potential to influence the natural history of disease [1,2]. As a result, IBD may have profound effects on weight gain, linear growth, and bone mineralization, some of which may not be reversible. Additionally, delayed sexual development may have significant adverse effects on self-esteem and socialization. Beyond treating the overt symptoms of disease, therapy in children with IBD must be directed toward overcoming nutritional deficiencies to allow the
maximal potential for growth. These issues add a level of complexity to the management of a child or adolescent with IBD. Finally, there is the issue of health care transition to adult oriented health system. This issue was the main topic of several recent conferences that emphasized the need for a development of uniform guidelines designed to help both patients and their families, as well as health care providers through this process.

Epidemiology

IBD is recognized as one of the most significant chronic diseases to affect children and adolescents [3]. Pediatric IBD population-based epidemiological studies are sparse for several reasons: high cost; potential for surveillance error; and difficult execution because of the large number of patients needed, and the results are often difficult to compare because of different criteria and design [4,5]. In the United States most of the data come from large tertiary care centers with a potential for a bias because of referral practice.

Recognizing the need for a large pediatric IBD registry, which would allow for centralized data collection and would simplify execution of true epidemiological studies, a pediatric consortium of six IBD centers was formed. The goal for this registry is to grow into a nation-wide project and its potential is in providing relevant information relating to risk factors associated with IBD, true epidemiologic distribution and trends, clinical features, and natural history [6]. The pediatric population is ideal for this type of research for various reasons. Environmental factors potentially leading to IBD may occur early in life; modification of early environment may be attempted; patients with early onset disease tend to show more aggressive disease with a stronger genetic influence; and access to patient’s relatives is easier than in adult population [6]. Epidemiologic data on the age of onset of IBD in 1074 pediatric patients from pediatric consortium are presented in Fig. 1 [7]. Up to 31% of children in this series had a member of extended family with IBD, while 4% and 12% had a sibling, or parent with a history of IBD, respectively.

Overall, the sex distribution of IBD among children indicates slightly increased preponderance of Crohn’s disease (CD) in boys [8], while ulcerative colitis (UC) affects both sexes equally. At the Center for Pediatric IBD at The Children’s Hospital of Philadelphia the authors follow approximately 1100 children with IBD. The demographic data on a sample of 425 children seen at the main hospital site during the last 12 months supports previously noted distribution as presented in Table 1. The age distribution follows a bimodal pattern of incidence with the first peak in the second and third decades, and a smaller peak in the sixth decade [9–11]. Up to 30% of all patients with IBD are diagnosed during childhood [3]. Most recently, a well-designed pediatric epidemiologic study of IBD in the United States was performed [12]. Data were prospectively collected on 193 newly diagnosed patients with IBD in the
Fig. 1. Pediatric IBD Consortium Data.
state of Wisconsin since January of 2000. Surprisingly high incidence rate of 4.5 per 100,000 was found in Crohn’s disease while the incidence rate for ulcerative colitis was 2.2/100,000. This is in agreement with the impression that during the last several decades incidence of IBD is increasing, more so for CD than UC [10]. Analysis of time trends indicates a rapid rise in incidence of Crohn’s disease from the 1960s to 1980s with subsequent stabilization [13], although some studies indicate a continuing rise in recent years [4,10,14]. The incidence of ulcerative colitis showed a more stable pattern, although again with a tendency for an increase over the years [10,14]. Pediatric incidence studies from Europe indicate similar patterns of increased incidence for both types of IBD, although lower than in adults (Table 2) [5,15–27]. The incidence rates for pediatric IBD range from 0.2 to 8.5 per 100,000 for CD and 0.5 to 4.3 per 100,000 for UC.

A recent hypothesis regarding the etiology of IBD supports the multifactorial theory encompassing genetic predisposition, internal and external environmental influences, and immune system disorder [6]. Genetic factors are well recognized with a high rate of concordance between monozygotic twins (44.4%) compared with dizygotic twins (3.8%) [28], and frequent multiple family members [29]. Increased genetic influence in early onset CD, or perhaps genetic anticipation, may account for the fact that patients with CD below 20 years of age have a family history of this disorder in 30% of cases, while only 13% of patients diagnosed later have a family history. The newly discovered NOD2 gene associated with CD supports the interaction between genetic predisposition and the environment since this gene regulates immune responses to bacterial products [30,31]. Other studies evaluated environmental factors, housing with hot tap water and a separate bathroom, and low infant mortality rate coincide with the higher incidence of CD. These results may suggest that clean environments delay exposure to

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Crohn’s disease and indeterminant colitis (%)</th>
<th>Ulcerative colitis (%)</th>
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<tbody>
<tr>
<td>Male</td>
<td>204 (48)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Female</td>
<td>123 (29)</td>
<td>56 (13)</td>
</tr>
<tr>
<td>0–5 years old</td>
<td>12 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>6–9 years old</td>
<td>26 (6)</td>
<td>8 (2)</td>
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<tr>
<td>10–13 years old</td>
<td>69 (16)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>14–17 years old</td>
<td>136 (32)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>18–23 years old</td>
<td>84 (20)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>White</td>
<td>268 (63)</td>
<td>80 (19)</td>
</tr>
<tr>
<td>African American</td>
<td>43 (10)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Total number</td>
<td>327 (73)</td>
<td>98 (27)</td>
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enteric infections, resulting in failure of the normal immunologic maturation process necessary to develop oral tolerance later in life [32–34].

