Health Maintenance and Vaccination Strategies in Pediatric Inflammatory Bowel Disease

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Abstract: The development of inflammatory bowel disease during childhood and adolescence is not uncommon. As advances in medical therapies continue to emerge, so does the recognition that treatment goals must include achieving and maintaining childhood wellness. Preservation of normal linear growth, development and psychosocial wellbeing along with appropriate vaccination and preventative care strategies are elements critical to assuring the complete health of the pediatric patient who is affected by inflammatory bowel disease.

(Inflamm Bowel Dis 2013;19:1740–1744)

Key Words: growth retardation in IBD, health maintenance in IBD, pediatrics, psychosocial aspects of IBD

INFLAMMATORY BOWEL DISEASE IN THE PEDIATRIC POPULATION

Pediatric inflammatory bowel disease (IBD) is not uncommon as approximately 25% of patients with IBD present at less than 20 years of age and 5/100,000 pediatric patients with IBD are diagnosed when they are less than 8 years old. The pediatric IBD population requires special consideration as the disease can have profound impact on growth, pubertal development, and the psychosocial well-being of the affected individual and also their family.[1] There is a delicate balance between treatment efficacy and the risk of treatment toxicity with the goal being remission of disease while maintaining the overall health and well-being of the patient. Which therapy is best for each patient is the subject of constant research and debate. Although therapeutic advances continue to be made, establishing effective health maintenance programs for today's pediatric patient with IBD is a primary intervention that can be made to improve the overall quality of delivered care.

HEALTH MAINTENANCE

Proper health maintenance is critically important to address when treating any patient with a chronic medical condition. For the pediatric patient with IBD, maintenance of appropriate linear growth, pubertal development, vaccination status, surveillance of disease activity, and the psychosocial impact of the disease and its therapy all must be considered. Routine health maintenance should be assessed at the time of diagnosis and continually evaluated and addressed throughout the disease course.

GROWTH AND BONE HEALTH

A general dietary and nutritional assessment should be performed at each office visit. The caloric requirements should be at least the same as all pediatric patients while recognizing that ongoing inflammatory activity will serve to increase those needs.[2] Those patients with significant small bowel inflammation are susceptible to various nutrient deficiencies and should be routinely monitored with measurements of complete blood counts, serum iron, folic acid, and vitamin D along with functional levels of vitamin B_{12}.[3] Consultation with an experienced dietician comfortable in treating inflammatory bowel disease should be considered in difficult cases with significant nutritional deficiencies.

Children have a limited window of opportunity in which to obtain linear growth. Uncontrolled inflammation in the pediatric patient with IBD can have a significant adverse impact on this very important outcome. It is therefore crucial to measure an accurate height and weight at each visit, to calculate a body mass index, and calculate the rate of weight gain and linear growth. In addition, a Tanner assessment should be made at each visit though pubertal maturation. Signs of poor growth, poor weight gain, or delayed pubertal development should prompt further evaluation as to the state of disease control and appropriate changes in therapy should be initiated to assure disease remission and appropriate growth and secondary sexual development.

Specific attention should be paid to the bone health of pediatric patients with IBD. Bone formation can be adversely affected through a combination of nutritional deficiencies, physical inactivity, inflammatory cytokines, muscle mass deficits, and glucocorticoid use.[4] It has been observed that substantial

Received for publication November 2, 2012; Accepted November 13, 2012.

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The authors have no conflicts of interest to disclose.

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DOI 10.1097/MIB.0b013e318281f5b5

Published online 17 May 2013.

deficits in bone mass are often observed in children at the time the diagnosis of Crohn's disease is made. In addition, these deficits can be acquired over the course and progression of the disease.[5] Prospectively, it was observed that there is a decrease in bone turnover in children with newly diagnosed IBD, and while there is indication of increased osteoblast activity during times of clinical improvement, bone mineral accrual does not accelerate.[6] As a whole, approximately 10% to 40% of children presenting with IBD have significant deficits in bone mass, more pronounced in Crohn's disease than ulcerative colitis.[5,6] Subsequently, such deficits may impact the attainment of peak bone mass, the most important determinant of long-term skeletal health, risk of fracture, and overall linear growth.

