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By NASPGHAN and The NASPGHAN Foundation
for Children's Digestive Health and Nutrition

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A Case-Based Monograph Focusing on IBD

Improving Health Supervision in Pediatric and Young Adult Patients With IBD

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Introduction

Though inflammatory bowel disease (IBD) is more prevalent in adults overall, it remains an important problem in pediatrics. IBD symptoms can lead to malnutrition and delayed growth, making early diagnosis and appropriate treatment of children essential to improving outcomes and alerting clinicians to screen for common comorbidities such as depression and osteoporosis.

Target Audience

This activity is designed for pediatricians, pediatric and adult gastroenterologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who are interested in treating children and young adults with IBD.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Utilize appropriate screening tools for the accurate diagnosis of IBD in pediatric, adolescent, and young adult patients in the primary care setting
- Initiate and/or monitor recommended pharmacotherapy
- Screen and diagnose IBD patients suffering from comorbid depression
- Develop collaborative care plans with primary and subspecialty providers in efforts to provide appropriate pharmacotherapy and social support for patients with IBD and their families

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and The NASPGHAN Foundation for Children's Digestive Health and Nutrition. NASPGHAN is accredited by the ACCME to provide continuing medical education for physicians.

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Dr. Rufo reported that he receives research support from TECHLAB®, Inc. *Conflicts with Dr. Rufo were resolved by restricting the presenters to best available evidence and the ACCME content validation statement.*
Dr. Denson has nothing to disclose.
Dr. Lu has nothing to disclose.
Dr. Szigethy has nothing to disclose.
Dr. Greifer has nothing to disclose.
Matt Kilby, medical writer, has nothing to disclose.
Karin McAdams, program manager, has nothing to disclose.

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Introduction

Inflammatory bowel disease (IBD) is the result of chronic gastrointestinal inflammation and is generally characterized into 2 clinical subtypes – Crohn disease (CD) and ulcerative colitis (UC).[1] Though IBD is more prevalent in adults overall, it remains an important problem in pediatrics. A significant percentage of adult patients are initially diagnosed with IBD during childhood, and current data suggests that between 7 and 20 out of every 100,000 children in the United States carry diagnoses of either UC or CD.[1] Children with IBD often present with abdominal pain, diarrhea, weight loss, and bloody stool.[2] Because these symptoms can lead to malnutrition and delayed growth, early diagnosis and appropriate treatment of children with IBD are essential to improve outcomes and alert clinicians to screen for common comorbidities such as depression and osteoporosis.

Case Study Introduction: Hayley

Hayley, a 13-year-old female patient, presents with a 4-week history of worsening stomach pain, diarrhea, and bloody stool, along with decreased height velocity over the past 6 months. She is a bright student and an accomplished athlete and plans to try out for her school softball team next year if she maintains good grades. She has excelled in her classes, but is afraid that her stomach issues will impact her ability to play softball or continue to do well academically.

Diagnosis and Assessment

Appropriate laboratory workup can expedite the referral of patients with symptoms suspicious of IBD for more definitive subspecialty testing and management. Initial studies should include white blood cell and platelet counts, inflammatory markers (ie, erythrocyte sedimentation rate (ESR) and C-reactive protein), hemoglobin or hematocrit, mean cell volume (MCV) to help distinguish between chronic (low MCV) and acute (normal MCV) blood loss, and serum albumin and liver function tests (ie, alanine aminotransferase (ALT), alkaline phosphatase, bilirubin).[3] Stool studies for occult blood and infectious pathogens (eg, *Clostridium difficile, Salmonella, Campylobacter jejuni*, and *Escherichia coli)* should be requested as soon as possible.[4-8] Placement of a purified protein derivative (PPD) to assess for exposure to tuberculosis should be considered, as patients with IBD may require long-term immunosuppressive therapy.[9]

Radiologic assessment with computed tomography (CT) or magnetic resonance imaging (MRI) can help to identify the location and severity of small and large bowel inflammation in patients with IBD.[10,11] Because recent data suggest that ionizing radiation from CT may impact considerably on the lifetime risk of cancer, MRI use may provide comparable cross-sectional information with less long-term risk overall.[12] Ultrasound examination of the bowel can be useful in assessing children with IBD and is often less costly and more readily available than MRI. However, this examination should be done only by radiologists experienced with this technique.[13] In all cases, the choice of radiologic evaluation should be based on a patient's previous history and clinical presentation.