**Clinical presentation**

The presentation of IBD in children and adults depends on the disease location and the extent of inflammation [35]. The most commonly encountered gastrointestinal symptoms are abdominal pain and diarrhea. The list of presenting clinical features compiled from several studies is presented in Table 3 [3,15,36–43]. Abdominal pain can be located anywhere in the abdomen, although in patients with CD it occurs frequently in the right mid quadrant, whereas in patients with UC it is located in the lower abdomen. Diarrhea may be associated with blood in the stool, more so in UC. Other gastrointestinal symptoms include loss of appetite, weight loss, nausea, vomiting, and perianal disease. Features like growth and pubertal

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Time period</th>
<th>CD</th>
<th>UC</th>
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<tr>
<td>Langholz et al [15]</td>
<td>Denmark</td>
<td>1962–1987</td>
<td>0.2</td>
<td>2</td>
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<tr>
<td>Barton et al [17]</td>
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<td>1968–1983</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Olafsdottir et al [26]</td>
<td>Norway</td>
<td>1984–1985</td>
<td>2.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Hildebrand et al [18]</td>
<td>Sweden</td>
<td>1984–1985</td>
<td>1.3</td>
<td>3.2</td>
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<tr>
<td>Asling et al [16]</td>
<td>Sweden</td>
<td>1990–1998</td>
<td>3.8</td>
<td>2.1</td>
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<tr>
<td>Cosgrove et al [19]</td>
<td>United Kingdom (Wales)</td>
<td>1983–1988</td>
<td>1.3</td>
<td>0.7</td>
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<tr>
<td>Hassan et al [23]</td>
<td>United Kingdom (Wales)</td>
<td>1995–1997</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>RCPHC [27]</td>
<td>United Kingdom</td>
<td>1993–1995</td>
<td>1.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Sawczenko et al [22]</td>
<td>United Kingdom/R. of Ireland</td>
<td>1998–1999</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Tourtelier et al [21]</td>
<td>France</td>
<td>1994–1997</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Kugathasan et al [12]</td>
<td>United States</td>
<td>2000</td>
<td>4.5</td>
<td>2.2</td>
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<tr>
<th>Symptom</th>
<th>Crohn’s disease (%)</th>
<th>Ulcerative colitis (%)</th>
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<tr>
<td>Abdominal pain</td>
<td>62–95</td>
<td>54–76</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52–78</td>
<td>67–93</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>14–60</td>
<td>52–97</td>
</tr>
<tr>
<td>Weight loss</td>
<td>43–92</td>
<td>22–55</td>
</tr>
<tr>
<td>Fever</td>
<td>11–48</td>
<td>4–34</td>
</tr>
</tbody>
</table>
Delay may cause confusion during the diagnostic process especially if they are predominant. These topics will be discussed separately.

Delay in diagnosis of IBD in the pediatric population continues to be a concern, even with increasing incidence and heightened awareness of IBD. Mean delay for CD in children is reported to be between 7 to 11 months, in UC between 5 to 8 months, and in IC 14 months [21,37,44]. At the same time the delay in adult population is even longer and is measured in years [45]. The time lag between onset of symptoms and correct diagnosis of Crohn’s disease appears to be prolonged if the disease affects more proximal bowel, and if presenting symptoms do not include diarrhea. The diagnosis is particularly difficult when the presenting symptoms are uncharacteristic and consist mainly of extraintestinal manifestations.

**Extraintestinal manifestations**

Up to 35% of pediatric IBD patients in some series have at least one extraintestinal manifestation as a presenting sign [46,47]. Common symptoms in a series of pediatric IBD patients from Israel, included anorexia, joint complaints, and anemia [48]. See list below for extraintestinal manifestations seen in children with IBD. These manifestations may also be noted concurrently with, or after the diagnosis of IBD is made [46].

**Skin**
- Erythema nodosum
- Pyoderma gangrenosum
- Perianal disease
- Metastatic Crohn’s disease

**Mouth**
- Cheilitis
- Stomatitis
- Aphtae

**Liver**
- Primary sclerosing cholangitis
- Hepatitis
- Cholelithiasis

**Pancreas**
- Pancreatitis

**Kidney**
- Nephrolithiasis
- Obstructive hydronephrosis
- Enteroavesical fistula
- Urinary tract infection
- Amyloidosis

**Growth**
- Delayed growth
Delayed puberty
Bone
  Osteoporosis
Eye
  Uveitis
  Episcleritis
  Conjunctivitis
Lungs
  Pulmonary vasculitis
  Fibrosing alveolitis
Vascular
  Vasculitis
  Thrombosis (pulmonary, limb, cerebrovascular)
Joints
  Arthralgia
  Arthritis
  Ankylosing spondylitis
Blood
  Iron deficiency anemia
  Anemia of chronic disease
  Thrombocytosis
  Autoimmune hemolytic anemia
  Vitamin B12 deficiency
General
  Fever
  Fatigue
  Weight loss
  Anorexia

Skin manifestations include erythema nodosum and pyoderma gangrenosum. Erythema nodosum is more common in CD and affects 3% of pediatric patients with CD [49]. It is estimated that 75% of the patients with erythema nodosum ultimately develop arthritis [50]. Pyoderma gangrenosum, on the other hand, is more common in patients with UC and affects less than 1% of patients.