Measurement of bone mass therefore becomes important in the routine health maintenance of the pediatric patient with IBD. The most readily available tool to measure this is the dual energy X-ray absorptiometry (DEXA) scan. As children with IBD often have delays in growth and maturation, the DEXA scan can underestimate bone mineral density when interpreted for chronologic age in these patients.[7] The bone mineral density is therefore expressed as a z score, which measures the deviation of the patient's bone mineral density from the normal mean for age and sex.[3] Convened in 2007, the International Society for Clinical Densitometry met to establish standards and guidelines for the assessment of skeletal health. It is recommended that children with IBD undergo a total body (minus skull) and lumbar spine DEXA screen at the time of diagnosis and then no sooner than at 6-month intervals. When evaluating bone mass, the interpretation must be adjusted for a pediatric patient and thus performed at a site with pediatric experience in DEXA scans.

A recent report by Papa et al recommends that children with IBD and any of the following risk factors should undergo a DEXA scan: (1) suboptimal growth velocity with a height z score less than −2 SD or downward crossing of height percentiles; (2) weight or body mass index z score less than −2 SD or downward crossing of weight or body mass index percentile curves; (3) secondary or primary amenorrhea (if female); (4) severe inflammatory disease course, especially when associated with decreased albumin level (<3 g/dL); (5) 6 months or longer of continuous systemic glucocorticoids; and (6) history of clinically significant fractures (fractures of long bones of lower extremities, spinal compression fractures, 2 or more fractures of long bones of upper extremity).[4] Z scores less than −2 are consistent with a significant deficit in bone mass and body composition. Such patients should undergo further evaluation including obtaining a bone age and measuring serum calcium, phosphorus, magnesium, blood urea nitrogen, creatinine, parathyroid hormone, ionized calcium, tissue transglutaminase IgA, and 25-OH vitamin D levels.[4] Referral to pediatric endocrinologist should be considered as well. A baseline DEXA scan with a z score less than −1 is an indicator to monitor closely and repeat the scan within 6 months after treatment of the IBD is commenced.

Although the serum 25-OH vitamin D levels required to prevent rickets are well established (≥12.5 ng/mL) and is the level that is associated with inadequate bone mineralization (<20 ng/mL), the levels necessary to impact positively on the potential extraskeletal effects of vitamin D remain undefined. Based on the recent data, 32 ng/mL has increasingly becoming accepted as the lower limit of acceptability for serum 25-OH vitamin D levels in IBD.[8] As discussed earlier, the routine health assessment of children with IBD should involve a full dietary assessment, including those foods that are enriched with vitamin D. Although dietary intake is important, most pediatric patients with IBD will require additional supplementation. The most recent report by Pappa points out that there are no efficacy studies in children with IBD to establish the dose of vitamin D supplementation needed to maintain levels >32 ng/mL. Recognizing the increased risk for low vitamin D levels in this populations, the authors recommend intake of 800–1000 IU/day in children with IBD and optimal vitamin D levels.[4] Yearly levels of serum 25-OH vitamin D should continue to be monitored thereafter to ensure levels remain >32 ng/mL. For the deficient patient, the authors recommended using a cumulative dose of at least 400,000 IU for levels <20 ng/mL. For levels >20 ng/mL but lower than 32 ng/mL, a cumulative dose of at least 250,000 IU was deemed reasonable. These doses can be administered in equal amounts divided once a week for 8 weeks.

PREVENTION AND SURVEILLANCE

Immunizations

Immunization status and maintenance of proper immunizations are paramount to maintenance of the general health and well-being of pediatric patients. This is even more crucial in the pediatric IBD population since the majority receive immunosuppressive treatments that include glucocorticoids, thiopurines, methotrexate, and biological agents. Therefore, it is best when, at diagnosis, a detailed immunization history and confirmatory serology are obtained. Documenting immunity to varicella and measles is crucial to allow for "booster" vaccination before the potential institution of immune-modifying therapies.

