ABSTRACT: Inflammatory bowel disease (IBD) encompasses a variety of clinical signs and symptoms, and the diagnosis is made with a combination of modalities, including radiographic, endoscopic, and pathologic studies. At this time, serum makers and genetic studies are not recommended to help in the diagnosis or the day-to-day management of IBD. This chronic disease requires long-term treatment; discontinuation of therapy leads to relapse. 5-Aminosalicylic acid drugs are sufficient therapy for ulcerative colitis; however, higher doses are often needed to control the disease. Because of its more aggressive nature, Crohn’s disease is treated with immunomodulators more frequently than ulcerative colitis. Anti-tumor necrosis factor therapy is used for both ulcerative colitis and Crohn’s disease, although at this time only infliximab is FDA approved for ulcerative colitis.

Key words: inflammatory bowel disease, Crohn’s disease, ulcerative colitis

Inflammatory bowel disease (IBD) is not uncommon; the prevalence is approximately 100 per 100,000 persons in the general population. In the United States, there are estimated to be more than 1 million cases, divided equally between Crohn’s disease (CD) and ulcerative colitis (UC). The incidence of UC has remained steady (2 to 6 per 100,000), whereas the incidence of CD has been increasing.

Patients with IBD often present first to, and are managed by, a primary care physician. Thus, in this article, we focus on the diagnosis and management of IBD in the primary care setting.

EPIDEMIOLOGY

About one third of cases of IBD present in the second decade of life. The peak incidence occurs between 10 and 30 years of age, although IBD does occasionally develop in very young children (2% of cases). There is also an increased incidence in older adults between the 6th and 7th decades. IBD is slightly more likely to develop in women than in men. Currently IBD most commonly occurs in North America, Western Europe, and Australia (all areas that are heavily populated by people of European descent).

Patients with IBD account for nearly 750,000 physician visits per year and are often hospitalized; CD is responsible for about two thirds of these visits and hospitalizations. There are an estimated 20,000 hospitalizations and 250,000 physician visits for UC each year, although these figures may change as outpatient treatment becomes more aggressive. Many hospitalizations for IBD involve surgery, especially in patients with CD (50% to 80% of these patients eventually require surgery). Other hospitalizations are usually for acute flares of the disease.

PATHOGENESIS

Although clinically it is convenient to divide IBD into the two spe-
cific entities of UC and CD, IBD is a spectrum ranging from mild to severe disease; UC and CD are simply part of this spectrum. The normal gut experiences local inflammation at times, but the key feature of IBD is failure to downregulate the immune system and control local inflammation.

The epidemiologic data support a genetic component in the pathogenesis of IBD, including twin studies, familial aggregation, and differences in ethnic disease prevalence. The inheritance of IBD is polygenetic; the data do not support a simple Mendelian model of inheritance.

The earliest gene found to be associated with CD is NOD2. The gene is located on chromosome 16q12 and is related to the immune response to bacteria activating downstream inflammatory cell signals, which supports the theory that IBD is secondary to a failure to downregulate the immune system. One copy of the mutated gene confers a 1.5- to 4-fold risk of CD. NOD2 has also been associated with a younger age at diagnosis, ileal disease, and stricture formation.

Several environmental triggers contribute to the onset of disease and disease flares; they include infection, NSAIDs, antibiotics, diet, stress, and smoking. These environmental triggers in conjunction with genetic and immunological factors are all involved in the development of IBD.

**DIAGNOSIS**

The diagnosis of IBD is typically based on the clinical manifestations along with radiographic, endoscopic, and pathologic findings. Despite the fact that the diagnosis can typically be made using these modalities, occasionally additional testing is necessary to confirm the diagnosis. Several serologic tests, stool protein tests, and unique imaging studies have been developed recently to aid in diagnosis.

**Sero logical tests.** Three specific immune markers have been identified in the serum of patients with IBD: pANCA, ASCA, OmpC, and CBir1.4 Antineutrophil cytoplasmic antibody with perinuclear highlighting (pANCA) was first described in 1990. About 60% of patients with UC and 25% of patients with CD are pANCA positive. However, while DNase sensitive pANCA is highly specific for IBD, fewer than 5% of persons who do not have IBD express DNase sensitive pANCA.