Mouth ulceration is the most common oral manifestation of IBD. It is more common in CD, frequently associated with skin and joint lesions, and together with skin and eye manifestations often parallels the activity of disease [36].

Ophthalmologic manifestations occur in about 4% of the adult population with IBD, but less frequently in children and adolescents with UC and CD [51]. The most common ocular findings are episcleritis and anterior uveitis.

Arthritis is the most common extraintestinal manifestation in children and adolescents, occurring in 7% to 25% of pediatric IBD patients [52].
The arthritis is usually transient, non-deforming synovitis, asymmetric in distribution, and involves the large joints of the lower extremities. In adults, the arthritis occurs when the disease is active, but in children the arthritis may occur years before any gastrointestinal symptoms develop [53].

Hepatobiliary manifestations in children may precede the onset of IBD, accompany active disease, or develop after surgical resection of all diseased bowel [54]. Hepatic manifestations include elevation of aminotransferases, chronic active hepatitis, granulomatous hepatitis, amyloidosis, fatty liver, and sclerosing cholangitis. Chronic active hepatitis develops in less than 1% of children with IBD [55]. Colitis at the time may be asymptomatic, although the hepatitis may proceed to cirrhosis. Sclerosing cholangitis develops in 3.5% of pediatric patients with UC, usually with extensive disease, and less than 1% of pediatric patients with CD [55]. In a series of 36 pediatric patients with IBD who developed sclerosing cholangitis only four had CD and 32 had UC [56]. The authors suggest heightened endoscopic surveillance once the diagnosis of IBD is made in the setting of sclerosing cholangitis since the time to dysplasia may be accelerated, as noted in three pediatric patients who underwent proctocolectomy because of dysplasia. Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography have significantly improved the ability to diagnose this disease in the pediatric population.

The urologic manifestations of IBD include nephrolithiasis, hydronephrosis, and enterovesical fistulae. Nephrolithiasis is a common renal complication in pediatrics, and occurs in approximately 5% of the children with IBD [3]. It usually is the result of fat malabsorption that occurs with small bowel CD. Dietary calcium binds to malabsorbed fatty acids in the colonic lumen and free oxalate is absorbed. This results in hyperoxaluria and oxalate stones [57]. In patients with an ileostomy, increased fluid and electrolyte losses may lead to a concentrated, acidic urine and the formation of uric acid stones. External compression of the ureter by an inflammatory mass or abscess may lead to hydronephrosis. Enterovesical fistulae, which are more common in males, may present with recurrent urinary tract infections or pneumaturia.

Thromboembolic disease is a rare but severe complication of IBD. Both UC and CD are thought to be associated with a pro-thrombotic state with enhanced parameters of coagulation [58]. Several different coagulation abnormalities have been reported in patients with IBD, imparting an increased risk for thrombotic vascular disease over the general population: increased fibrinogen, thrombocytosis and abnormal platelet activation, accelerated thromboplastin generation, elevation of factors V and VIII, decreased antithrombin III, protein S and C deficiency, elevated anticardiolipin antibodies, high plasma factor VII coagulant activity, resistance to activated protein C, and prothrombin gene mutation (G20210) [59–61]. Thromboembolic complications are reported in 1.3% to 6.4% of pediatric patients with IBD [58,60]. In the adult population, pulmonary, abdominal,
and peripheral veins and arteries are more commonly involved than cerebral or retinal vessels. In pediatric IBD patients, cerebral and retinal vessels seem to be affected more frequently than other sites, and thrombosis in these sites carries a better prognosis than in adults. Most patients have active disease at the time of the thromboembolic event, more so in children than in the adult population.

Other extraintestinal manifestations may develop because of the side effects of treatment. Those include pancreatitis, pericarditis, alopecia, osteoporosis, cataracts, acne, hepatitis, anemia, neutropenia, fibrosing alveolitis, interstitial pneumonitis, and peripheral neuropathy. For example, pancreatitis may result from therapy with 5-aminosalicylic acid, 6-mercaptopurine, corticosteroids and methotrexate; and peripheral neuropathy may occur with metronidazole therapy, whereas corticosteroid therapy is associated with acne, cataracts, and osteoporosis.

Disease distribution and natural history of IBD in children versus adults

The anatomic distribution of IBD is an important clinical feature, which when thoroughly documented and described allows for improved comparisons of response to therapy and natural history among reported studies.

**Crohn’s disease**

In 139 adult patients with CD at the time of diagnosis 27% had small bowel, 28% large bowel, and 43% ileocolic disease [62]. The extent of disease progressed with time and, eventually 75% of patients had ileocolic disease, whereas 88% underwent at least one operation. Pooled data of 14 pediatric studies with a total of 1153 children with CD revealed isolated small bowel disease in 38%, small bowel and large bowel in 38% and large bowel alone in 20% of cases [63]. In children 10 years of age and younger 40% had ileocolonic disease, which over time increased to 60%, and 43% of patients required surgery [39]. In the authors series of children 5 years of age and younger, isolated small bowel disease was seen in 11%, small bowel and large bowel in 59%, and isolated large bowel disease in 30% of cases [64]. Perianal disease is seen in 11% to 18% of children with CD [8,65], while in children younger than 5 years of age the documented rate was significantly higher at 34%, similar to adult rate of 36% to 46% [64,66–71]. Upper gastrointestinal CD is seen in 30% to 40% of children, while endoscopic studies have shown even higher rates of up to 80% [3,72,73].