In 2004, the Crohn's and Colitis Foundation of America published guidelines for immunizing patients with IBD.[9] The committee recommended that immunization in patients with IBD should not deviate from recommended schedules with respect to inactivated vaccines. These include tetanus–diphtheria–acellular pertussis (Tdap), hepatitis B vaccine, hepatitis A vaccine, influenza (injectable only), pneumococcal, human papillomavirus, and meningococcus (Table 1).[9] The IBD committee of the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) concurred with these recommendations and also emphasized that patients should be tested for hepatitis B immune status as treatment with anti-TNF agents has been reported to result in hepatitis B viral reactivation.[3]

Although the immunogenicity of individual vaccines in this patient population requires further study,[10] these inactivated vaccines do not present a risk of infection to patients with IBD regardless of the immunosuppressive medications used.[11,12] Also, with regard to vaccine efficacy, there has been encouraging data

TABLE 1. Live and Inactivated Vaccines

Live Vaccines	Inactivated Vaccines
Rotavirus	Tetanus–diphtheria–acellular pertussis
Measles–mumps–rubella	Hepatitis A
Varicella	Hepatitis B
Zoster	Human papillomavirus
Intranasal influenza	Injectable influenza
Typhoid	Pneumococcal
Yellow fever	Meningococcal

from 2 studies showing response to influenza vaccine in pediatric patients with IBD regardless of their IBD medical regimen[13,14] and similar efficacy has recently been reported with human papillomavirus vaccine.[15]

Whereas inactive vaccines are recommended, current guidelines warn against the administration of live viral vaccines in patients receiving immune-modifying therapies. Live viral vaccines include rotavirus, measles–mumps–rubella, varicella, zoster, and intranasal influenza. There are specific live viral vaccines often recommended for world travel that need to be avoided in the presence of immunosuppressive therapies and these include oral typhoid and yellow fever (Table 2). Those who are steroid free and on topical agents such as mesalamine products should continue to receive live viral vaccines.[9] For the purposes of safe vaccine administration, immune compromise has been defined as the following: (1) treatment with glucocorticoids (≥prednisone 20 mg/d equivalent or 2 mg/kg/d if less than 10 kg, for 2 wk or more, or within 3 wk of stopping steroids); (2) treatment with effective doses of 6-mercaptopurine/azathioprine or within 3 months of stopping such agents; (3) treatment with methotrexate or within 3 months of stopping methotrexate; (4) treatment with an anti-TNF or other biological agent or within 3 months of stopping such an agent; and (5) significant protein malabsorption (Table 3).[9] As such, it is important to emphasize that efforts should be made in those younger patients with IBD to vaccinate with any required live vaccines before the initiation of any immunosuppressive therapy as outlined above. Particular focus should be paid to the varicella status of patients with IBD. Current guidelines from the Advisory Committee on Immunization Practices of the Centers for Disease Control should be used to confirm immunity (Table 4). These include documentation of natural infection by a health care provider with a confirmatory antibody titer if there is any lack of certainty.[3,16] For children and young adults born after routine varicella immunization was begun, documentation of the administration of 2 doses of varicella vaccine is considered adequate, especially since commercial assays for varicella antibodies may not reliably demonstrate vaccine acquired immunity.[16] Those requiring vaccination should receive this at least 4 to 6 weeks before starting immunosuppressive therapy as defined above. Although there is controversial expert opinion especially with regard to varicella,[17] if the patient is already on immunosuppressive therapy, current recommendations are that all live vaccines should not be given until 3 months after discontinuation of such therapy.[9,12]

TABLE 2. Checklist for Health Maintenance of the Pediatric Patient with IBD

Linear growth and skeletal health
Pubertal development
Vaccination status
Psychosocial impact of the disease
Surveillance of disease activity

TABLE 3. Definition of Immunocompromised Status Requiring Avoidance of Live Vaccinations

Treatment with glucocorticoids: ≥20 mg/d prednisone equivalent or 2 mg/kg/d if less than 10 kg, for 2 wk or more, and within 3 mo of stopping
Treatment with 6-mercaptopurine/azathioprine and within 3 mo of stopping
Treatment with methotrexate and within 3 mo of stopping
Treatment with tumor necrosis alpha inhibitors or other biologic and within 3 mo of stopping
Significant protein–calorie malnutrition

Cancer Screening

Several studies have shown an increased risk of nonmelanoma skin cancer in patients with IBD associated with previous and current use of the thiopurine medications, 6-mercaptopurine, and azathioprine.[18,19] It is also suggested that patients with IBD might have a baseline increased risk of nonmelanoma skin cancer regardless of thiopurine use.[20] Although IBD-specific evidence-based guidelines for nonmelanoma skin cancer prevention do not currently exist, current recommendations for the prevention of skin cancer in the general population should be followed.[21] These recommendations include primary prevention through sun avoidance and the use of broad-spectrum sun protection.[21] Regularly scheduled, routine screening by a dermatologist may be a reasonable consideration.

