Medical Management Based on Severity, Location of Crohn’s Disease

By Tesneem Ahmed, DO

Crohn’s disease is a chronic, relapsing inflammatory disease of the gastrointestinal tract. The goal of medical therapy is to achieve disease quiescence, prevent complications, maintain a good quality of life and prevent or delay surgical intervention as long as possible. Medical management in Crohn’s disease patients is based on disease severity and location, with treatment endpoints consisting of bringing active disease into remission and keeping it in remission.

The mainstays of medical therapy have included sulfasalazine, 5-aminosalicylic acid products, corticosteroids, 6-mercaptopurine, azathioprine, methotrexate, infliximab (Remicade®) and adalimumab (Humira®). Most recently, certolizumab pegol (Cimzia®) and natalizumab (Tysabri®) have been approved as alternative biologic agents for Crohn’s disease. All of these medications, through different mechanisms, modulate the immune system in order to decrease the intestinal inflammation seen in active Crohn’s disease.

Sulfasalazine and 5-aminosalicylic acid products work on local mediators in the inflammatory cascade to decrease intestinal inflammation. These drugs are available both orally and in rectal suppository/enema forms and are generally well tolerated as they predominantly act locally in the gut. They generally do not work as well in Crohn’s disease as they do in ulcerative colitis, but have
Distinguishing Ulcerative Colitis from Crohn’s Disease Is Not Always Easy

recent discovery that patchy disease involvement can be associated with UC, this endoscopic finding can no longer reliably distinguish UC from CD. Nonetheless, a diffuse distribution of inflammation beginning in the rectum remains a very important finding that strongly favors the diagnosis of UC.

**Major diagnostic features**

In the context of IBD, two major microscopic diagnostic features establish an unequivocal diagnosis of CD: true granulomas and discrete collections of lymphocytes penetrating through the full thickness of the bowel wall.

True granulomas consist of specialized types of inflammatory cells that pathologists recognize microscopically. Unfortunately, true granulomas are only sampled in a minority of endoscopic biopsies from CD patients (10 to 15 percent). They also are commonly mimicked by several other pathologic processes and require expertise by the pathologist for a correct diagnosis.

Lymphocytes are another specialized type of inflammatory cell that form discrete collections or aggregates extending throughout the full thickness of the bowel wall in CD, but not in UC.

UC is characteristically limited to only the inner-most lining of the bowel (the mucosa), which makes up less than 5 percent of the full intestinal wall thickness. Endoscopic biopsies only go deep enough to sample the mucosa. Thus, identification of the deeply penetrating collections of lymphocytes, which occurs in all CD patients, requires that the pathologist examine the entire bowel wall, a process which can only be done in surgically resected specimens.

In summary, distinguishing between UC and CD requires synthesis of all available endoscopic, clinical, radiologic and pathologic findings for each patient. The pathology on resected specimens is far more definitive, but remains uncertain in up to 10 percent of patients, who are ultimately diagnosed as having IBD of indeterminate type.

*Dr. Bronner is Director of Gastrointestinal Pathology and Section Head of Molecular Pathology at Cleveland Clinic.*

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**New Staff**

Jessica O'Connor

*Clinical Research Digestive Disease Center Study Coordinator*

Ms. O’Connor is a graduate of Wittenberg University with a bachelor of arts degree in biology and chemistry. After graduating, she worked with the Cooperative Human Tissue Network at Case Western Reserve University. In 2001, she attended Ross University School of Medicine in Dominica, West Indies, for two years of course work. She joined Cleveland Clinic in 2005 and worked in the Department of Pathology for two years before joining the research section within the Digestive Disease Institute in May 2007.
Why Bone Health Is So Important in Children with Crohn’s Disease

By Franziska Mohr, MD

Inflammatory bowel disease (IBD) has been recognized as one of the most significant chronic gastrointestinal diseases affecting children in the United States, with an estimated 10 percent of all cases being diagnosed in patients under the age of 18.

The initial presentation frequently occurs in a vulnerable period of growth and development. Children are at risk for malnutrition and poor growth through a combination of factors including decreased oral intake due to loss of appetite and pain, decreased absorptive capacity and increased metabolism. Two of the most common and serious complications are growth failure and bone demineralization.

Growth is a sensitive indicator of health and well-being in children and is often significantly impaired in those with Crohn's disease. Linear growth parameters such as height, weight and Body Mass Index (BMI) are used as indicators of disease activity and treatment success. Impaired growth may precede the presentation of classical gastrointestinal symptoms by several months or even years. Studies have shown that up to 46 percent of children will have a reduced height velocity before the onset of any symptoms and only 12 percent of pediatric Crohn's patients have a normal height velocity at the time of diagnosis.