The studies of natural course of CD in adults more likely indicate a benign course if patients stay in remission in the year after diagnosis [74]. However, predicting the course is difficult until 2 years into the course of disease [75]. Early age at diagnosis was shown to be associated with more complicated disease in adults [11], although a more recent study indicated that age had no
influence on change of location or behavior of the disease [76]. Studies on the 
natural course of disease in children with CD are lacking. In one study 
children with ileal disease had a better prognosis than ones with ileo-colonic 
disease [49]. In a series of 100 consecutively diagnosed prepubertal patients 
from Toronto, one third had mild disease never requiring corticosteroid 
therapy, and one third had at least one exacerbation requiring corticosteroids 
[77]. An additional 19% of patients had chronically active disease, but 
achieved sustained remission with the use of immunomodulatory or surgical 
therapy, and 10% of patients had chronically active steroid-dependent, or 
steroid-refractory disease. In the same series, 36% of patients required 
surgical therapy, which is significantly less than reported in earlier studies 
[78,79]. The proportion of pediatric patients with CD requiring surgery was 
28% in a recent study and it was shown to decrease over time, which was 
mainly attributed to advances in medical therapy [5]. After the year of 
diagnosis about 50% of patients with CD will be in a remission during any 
given year [15], and less than 1% of patients have only a single episode of 
disease activity [42].

In the series of 639 Swedish children with IBD, 8% of patients were 5 years 
of age and younger and almost half of these patients carried a diagnosis of 
indeterminate colitis (IC) [5]. The number of children diagnosed with IC is 
higher than that seen in the adult population. In a large multi-center adult 
study in Europe, 5% of adult patients were diagnosed with IC and a similar 
proportion of 6% was seen in a series of 475 patients newly diagnosed with 
IBD in Netherlands [80]. In the pediatric series of older children, 14% to 
23% were diagnosed with IC [16,18,81]. In the authors’ experience with 
82 children diagnosed with IBD at 5 years of age and younger, 23% were 
diagnosed with IC [64]. Reasons for this difference are unclear, but one 
possible explanation is a longer duration of disease in adults with a better 
chance of establishing the specific diagnosis of CD or UC. Also, pediatric 
gastroenterologists have in the past exhibited a less aggressive approach to 
colonoscopy. During the period from 1984 to 1995 in the study of pediatric 
IBD by Lindberg et al [5], the percentage of diagnoses made by colonoscopy 
as opposed to rectosigmoidoscopy increased significantly from 50% during 
1984 to 1986 to 90% in 1995. With recent more extensive colonoscopy and 
histologic sampling of the terminal ileum, the proportion of children 
diagnosed with IC is likely to decrease.

Ulcerative colitis

In UC, the distribution of disease is categorized as distal disease (disease 
involving the rectum, or rectum and sigmoid colon), left-sided disease (disease 
extending beyond the recto-sigmoid region), and pancolitis (disease involv-
ing the whole large intestine). In a large cohort of 1116 adult patients the 
disease distribution was 63% with distal and left-sided colitis and 37% with 
pancolitis [82]. Data compiled from several studies indicated that 14%
to 37% of adult patients have pancolitis, 36% to 41% left-sided colitis, and 44 to 49% involve the rectum/sigmoid colon [9]. Barton et al [63] found that the distribution of disease in a group of 37 Scottish children with UC corresponded with seven additional studies in 357 aggregate patients. Proctitis was present in 22% of patients, left-sided colitis in 35%, and extensive disease or pancolitis in 43% of patients. Most recent pediatric epidemiologic study in 60 newly diagnosed patients with UC indicated high proportion of 90% of patients with pancolitis [12]. The course and prognosis of idiopathic ulcerative proctosigmoiditis was studied in 85 young patients whose symptoms had begun before the age of 21 and the results were compared with those in onset of similar disease as adults. The natural history of proctosigmoiditis in young patients was found to be somewhat different from that in adults, being characterized by a greater tendency to proximal extension (38% versus 10%). When the disease remained confined to the rectosigmoid region, the course and prognosis were no different than in adults. Extension of the disease was unpredictable in individual patients, but occurred in 73% of patients within 5 years from the onset of symptoms [83] in contrast to proximal extension that was noted in 27% of adult patients in a separate study [84].

In a study by Langholz et al [15] comparing clinical features and natural history of UC in Swedish children and adults, abdominal pain was more frequently found in children. The distribution of the disease was pancolitis in 29%, and proctitis in 25% of children, compared with 14% and 46% in adults, respectively. The cumulative colectomy rate after 20 years in childhood onset UC was 29%, which was the same as in adults. Extension of the disease was noted in 65% of the pediatric patients, and 70% of patients were in remission during 1 year. In a study at the Cleveland Clinic, pancolitis was seen in 63% of patients, left-sided colitis in 22%, and proctitis in 15% [85]. In the largest reported series of 171 children with UC, 22% had proctosigmoiditis, 36% left sided colitis, and 43% pancolitis [86]. Mild disease was initially seen in 43%, and moderate to severe in 57% of patients. Ninety percent of patients in the mild group had cessation of symptoms within 6 months, compared with 81% in the moderate to severe group. The response was independent of disease distribution and the overall 5-year risk for surgery was 19%. During any subsequent year of follow-up 55% of patients were symptom-free, 38% had chronic intermittent symptoms, and 7% had continuous symptoms. In their review Hofley and Piccoli [42] reported that 10% of children had only a single episode, 20% had intermittent symptoms, 50% had chronic symptoms but were not incapacitated, and 20% had incapacitating disease. Ten percent of patients had fulminant colitis defined as less than 6 bloody bowel movements, abdominal tenderness, fever, weight loss, anemia, leukocytosis, and low albumin.