Monitoring Considerations in Pediatric IBD Patients

Health supervision in children with IBD should include interval assessment of general health parameters (eg, height, weight, and body mass index), attention to bone and mental health, as well as cancer surveillance.

Significant decreases in bone mass have been observed in 10%-40% of children with IBD.[14,15] The International Society of Clinical Densitometry recommends that children with IBD receive a full-body dual x-ray absorptiometry scan, minus the skull, at diagnosis with repeated measures no sooner than 6 months apart.[16] Appropriate growth and normal bone mineralization depend upon adequate intake of vitamin and micronutrients (eg, vitamin D, calcium, and zinc) through either diet or dietary supplements.[17-19]

The increased risk of colon cancer in patients with IBD necessitates colonoscopic examination with surveillance biopsies every 1-2 years, starting approximately 7-10 years after initial diagnosis.[20] Skin cancer assessment should be performed as part of routine physical examination.

Immunization of Pediatric IBD Patients

Primary providers should take the opportunity to review the patient's immunization status. Current guidelines recommend that patients with IBD complete inactivated vaccine series, including diptheria, pertussis, and tetanus; hepatitis A and B; and *Haemophilus influenzae* type b in early childhood, and influenza (intramuscular), pneumococcus, and meningococcal immunizations in adolescence.[21] Specific effort should be made to immunize children with IBD with any required live viral vaccines (eg, rotavirus, measles-mumps-rubella, varicella, and intranasal influenza) before the need for immunosuppressive therapy arises, as these vaccines are contraindicated once immunosuppressive therapy begins. Completion of these series can often be accomplished while the patient is awaiting subspecialty evaluation.

Varicella vaccine warrants special consideration. This vaccine should be administered to all patients not receiving immunosuppressive therapy if the patients or their parents cannot recall a history of

natural infection.[22,23] If they are unsure, varicella antibody titers should be checked. If patients have no history of varicella infection or immunization, vaccination should be administered before patients begin immunosuppressive therapy, including treatment with corticosteroids (≥ prednisone 2 mg/kg/day or equivalent, or prednisone 20 mg/day or equivalent, for ≥ 14 days); cyclosporine or tacrolimus; immunomodulators including 6-methyl mercaptopurine (6-MMP), azathioprine, and methotrexate; or biologic therapy (eg, infliximab, adalimumab, or certolizumab pegol). Ideally, patients should wait ≥ 1 month after discontinuing corticosteroids before immunization with this vaccine.[24]

The approach to varicella-naïve patients who are being treated with immunosuppressive agents is less clear. Increased morbidity and mortality in older children and adults with primary varicella infections are considerable and even more significant in children receiving immunosuppressive therapy.[25] These concerns should be included in any discussion of the risk-benefit ratio of varicella vaccination in these patients. There are currently no studies that examine the safety and immune response to the varicella vaccine in this patient population. However, 1 case series of 6 children with IBD who received varicella vaccine demonstrated that this vaccine was tolerated, and all but 1 patient were successfully immunized.[25] Nonetheless, providers should consult infectious disease specialists before making decisions about the use of varicella/zoster vaccines in these patients. If immunocompromised patients have no immunity against varicella and experience a significant exposure, treatment is warranted.[23] Varicella zoster immune globulin should be administered as soon as possible and, preferably, within 96 hours of exposure. If ≥ 96 hours have elapsed since the exposure or varicella zoster immune globulin is unavailable, experts may suggest giving acyclovir for a period of up to 7-10 days after the initial exposure. If immunocompromised patients acquire varicella infection, admission for intravenous acyclovir is recommended.