Anti-Saccharomyces cerevisiae (ASCA) was first described in patients with CD in the late 1980s. Saccharomyces cerevisiae is a form of baker’s and brewer’s yeast. ASCA is present in about one-half to two-thirds of patients with CD. However, unlike DNase sensitive pANCA, which is present in both UC and CD, ASCA is very specific for CD only. It is rarely expressed in persons who do not have IBD. A subset of patients with colonoscopy/histology-proven CD do not express ASCA antibodies. OmpC and CBir1 are protein markers that are more specific to CD.

These serologic tests are most helpful when the diagnosis of IBD is apparent but the type is in question, or when diagnostic certainty is needed. For example, it is important to order these tests before planned colectomy. Diagnostic certainty is crucial before pouch formation because pouchitis is more likely to occur in patients with CD than in those with UC. These tests can also aid in the diagnosis of IBD when extraintestinal manifestations, such as ankylosing spondylitis, arthritis, pyoderma gangrenosum, or uveitis, are the predominant symptoms.

**Stool protein tests.** Several neutrophil-derived proteins in feces have been studied, including fecal lactoferrin and calprotectin. Both of these proteins are products of activated neutrophils.5 Lactoferrin testing is available commercially as the IBD Quick Chek® and the LeukoTest®. Calprotectin is available commercially as the PhiCal Test®. These tests are most helpful in discriminating between irritable bowel syndrome and IBD, especially when invasive testing must be avoided.

**Imaging studies.** Although traditional colonoscopy is typically used for the diagnosis of CD, it limits the endoscopic evaluation to the colon and terminal ileum. Because CD can affect any part of the GI tract, many lesions may be missed by colonoscopy. Several new imaging modalities have been developed to evaluate the small intestine in CD. Capsule endoscopy has been approved for this use, and its benefit in diagnosing intestinal CD has been demonstrated in several case series.6 CT and MR enterography and enteroclysis are other imaging modalities that not only can demonstrate small intestinal disease but also can noninvasively detect colonic changes consistent with IBD.7

**MEDICAL THERAPIES**

IBD is characterized by acute flares separated by periods of quiescence. It is therefore important to develop maintenance strategies to prevent frequent flares, complications, and premature mortality.

The primary goals of IBD therapy are to minimize symptoms, enhance patient well-being, and prevent the complications of IBD.8 Waiting until a patient with IBD has a clinical flare-up to attempt to induce remission with corticosteroids, aminosalicylates, and/or immunomodulators may lead to cumulative toxicity, such as increased risk of avascular necrosis, calcium loss, cataracts, or diabetes from the pulse of corticosteroids needed. In addition, patients may experience more symptoms—
such as diarrhea, weight loss, or bleeding—until their reactivated disease is controlled.

Because corticosteroids do not prevent relapse in either UC or CD, they should not be used for long-term disease suppression, since these drugs are associated with long-term toxicity. In patients with UC, even in the absence of overt disease, enough disease activity may be present to cause dysplasia and increase the risk of cancer; thus, a watchful waiting approach is inappropriate. Finally, especially for patients with CD, keeping disease activity under control may prevent strictures, fistulas, and other complications that could lead to surgery.

**Ulcerative colitis.** When selecting an agent to induce remission, consider the extent and severity of the disease. For UC, guidelines stress the importance of endoscopically determining the proximal extent of the disease: whether it is limited to the rectum, extends to the splenic flexure (proctosigmoid disease), or extends proximally beyond the splenic flexure (pancolitis).9

The cornerstone of therapy for mild to moderate UC is 5-aminosalicylic acid (5-ASA) drugs (including mesalamine, sulfasalazine, and balsalazide), either oral or topical formulations (rectal mesalamine enemas or suppositories), depending on the proximal extent of disease. The effectiveness of oral aminosalicylates is thought to be dose-dependent. Because of the favorable safety profile of these drugs, up to 4.8 g/d can be used to treat active disease. It generally takes about 10 to 14 days to start to see a true effect, but patients may note a difference within a week. In at least 7% of patients, their condition worsens with 5-ASA drugs; this is a hypersensitivity reaction that precludes the use of any of these agents.