Disease in patients with early onset of UC has been reported to have variable courses. In young children (< 10 years of age) with UC 11% of patients had severe, 37% moderate, and 53% mild disease [87]. Eventually
89% had total colonic disease within 2 to 10 years of the disease, from 75% at the presentation. An early study indicated that mild disease at presentation was usually followed by a mild course [88]. In the authors’ series of 36 children with UC less than 5 years of age, 60% had proctitis and left-sided disease, while 40% had pancolitis [64]. Four patients (11%) required colectomy. In a series of patients diagnosed with UC before the age of 20, 22% required surgery after a mean follow up of 18 years [89], whereas up to 73% of steroid dependent patients with pancolitis required the same [90].

Nutritional aspects of IBD

Treatment of children and adolescents with IBD is often based on experience first obtained in the adult population. Treatments become available in the adult population before the pediatric population, and many treatments never receive a formal pediatric indication. For many aspects of IBD, this is acceptable. However, there is a particular aspect of IBD for which there is no adult equivalent—the effects on growth and development.

It is widely accepted that IBD has significant effects on nutritional status. A combination of decreased intake and increased metabolic demands present an especially large burden for the body afflicted with IBD. The situation is exacerbated by the already increased nutritional demands to maintain normal growth and maturation. When IBD is active during critical periods of growth, it is extremely difficult to compensate for the increased demands with oral intake alone [91–93]. The effects of poor nutrition during childhood are long lasting, making the recognition and treatment of malnutrition a critical aspect for the care of children with IBD.

By the time most children are diagnosed with IBD, they are already malnourished to a degree. Up to 85% of children with CD, and as many as 65% of those with UC, will have growth failure at the time of diagnosis [94]. The earliest sign of growth failure may be decreased linear growth, with almost 90% of children and pre-pubertal adolescents demonstrating reduced height velocity before diagnosis, almost one-half of whom develop alterations in growth before the development of gastrointestinal symptoms [95].

Poor intake may be the most important contributor to malnutrition in IBD [3,96,97]. Several studies have documented that dietary intake is chronically deficient in most growth-retarded children with Crohn’s disease [93,98,99]. Nausea, abdominal pain, bloating, and diarrhea may cause patients with IBD to limit their intake. Anticipation of these symptoms may lead to behavioral conditioning and anorexia, which may be further exacerbated by depression [100].

Nutritional status can be markedly improved with calorie supplementation. Intravenous nutrition administered during acute exacerbations can maintain fluid and electrolyte status and arrest some of the early catabolism of protein stores [101,102]. Growth retardation also responds to enterally
administered calories, as evidenced by a series of patients in whom caloric intake was increased through nasogastric feedings [103]. By improving caloric intake over a 1-year period, significant improvement was seen in both height and weight velocity revealing that calorie supplementation alone is adequate to promote growth in many cases. Even short-term enteral nutrition is adequate to induce improvement in weight gain. Lean body mass increased in a series of adolescents with IBD, based on radiolabeled leucine metabolism, after only 3 weeks of increased enteral calories when protein intake was increased from 2.3 to 3.2 g/kg body weight per day [98].

Despite the opportunity to intervene with nutritional therapy, however, some consequences of malnutrition during childhood may be irreversible. When adjusting height for genetic potential based on parental height, many patients with CD never achieve expected levels [97] as demonstrated by measuring body composition in 132 subjects with CD and 66 controls, aged 5 to 25 years. In this population, adjusted height Z-scores were significantly lower than predicted heights. These findings were most pronounced in male patients, in whom the average adjusted height Z-score was a full standard deviation below expected.

**Growth assessment**

Accurate assessments of growth and nutritional status are the cornerstone for successful treatment. When dealing with growth measurements in children, inaccuracy of even 1 or 2 cm of height measurement can drastically change interpretations. Therefore, trained personnel, under standard conditions should perform growth assessments. The same scale should be used for serial assessments, a stadiometer should be used for all height assessments, and the patient should be assessed wearing a similar amount of clothing each time (most easily accomplished with the patient disrobed).

Growth irregularities in children with IBD have been measured in various ways, including weight for age, height for age, height and weight adjusted Z-score, height velocity, and various anthropometric measures, such as head circumference, midarm circumference, and triceps skinfold thickness [94,104]. The need for specialized training and equipment precludes the use of all these assessments with each visit; accurate measurements of height and weight usually suffice for clinical purposes. Height and weight measurements should be plotted on a standard growth curve, which allows comparison against an age-matched population. Height and weight deficit calculations expressed as a ratio of the actual height or weight divided by the expected value based on the 50th percentile for age, can give insight into the duration of malnutrition. In cases of short-term deficiencies, one can expect weight deficit (wasting), while long-term malnutrition often results in height deficit (stunting) [104].