Patients being treated with immunosuppressive agents should receive annual inactivated influenza vaccines and, when available, combined influenza/swine flu vaccines.[26] When influenza infection is known or suspected, physicians often hold administration of immunosuppressive therapy until a patient clinically improves. Children with IBD should be treated with antiviral medications (eg, oseltamivir phosphate) when clinically indicated.

Patients should be tested for latent hepatitis B or seronegativity (hepatitis B surface antibody negative), as treatment with anti–tumor necrosis factor agents has been reported to result in hepatitis B virus (HBV) reactivation.[23] Physicians should also consider checking hepatitis A and C status, and seronegative children should be vaccinated for HBV and hepatitis A virus (HAV).

Case Study Hayley: Diagnosis and Immunization

Hayley is diagnosed with Crohn disease of the terminal ileum and left colon after completing colonoscopic and radiologic evaluation. She receives her remaining vaccinations in anticipation of beginning immunosuppressive therapy. HAV and HBV testing reveal existing immunity, and her hepatitis C and PPD test results were negative.

Treatment of Pediatric IBD Patients

Decisions about treatment should be individualized and based on the specific needs and preferences of each patient. Physicians should review all potential variables with both the patient and their parents.[27] The choice of medication should take into consideration dosing format and formulation, the underlying disease (ie, CD or UC), the location of a patient's disease (ie, upper gastrointestinal, lower gastrointestinal, or both), potential adverse effects, and a patient's prior history and clinical severity.

Similar to other chronic inflammatory diseases, patients with IBD typically experience a waxing and waning clinical course that may cause them to go for extended periods with few symptoms.[27] As such, treatment of patients with CD and UC occurs in 2 phases, induction and maintenance, to address periods of clinical activity and inactivity, respectively.

Induction Phase

Patients with clinically active disease are often treated with induction agents. These medications are often more potent and enable clinicians to bring intestinal inflammation under control as quickly as possible. **Table 1** provides an overview of the commonly prescribed medications used in the induction phase of treatment in children and adolescents with IBD.

Maintenance Phase

Maintenance agents are chosen to help control inflammation and prevent the development of symptoms in patients who are in clinical remission. In some cases, the same medications that are used in the induction phase can also be continued to maintain disease remission. **Table 2** provides an overview of common medications used in children and adolescents with IBD.

Table 1. Induction phase treatment for pediatric IBD.[2,28-32]

Treatment	IBD Subtype	Common Adverse Effects	Monitoring
Aminosalicylates (eg, Balsalazide, Mesalamine*, Olsalazine*, Sulfasalazine)	UC	Nausea, anorexia, headache, diarrhea	Complete blood count (CBC) with differential, liver chemistries, blood urea nitrogen (BUN)/creatinine, urinalysis
Antibiotics (eg, Metronidazole, Ciprofloxacin)	CD	Nausea, metallic taste, headache, dry mouth, furry tongue, glossitis, stomatitis, urticaria, vaginal and urethral burning, vaginal yeast infection, upper abdominal pain	N/A
Biologics (eg, Adalimumab†, Certolizumab†, Infliximab*, Natalizumab†)	CD/UC	Infusion reactions, nausea, fever/chills, hives, fatigue, psoriatic skin rash	PPD, chest x-ray (if symptomatic), routine skin examination, CBC, liver chemistries
Corticosteroids (eg, Budesonide‡, Prednisolone‡, Prednisone‡)	CD/UC	Growth disturbance, bone loss/disease, hypertension, hyperglycemia, acne, hirsutism, facial swelling, weight gain, increased infection risk	Growth monitoring, eye examination with pressure measurement, PPD, chest x-ray (if symptomatic), varicella titer; immunize before therapy, if possible
Enteral Nutrition (eg, Elemental, Semielemental, Nasogastric, Polymeric)	CD	Loose stools, nausea, nighttime awakening (during nocturnal nasogastric feeding), diarrhea	Assess resting energy expenditure, if possible; check height, weight, skin folds, and pubertal stage at office visits
Immunosuppressants (eg, Cyclosporine, Tacrolimus)	UC	Hypertension, nausea, increased liver function values, infections, nephrotoxicity, glucose intolerance, seizures	Prophylaxis against *Pneumocystis carinii* pneumonia, baseline electrolytes, BUN/creatinine, CBC, liver enzymes, lipids, cholesterol, fasting glucose, serum albumin