The etiology of growth failure in these patients is multi-factorial and poorly understood, but results from a combination of chronic inflammation, malnutrition and, in some cases, prolonged steroid use. While nutrient deficiencies may have a direct effect on the growth plates, immune factors such as cytokines can affect growth either directly or indirectly through key hormones, including insulin-like growth factor and adrenal steroids resulting in compromised skeletal and sexual maturation.

Therapy with enteral nutrition and supplementation of vitamins and trace minerals is used to improve nutritional status and to provide adequate calories to allow for healing. In addition, immunosuppressive therapy with a variety of agents is aiming at interrupting the cycle of chronic inflammation and its effects on growth.

Skeletal health
Skeletal health is significantly impaired in many pediatric Crohn's patients. Their process of normal bone modeling that leads to increased bone formation and peak bone mass between puberty and early adulthood is often disrupted. Nutritional deficiencies, particularly vitamin D and calcium deficiency, immunologic factors like T-cells and cytokines, long-term systemic steroid use and physical inactivity all lead to decreased bone mineralization and increased fracture risk.

Bone mineral density should be monitored closely in children with IBD and, if found to be deficient, supplementation with vitamin D and calcium is recommended. Long-term steroid use should be avoided and, in general, a steroid sparing therapy approach should be taken in growing children. Use of immunomodulator therapies such as azathioprine or methotrexate or biologic agents such as infliximab is considered earlier in the disease process for this reason.

Although bisphosphonate therapy has been shown effective in adults, it is unclear whether their use will prevent bone demineralization in children with Crohn's disease and there are insufficient data available to recommend their use in pediatric patients.

Conclusion
In addition to the many clinical challenges faced by adults with Crohn's disease, children are faced with a variety of issues unique to their age group and growing bodies. The two most serious and common complications that affect not only their general health, but also their psychosocial development, include impaired growth and bone demineralization.

Adequate medical management, close monitoring and a strong patient/parent and physician partnership remains paramount to minimizing complications and maximizing growth potential, bone health and quality of life.

Dr. Mohr is a pediatric gastroenterologist at Cleveland Clinic. To schedule an appointment with her, please call 216.444.9000.
Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the intestines of unknown cause. They share many clinical and pathologic features, frequently making them difficult to distinguish. For this reason, the blanket term "inflammatory bowel disease" (IBD) is often used for both.

Distinguishing the two becomes very important, however, if surgical treatment becomes necessary. UC can be cured by removing the entire colon and rectum, whereas surgery for CD will likely result only in short-term remission for many patients.

As recently as 10 to 15 years ago, UC was believed to virtually always affect the colonic lining (the mucosa) in a diffuse manner. However, extensive research has more recently shown this not to be the case in a significant group of UC patients. It remains true that UC usually involves the end of the colon, also known as the rectum, in continuity with a variable length of more proximal colon, and, frequently, the entire colon.

There are numerous reported exceptions to this fact and we now know that one-third of UC patients may also have patchy inflammation. This usually occurs in patients with longstanding disease (>8 to 10 years) or those in clinical remission. The patchy inflammation may also be due to the effects of medications.

Unlike UC, CD may affect any part of the gastrointestinal tract from the mouth to the anus. Non-colonic involvement is a primary way that CD can be distinguished from UC. The small bowel alone is affected in about 30 percent of patients with CD and the small and large bowel are affected together in about 55 percent. The colon is thought to be affected by itself in 15 percent of the cases, but this is probably overestimated due to newer knowledge that UC may also be patchy in its distribution. In the most common pattern of involvement, CD affects the end of the small intestine (the terminal ileum) together with the adjacent portion of the colon (the cecum).

Inflammatory lesions of the anus, where the rectum opens onto the skin, are particularly characteristic of CD and may occur even in the absence of inflammation of the colon. They are far less common in UC, but not unheard of.

A discontinuous pattern
CD almost always affects the bowel in a discontinuous or patchy manner. The typical discontinuous pattern of inflammation produces an endoscopic appearance of segments or regions of inflamed mucosa separated by normal bowel, which are also called "skip" areas. In about half the patients who have CD with colonic involvement, the rectum is spared both endoscopically and histologically. The term histologically refers to the appearance of tissue samples as seen magnified under a microscope. Microscopic examination of the tissues is performed by pathologists, another group of specialized physicians who work with gastroenterologists and surgeons to care for and ensure the correct diagnoses for IBD patients.

The endoscopic appearance of CD may closely resemble that of UC if the CD patient has diffuse inflammation involving most of the colon. However, this is distinctly unusual in CD. With the more

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a role mostly in patients with Crohn's that involves the colon.