The value of an accurate height and weight measurement, however, goes beyond these values at any one point in time. To thoroughly understand whether a patient’s growth is normal it must be considered in the context of
the patient’s genetic potential, often assessed using mid-parental height [105]. There is more value in following several growth points over time than any individual value. Reduction in growth velocity may be evident in patients who remain in the normal range on a standard growth curve [95]. Accordingly, growth velocity (rather than height for age percentile) has been incorporated into the scoring system of the Pediatric Crohn’s Disease Activity Index (PCDAI) (Fig. 2). This index has been developed and validated by a group of senior pediatric gastroenterologists in 1991 [106] and correlates well with the original Crohn’s Disease Activity Index (CDAI) developed for adult patients [107].

Another important reflection of overall nutritional status is progression of sexual development. Delay in the onset of pubertal development is common among adolescents with IBD, and active disease could potentially delay the onset of puberty indefinitely [108]. Once an adolescent enters puberty, changes in disease activity can slow down or arrest its progression. These potential derangements have important implications for the adolescent patient.

Once a patient has developed secondary sexual characteristics, growth potential may be irreversibly lost, whereas those whose disease is in remission before entering puberty generally experience improved height velocity and catch-up growth [109]. Accurate staging of sexual development can be accomplished by monitoring breast and pubic hair development in girls and by monitoring genital and pubic hair development in boys [110]. Tanner stage should be regularly included as part of the evaluation of young patients with IBD.

**Nutrient deficiency**

Although growth parameters and sexual development may give a very good overall representation of nutritional status, vigilance is needed to avoid the development of deficiencies in micro and macronutrients. Periodic assessment of dietary intake through diet records is an easy way to assess whether patients receive a diet sufficiently balanced in protein, carbohydrates, and fats and whether it provides daily requirements in important micronutrients.

Particular attention should be paid to intake of iron. Up to 70% of children and adolescents with IBD are iron deficient [111], because of a combination of inadequate intake, decreased absorption, and increased losses. Iron supplementation is commonly associated with gastrointestinal side effects, which may decrease patient compliance [112]. It is important therefore, to monitor both a patient’s intake of iron (through dietary records) and objective parameters of iron deficiency such as hemoglobin concentration, reticulocyte count, mean corpuscular volume, red blood cell distribution width, and levels of iron, ferritin, and transferrin saturation. Absorption of other micronutrients, in particular vitamin B12, folic acid, vitamin D and calcium, may also be impaired under various conditions in IBD, such as after intestinal resection or with the use of certain medications.
Bone disease in pediatric inflammatory bowel disease

Calcium homeostasis and bone growth is one of the most important aspects of malnutrition in pediatric IBD. The acquisition of bone mineral should occur throughout growth and development. It is now believed that peak bone mass (PBM) is a major determinant of the risk for osteoporosis later in life [113]. With at least 90% of PBM acquisition occurring during
childhood and adolescence, 25% of which is during the time of peak height velocity, anything that interferes with normal bone development during childhood has the potential for lifelong implications [114]. Effective prevention of osteoporosis and its consequences must therefore occur during childhood, and identifying those patients at risk for abnormal bones is of paramount importance.

Factors associated with bone disease in IBD include malnutrition and the effects of cytokines and glucocorticoid therapy. Malnutrition can lead to abnormalities in both calcium and vitamin D homeostasis. Vitamin D deficiency is common among patients with IBD, and CD in particular, with over 50% of patients demonstrating abnormal levels [115]. Calcium deficiency may occur in the setting of decreased dairy intake because of lactose intolerance and fat malabsorption, both of which may be related to small bowel involvement in CD. Various inflammatory cytokines have been implicated in the development of bone disease [116,117]. Glucocorticoid therapy has negative impact on calcium homeostasis [118,119] and on bone remodeling [120,121]. Corticosteroids also depress calcitonin levels, resulting in further bone resorption [122]. Despite the negative effects of glucocorticoids on bone density, however, growth failure and significant bone disease can be present before treatment with corticosteroids [123,124].

The prevalence of osteopenia in children with CD has been reported on a series of 119 patients [125]. In this report, 70% of patients had bone mineral density 1 standard deviation below age-matched norms, with nearly one-third having scores 2 standard deviations below normal. A follow up report found that the risk of having low bone mineral density was most associated with hypoalbuminemia, the need for nasogastric or parenteral nutrition, the use of the immunomodulator 6-mercaptopurine, and the use of corticosteroids [126]. Specifically, an average corticosteroid dose of 7.5 mg per day, a cumulative lifetime dose of 5 g, or 12 months of lifetime exposure were associated with the worst bone density.