*Not US Food and Drug Administration (FDA)-approved for use in children with UC
†Not FDA-approved for use in patients with UC
‡Not FDA-approved for use in children with CD or UC

Table 2. Maintenance phase treatment for pediatric IBD.[2,28-32]

Treatment	IBD Subtype	Common Adverse Effects	Monitoring
Aminosalicylates (eg, Balsalazide, Mesalamine*, Olsalazine*, Sulfasalazine)	CD/UC	Nausea, anorexia, headache, diarrhea	CBC with differential, liver chemistries, BUN/creatinine, urinalysis
Biologics (eg, Adalimumab†, Certolizumab†, Infliximab*, Natalizumab†)	CD/UC	Infusion reactions, nausea, fever/chills, hives, fatigue	PPD, chest x-ray (if symptomatic), routine skin examination, CBC, liver chemistries
Immunomodulators (eg, 6-MMP‡, Azathioprine‡, Methotrexate‡)	CD/UC	Nausea, vomiting, diarrhea, rash, fever, malaise, leukopenia, thrombocytopenia, pancytopenia, myelosuppression, hepatotoxicity, pancreatitis, anorexia, stomatitis	Thiopurine methyltransferase before prescribing; 6-MMP and 6-thioguanine nucleotides during treatment; CBC weekly for 1 month, every 2 weeks for 2 months, and every 2-3 months thereafter; ALT monthly for 3 months, then every 3 months thereafter

*Not FDA-approved for use in children with UC
†Not FDA-approved for use in patients with UC
‡Not FDA-approved for use in patients with CD or UC

Considerations for Pediatric IBD Patient Management

Compliance is a major concern in children with IBD and likely plays a significant role in maintaining disease remission. Adherence rates in children with chronic disease are approximately 50% and are lowest in adolescence and during remission.[33] Therefore, it is important to re-emphasize the importance of proper dosing and compliance with patients and their parents during each office visit.

The office management of children with IBD should be tailored to meet each patient's specific needs, age, stage of development, and disease course. Physicians treating children with IBD individualize the frequency of scheduled follow-up based on a patient's disease activity, compliance history, age, stage of growth and development, and choice of medical therapy. In general, patients in remission that are maintained on aminosalicylate therapy are typically seen every 4-12 months, and those being treated with immunomodulatory or biologic agents are seen every 3-6 months. Patients recovering from a flare in their disease or with intercurrent viral (eg, Epstein-Barr) infections will likely require closer follow-up.

Case Study Hayley: Treatment

After reviewing treatment options with Hayley and her parents, Hayley is started on infliximab 5 mg/kg and tolerates her initial infusion well, with only minor headache and nausea. Her next infusion is scheduled for 2 weeks later.