The increased risk of the development of colorectal cancer in patients with ulcerative colitis or substantial colonic CD is well documented.[22–25] Current recommendations therefore call for

TABLE 4. Criteria for Evidence of Immunity to Varicella

Criteria for Evidence of Immunity to Varicella (at least 1 of the following):
• Documentation of the administration of 2 doses of varicella vaccination
• Diagnosis or verification of a history of varicella by a health care provider
• Diagnosis or verification of a history of herpes zoster by a health care provider
• Laboratory confirmation of post-disease varicella IgG antibody titer

colonoscopic surveillance with random biopsies every 1 to 2 years beginning 8 to 10 years from the initial diagnosis and assuring adherence with these guidelines can serve as a significant marker of quality assurance in an IBD practice.[26–28]

Psychosocial Assessment

Routine health maintenance for the pediatric patient with IBD includes a thorough psychological assessment of the child's well-being. A new diagnosis of IBD itself compounded with any waxing and waning clinical course can impact disproportionately on those patients trying to reconcile their disease with the demands of their social, academic, and athletic lives.[29] Pediatric patients with IBD have been shown to be at an increased risk of developing depression, anxiety, isolation, altered self-image, family conflict, school absences, and medical adherence problems stemming from concerns of their diagnosis, fear of being different, and fear of stool incontinence among other reasons.[30] Szigethy et al[31] showed that up to 25% of adolescents with IBD exhibited clinically significant depressive symptoms based on the Children's Depressive Inventory (CDI) score. Pediatricians and gastroenterologists must be aware of these possible psychosocial changes in their patients with IBD and inquire about them on a routine basis during follow-up visits. Appropriate screening and treatment can have an impact on the clinical outcome and health-related quality of life of these patients.

At the most basic level, clinicians should foster a comfortable environment for their patients to allow for discussions of psychosocial well-being. Questions focusing on mood, academic and athletic functioning, appetite, and social interaction with peers should be standard. For a more detailed screen, the validated measures such as the CDI may be used. The CDI is the most widely used and reliable measure of depressive symptoms and impaired social functioning in children ranging from 6 to 17 years of age.[3] On an individual basis, offering a personal and supportive relationship, enlisting the help of social workers, and encouraging support groups/summer camp programs can provide significant benefit for the pediatric patient with IBD. For those patients who, based on the physician's assessment and through measures such as the CDI, are seen to be at a higher risk for depressive symptoms, referral to a mental health professional for more personal treatment should be made.

ROLE OF PEDIATRICIAN VERSUS ROLE OF GASTROENTEROLOGIST

Caring for the pediatric patient with IBD presents a unique situation in which achieving excellent health maintenance will require a team that includes the primary pediatrician, the pediatric gastroenterologist, a dietician, and psychosocial support team. Vaccines are routinely given by the primary pediatrician, and this must be performed in consultation with the pediatric gastroenterologist who prescribes the disease-specific therapy which is often immunosuppressive. In addition, there is evidence that physicians need to be more informed when it comes to effects and timing of vaccines with respect to medical therapies. A survey of adult gastroenterologist showed that although 85% of the physicians agreed that it is important for their patients with IBD to be up to date with their immunizations, only 14% admitted to taking a detailed vaccination history. Thirty-nine percent of the physicians stated that they had concerns about potential side effects of vaccines while on IBD therapy and 23% did not know whether live vaccines should be avoided.[32,33] Vaccination schedules serve as just one example of the importance of continued education regarding health maintenance requirements of pediatric patients with IBD. Patients will benefit most from a multidisciplinary team approach in their overall care with a close working relationship between the primary care physician and pediatric gastroenterologist.

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