Calcium supplementation seems to be one of the best ways to prevent bone disease. Even among normal children who receive the recommended daily allowance of calcium, supplementation can result in improved bone mineral density [127]. Furthermore, among children with inadequate calcium intake, supplementation results in improved bone mineral density [128]. These results are reversible, however, because the benefits of supplementation disappears 18 months after supplementation is discontinued [129]. It may be most important to begin supplementation early in childhood, as success seems to decline as subjects enter puberty [127,130,131]. The implications for pediatric patients with IBD are clear. Given that pediatric patients with IBD are at risk for inadequate calcium intake, it is very likely that they will benefit from supplementation, optimally given before puberty starts. Further success in preventing bone disease may be seen with low impact exercise programs that will compensate for decreased physical activity in those whose disease is active [132].
It remains controversial as to whether bisphosphonates have a role in the treatment of pediatric patients with IBD. Effective in the prevention of vertebral compression fractures associated with corticosteroid use [133,134], these compounds are being considered as a potential treatment for bone disease associated with IBD. One of these compounds, alendronate, was shown to improve bone mineral density in adult patients with CD also supplemented with calcium and vitamin D, as compared with a group receiving placebo for 12 months [135]. Potential effects on bone remodeling, however, raise some concern over the use of bisphosphonates in pediatric patients. To date, long-term adverse effects of these medications on bone remodeling have yet to be demonstrated in pediatrics [136]. There have also been studies that have shown normal vertebral remodeling in children receiving bisphosphonate for other bone disorders [137]. Nevertheless, because of the relative lack of data specific to pediatric IBD, use of these medications should be limited to those with severe osteoporosis unresponsive to the proven, better-studied modalities. Controlled trials of these medications are needed in the pediatric IBD population, and it is likely that more information on the long-term effects of bisphosphonates will be available soon.

Quality of life and coping strategies

Childhood and adolescence is a period of intense physical, emotional, social and intellectual growth and change. The transition into adulthood is a turbulent time when adolescents are finding their identity, improving their social skills and cognitive abilities, and when their belief systems are being shaped. To a great extent this development affects how they will respond to events as adults later in life. This may explain why various psychologic and social issues may be more pronounced in children and adolescents than adults with IBD. Adults may be better equipped to express their wants, needs, and feelings in a social situation or with their family. Furthermore, adults may have developed problem-solving skills that allow them to adjust to these situations better than children who have yet to develop these skills.

Physicians are becoming increasingly aware that traditional methods of evaluating clinical status of patients with IBD may not accurately reflect how patients feel about their illness, how they function on a day-to-day basis, and their worries and concerns [138]. This is why health-related quality of life (HRQOL), defined as “a global measure of the patient’s perceptions, illness experience, and functional status that incorporates social, cultural, psychological, and disease-related factors” [139], becomes an important aspect of care. HRQOL questionnaires have been studied extensively in adult populations, but similar child and adolescent studies are lacking [140–145]. A disease-specific quality of life measure that encompasses the issues unique to pediatric population is currently being developed and validated.

The concerns of children and adolescents diagnosed with IBD mostly overlap with those of adults, but some are unique to the pediatric
population. It has been reported that children initially deny that IBD interfered with their lives, but with further probing, many admit frustration and anger about their physical symptoms, unpleasant treatments, and the lack of understanding of the illness by others [146]. Major concerns of children are also energy level and body image [147,148]. Children often feel a lack of control with their choices regarding a variety of activities ranging from leisure and sports to school and employment. They believe they are missing opportunities because of lack of energy, exacerbation of the disease, and feelings of isolation. In a meta-analysis of different chronic diseases in children, IBD had the most profound effect on mental health of all the medical diseases reviewed [149].

When a child or adolescent is diagnosed with IBD parents and siblings also have to learn how to cope with illness [150]. The dynamics of the family may change by bringing more attention to the child with the illness, which may cause jealous feelings in siblings. Parents may have worries and fears about how the disease will affect the child’s future, potential problems at school, side effects of medications, and feelings of guilt. The most common concerns of siblings of IBD patients are that they are being kept in the dark about the disease, fear about the disease and treatment, and feeling jealous of parents’ overprotection of the ill child.

Children with IBD experience a multitude of stressors, including altered physical appearance, decreased physical functioning, demanding treatment regimens, pain, diarrhea and fecal incontinence, and school absences. Some of the variability in children’s adjustment to illness may be because of differences in the degree of disease severity, age, and sex of the child. However, psychosocial factors also influence adjustment to IBD [151]. Thus, the way a child responds to illness-specific stressors must be considered because this affects the course of the illness and the child’s overall adjustment [152]. Understanding the role of coping strategies is thus essential to facilitating maximal adjustment to a chronic illness.

Coping strategies are commonly classified as either problem-focused or emotion-focused. Children who use problem-focused strategies cope by gathering information [153]. They then make educated decisions regarding how to most effectively manage the situation through direct action. Emotion-focused strategies seek to manage somatic, subjective, and affective responses to the stressor [154]. In this case, typical coping mechanisms include denial and distraction. Social support has been found to positively influence the quality-of-life of adolescents with IBD [155]. Gillman [156] notes that these children with IBD may have difficulty recognizing or acknowledging stressors, and may therefore continually use ineffective coping strategies. A positive approach style includes problem-focused strategies of cognitive restructuring and problem-solving, emotional regulation, and social support. A negative avoidance style includes emotion-focused strategies of distraction, denial, wishful thinking, and resignation, also social withdrawal, blaming others, and self-criticism. An additional factor determining adjustment to
illness is the presence of mental health issues such as anxiety and depression. Underlying mental disorders may affect the way a child responds to her or his stressors, and thus to her or his illness.