In terms of corticosteroids, both prednisone and budesonide have been effective in inducing treatment response; however, their long-term use has not been shown to be effective in maintenance of disease remission. Moreover, the risk of osteoporosis, diabetes mellitus, cataracts and glaucoma, in addition to a number of other adverse side effects, has been the leading deterrent against prolonged steroid use in Crohn's disease. Patients on long-term steroids must be checked for osteoporosis with a bone density scan known as a DEXA scan as well as be placed on daily calcium and vitamin D supplementation.

Patients who are steroid-dependent can be treated with 6-mercaptopurine (6-MP) and azathioprine (Imuran®) for maintenance of disease remission. Patients who are on these medications should have their blood counts and liver enzymes monitored closely, as serious side effects of these drugs may include increased risk of infections, liver toxicity and bone marrow suppression.

Biologic agents

In patients who prove to be refractory to the above medical therapy or those with more aggressive disease, biologic agents have become increasingly acceptable and widespread in their use.

The two most widely used biologic agents are infliximab (Remicade) and adalimumab (Humira). Infliximab acts as a monoclonal antibody blocking the effects of TNF-α (tumor necrosis factor alpha), which is one of the key parts of the inflammatory response seen in Crohn's disease. It was approved by the FDA in August 1998 and is given as an intravenous infusion at 0, 2 and 6 weeks for induction and then every 8 weeks for maintenance. Humira is an alternative drug that received FDA approval in February 2007 for Crohn's disease. Humira is similar to Remicade in that it targets the effects of TNF-α. Humira is a self-administered subcutaneous injection given at a dose of 160 mg at the beginning of treatment, 80 mg at week 2 and then 40 mg every other week beginning at week 4. Patients should be screened for tuberculosis and Hepatitis B prior to starting either of these medications. These medications are not to be used in patients who have lymphoma, or have been treated in the past for it.

Newer agents

Advances in medical therapy have led to the emergence of two new biologic agents: natalizumab (Tysabri) and certolizumab pegol (Cimzia).

Tysabri, originally developed for treatment of multiple sclerosis, was approved by the FDA in January 2008 for treatment of Crohn's disease and functions as an antibody targeting alpha-4 integrin, which leads to the blocking of inflammatory cells into the gut. It is available as an intravenous infusion every 4 weeks and is indicated for patients with moderate to severe Crohn's disease that has not responded to other therapies. Serious side effects are most notable for the risk of a very rare brain infection called progressive multifocal leukoencephalopathy (PML) caused by the JC virus in addition to the risk of opportunistic infections and liver toxicity.

Cimzia, approved by the FDA in April 2008, is another antibody which targets TNF-α. It is available as a self-administered subcutaneous injection which is given once per month.

Individualizing care

A customized treatment protocol must be devised for each individual Crohn's patient with the goal of induction and maintenance of remission of disease while balancing potential side effects and maintaining quality of life.

The area of medical therapy for Crohn's disease is ever expanding, and several new medications are being designed and investigated in clinical trials.

For an appointment with Dr. Ahmed, call Cleveland Clinic's Digestive Disease Institute at 216.444.6536.
Exercising Your "Abs:" Biologic Therapy for Crohn's Disease

By Bret Lashner, MD

We are in the midst of a new era for the treatment of Crohn's disease. Four biologic therapies, or genetically engineered molecules, have been approved by the FDA for the treatment of Crohn's disease. Each of these therapies is an antibody (hence the "ab" terminology) directed to eliminate the effect of a specific antigen.

For example, an antibody to tumor necrosis factor (TNF) will eliminate TNF circulating in the bloodstream and bind to TNF that sits on the outer membrane of some inflammatory cells, thereby causing cell inactivation. Some details of these biologic therapies are listed below.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer/Year approved</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Remicade®</td>
<td>Centocor/1998</td>
<td>Anti-TNF</td>
<td>Intravenous</td>
<td>Every 8 weeks</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira®</td>
<td>Abbott/2007</td>
<td>Anti-TNF</td>
<td>Subcutaneous</td>
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<tr>
<td>Certolizumab</td>
<td>Cimzia®</td>
<td>UCB/2008</td>
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<td>Every 4 weeks</td>
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<tr>
<td>Natalizumab</td>
<td>Tysabri®</td>
<td>Elan/2008</td>
<td>Anti-integrin</td>
<td>Intravenous</td>
<td>Every 4 weeks</td>
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In general, these medications work better than conventional therapies, but have certain risks and costs associated with them. They should be part of the discussion with your doctor regarding medical therapy options for Crohn's disease.