Depression in Pediatric IBD Patients

Children with IBD are at an increased risk for depression, anxiety, social isolation, and altered self-image.[34] Up to 25% of these children display symptoms of depression, but 97% would have symptoms unrecognized unless specifically queried by their physician.[35] Using pupillary response to negative emotional stimuli as a proxy for brain activity, depressed adolescents with IBD receiving high-dose steroid treatment showed unique changes in pupil constriction compared to healthy controls, suggesting a neurobiologic basis for depression.[36] Depression is significantly associated with abdominal pain, diarrhea, weight loss, and an elevated ESR in pediatric IBD patients, so proper assessment and treatment is critical.[37]

Diagnosing Depression in Pediatric IBD

Depression in children can manifest as a flat affect, emotional avoidance, or a failure to regulate emotion after exposure to negative information.[36] Patients may also experience persistent changes in mood; appetite; and levels of social, athletic, and academic functioning.

Physicians should inquire about changes in mood (eg, irritability and anhedonia), behavior, and performance as part of every routine medical visit.[38] If symptoms persist and appear to impact the patient's developmental function, a diagnosis of clinical depression should be considered. The acronym MESSAGE is a quick screening tool for recognizing symptoms of depression, as shown in **Table 3**. Other diagnostic tools include the Children's Depressive Inventory (CDI), a 5-minute measure of symptoms and impaired social functioning in children aged 6-17 years[39]; the CDI-Parent Report, a similar measure for parental functioning; and the Luebeck Interview for Psychosocial Screening, a rating tool for psychosocial stress specific to IBD patients.[40]

Table 3. MESSAGE acronym for depression screening.

M	Mood (depressed or irritable) and Motor (hyper or hypo)
E	Energy (fatigue)
S	Sleep (insomnia or hypersomnia)
S	Suicide and Self-Esteem
A	Anhedonia (lack of pleasure)
G	Guilt
E	Eating (change in appetite)

Courtesy of Eva Szigethy, MD, PhD

Treating Depression in Pediatric IBD Patients

The goal in treating depression in children with IBD is to improve quality of life and overall level of functioning. Treatment may consist of pharmacologic agents, nonpharmacologic options, or a combination of both and should be individualized to meet each patient's needs.

Pharmacologic Therapy

Use of antidepressants for treating depression was reported to reduce anxiety and improve symptoms of depression in adults with IBD.[41-43] However, the efficacy and appropriate use of these agents in children has yet to be determined, and adherence may be reduced by adverse effects (eg, nausea, vomiting, and diarrhea) and polypharmacy.[44] Physicians must also be aware of potential interactions between these medications and agents used to treat a patient's underlying IBD.

Nonpharmacologic Therapy

Cognitive behavioral therapy (CBT) has shown efficacy in improving depression symptoms and functioning in children with IBD by working to modify problem behaviors and thought processes.[45] Hypnosis has also improved quality of life and inflammation in adult IBD patients and may also be a promising modality for addressing emotional symptoms in pediatric patients.[46] Patients and family members may also benefit from participating in support groups and experience-sharing Web sites, such as www.experiencejournal.com, www.ccfa.org, www.ibdsf.com, www.starlight.org, www.cdhnf.org, and www.myibd.org.[37]

Case Study Hayley: Depression

After 3 months, Hayley comes in for a routine checkup, and her parents are concerned about changes in her mood. An ill-timed flare caused her to miss softball tryouts, and she has suffered an uncharacteristic loss of energy and motivation. Her parents expected her to bounce back after a few days, but Hayley has been consistently "down" for nearly 3 weeks. To avoid exacerbating her IBD symptoms with additional medications, she is started on CBT and provided with resources to an online support group for teens with IBD.

Summary

IBD frequently manifests during childhood. Because this is such a unique stage of growth and development, it is essential that physicians appropriately recognize symptoms consistent with IBD in their patients and expedite referral when clinically indicated. Primary providers also can play an important role by ensuring immunization status of these patients and assessing for comorbidities, including the impact of these disorders on bone and mental health. Treatment should be individualized to meet each patient's specific needs and should always include a thorough discussion with patients and their parents of the benefits and potential risks associated with different pharmacologic options. Regular assessment of mood and behavioral changes in patients is also critical to ensure timely treatment initiation in depressed patients.

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