Multidisciplinary teams treating patients with IBD and their families need to recognize the aforementioned concepts, and use this information accordingly. Psychological treatment may be used to teach patients ways to facilitate their adjustment and maintain their typical daily lives. For example, these patients may be guided to use family and peer support to adjust to changes in their appearance caused by medications. They may learn to schedule activities when they feel most energetic, and to rest at other times. They may get through episodes of pain by performing learned techniques such as muscle relaxation and deep breathing, and by becoming attuned to the specific techniques that are most helpful to their personal illness experience. Educational intervention is crucial, to inform children and adolescents about their medical condition so that they can use appropriate coping strategies. Education may be achieved through informal conversation with their parents and professional staff and through formal educational programs and literature. Parents will also benefit from intensive education about their children’s conditions and learning strategies to help them gain control and adapt to living with a child with a chronic illness. Teaching parents strategies to facilitate appropriate systemic involvement, such as school participation with medications and special arrangements, will help them gain their own sense of competency and control while simultaneously helping to improve their children’s quality of life.

Team approach

Because of a complex nature of issues surrounding the care of a child or adolescent with IBD it is necessary to adopt a multidisciplinary approach, and devise an individual plan for therapy. In addition to parents, siblings, and family members, teachers and school nurse should also be part of the team. They should be informed about important aspects of IBD, especially symptoms. The medical support team ideally should include physician, nurses and nurse practitioners, nutritionist, social worker, and psychologist (Fig. 3). The authors believe that a team effort is necessary to ensure comprehensive, state of the art, care which allows IBD patients to achieve appropriate levels of physical, mental, and social sense of well being.

Transition of the patient with inflammatory bowel disease from pediatric to adult care

The needs of adolescents with chronic conditions and their health care transition to adult-centered services have been a focus of interest of several conferences during the last two decades. However, no clear model for
transition exists in the United States. Therefore, the American Academy of Pediatrics sponsored a national invitational conference that made the health care transition one of the priorities in an effort to assure comprehensive community-based service system for all children and youth with special health care needs by the year 2010 [157]. The consensus statement has identified these critical initial steps: (1) identification of a health care professional who assumes the responsibility for health care planning, (2) identification of the core knowledge and skills required to provide transition services, (3) creation of up-to-date medical summary that is portable and accessible, (4) creation of a written health care transition plan, (5) application of the same guidelines for primary and preventive care for all adolescents and young adults, and (6) provision of affordable, continuous health insurance coverage.

What is transition? The position paper by the Society for Adolescent Medicine defines transition as “the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care system” [158]. The passage from adolescence to adulthood is a time of internal turmoil and intense examination of personal goals and wishes. Being ill during this time of growing and changing may cause frustration about the present and anxiety about the future. The growing adolescent must be able to progressively shed the sheltered environment of childhood and achieve self-reliance and independent living as a decision-maker. For the chronically ill adolescent, this period of transition can be stressful not only for the patient but also for their families and their health care providers [158–162].

For the process of transition to be successful some prerequisites should be met [163]. For example, adolescents have to be ready, should consent to transition, and they should be educated about the important issues relating to
their condition and treatments. They should be able to recognize emergencies and be aware of the support system available. The process of transition should begin when a patient enters mid adolescence. The pediatric gastroenterologist should begin seeing adolescent patients without their parents to build a relationship which promotes independence and self-reliance. It is important to discuss with the patient and the family that in the future they will need to transition to a gastroenterologist who is also trained in internal medicine with expertise in dealing with medical problems that occur during adulthood, including pregnancy, fertility, and cancer surveillance.

During the transition several obstacles may be encountered [164]. Patients, parents, and other family members may feel threatened by changes in the pattern of care, and resentful of the effort required to adjust to a new setting and different staff. They frequently regard strong source of advocacy form pediatric team as a permanent arrangement. In contrast, they may perceive the internist who expects to care for an independent individual as less involved or less sensitive to the developmental and social aspects of their medical conditions. Health care providers may also feel ambivalent during this period of change. The pediatrician may view the maturation of the child as a professional and personal achievement, and find difficulty in relinquishing the patient to others whose style of practice he or she may not know well. Internist–gastroenterologist may find patients with childhood onset IBD immature and their families demanding.

Once the decision to pursue a transition program has been made the pediatrician or pediatric gastroenterologist should have a well-thought transition plan ready. They need to prepare a detailed medical summary describing the course of the disease, therapy, allergies, and so on. Copies of the relevant tests should also be prepared. The next step is to identify a skilled gastroenterologist who cares for young adults. This individual must realize that a young adult with childhood onset IBD may have a different set of expectations than the young adult with recent onset of IBD. They may expect for a gastroenterologist to spend more time with them than what is customarily spent with other adult patients, which in some instances may require reorganization of a practice to allow for additional time. These patients may expect ready access to nurse practitioner or physician. They have a heightened risk for the development of cancer and will require an increased need for cancer surveillance. In a case where there is additional growth potential present as a result of delayed puberty the pediatric gastroenterologist should remain on the team to provide necessary expertise [164].

A transition program should result in improved compliance with therapy and effective planning of long-range life needs. These also include the need for a benefits package to be designed covering issues of continuing health insurance, life insurance, disability, and so on.

The successful transition from pediatric to adult health care systems is an ongoing process, which should address medical, behavioral, and social issues and not be seen as merely a transfer of care.
References