For more active disease, or when the 5-ASA drugs may not be sufficient to suppress symptoms rapidly, a short course of an oral corticosteroid at a moderate dosage (prednisone, 40 to 60 mg/d), with a rapid taper once symptoms are controlled, is recommended. Infliximab also has FDA approval to control signs and symptoms of active UC in the outpatient setting. For localized rectal disease, hydrocortisone enemas, foams, or suppositories may be used. Finally, for severe disease, hospitalization with intravenous corticosteroids is recommended; failure to respond to intravenous steroids warrants discussion about infliximab, intravenous cyclosporine, or surgery.

To establish remission in patients with UC, fairly high doses of 5-ASA drugs may be necessary (up to 4.8 g/d). Remember that the doses of the various forms of these medications are not equivalent. For example, 2.4 g of mesalamine is equivalent to 6.75 g of balsalazide. A combination of rectal and oral therapy to treat left-sided disease is superior to either alone (Table 1).

Once remission has been achieved, maintenance therapy is indicated. If 5-ASA products have successfully induced remission, they are continued to maintain remission. Medications are not stopped just because a patient feels well. For patients who have a steroid-induced remission, corticosteroids (either oral or topical) do not maintain remission and should not be used because of toxicity. Those patients whose conditions worsens when their corticosteroid doses are reduced or stopped may truly be corticosteroid-dependent, and other therapy such as immunosuppression with azathioprine 1.5 to 2.5 mg/kg/d or infliximab should be considered.

**Crohn’s disease (inflammatory disease).** In the treatment of CD limited to the colon, 5-ASA drugs can be effective in establishing and maintaining remission, particularly if given in high (4 g or more per day) doses (Table 2).10 Most patients, however, require immunosuppressants to induce remission, and this is often achieved in the short term with corticosteroids. Steroid-sparing immunomodulators, including azathioprine 2.5 mg/kg/d, 6-mercaptopurine (6MP) 1.5 mg/kg/d, or methotrexate 25 mg given subcutaneously once a week are used.

### Table 1 – Therapies used to establish remission in ulcerative colitis

<table>
<thead>
<tr>
<th>Severity of disease</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>Mild to moderate</td>
<td>Aminosalicylates</td>
</tr>
<tr>
<td>Distal disease</td>
<td>Topical or oral</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>Oral or combination therapy</td>
</tr>
<tr>
<td>Moderate</td>
<td>Short course of corticosteroid therapy with a rapid taper; infliximab</td>
</tr>
<tr>
<td>Severe</td>
<td>Intravenous corticosteroids; intravenous cyclosporine or infliximab</td>
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</tbody>
</table>
week, have been effective both in inducing remission and in weaning patients with steroid-dependent CD from corticosteroids. Methotrexate works more quickly than the other immunomodulators, but it requires monthly monitoring of liver enzymes as well as blood cell counts and is absolutely contraindicated in women who are considering childbearing. It is particularly useful for those patients who have arthralgias associated with their active disease. If there is no response to methotrexate after 12 weeks, consider an alternative.

Azathioprine and 6MP have been used for over 30 years and are considered the standard of care, but they are long-term management tools because they take 3 to 6 months to result in a benefit. Antibiotics such as metronidazole and ciprofloxacin are sometimes used as adjunctive therapy, but they are more useful for treatment of fistulas.

The anti-tumor necrosis factor (anti-TNF) agents include infliximab, adalimumab, and certolizumab pegol. All three are FDA approved for the treatment of moderate to severe disease. Infliximab was the first anti-TNF agent and is 75% human and 25% murine. It is given intravenously at weeks 0, 2, and 6 and then every 8 weeks for maintenance. Adalimumab is 100% human and is administered subcutaneously via syringe or an EpiPen-like device. It is given with a loading dose of 160 mg (4 injections) at week 0, 80 mg (2 injections) at week 2, and then 40 mg (1 injection) every other week. Certolizumab pegol is a Fab fragment; it is given subcutaneously as a loading dose of 200 mg at week 0, 2, and then monthly. Because the data from controlled trials demonstrate comparable efficacy and safety for each of these agents, the selection of initial therapy is based on physician experience, insurance coverage, and patient preferences.

Crohn’s disease (fistulizing disease). Antibiotics such as metronidazole and ciprofloxacin have been used to treat fistulas and can eliminate drainage and promote healing in about one-third of patients. Azathioprine and 6MP are effective but take 3 to 6 months to heal fistulas. The anti-TNF agents are also effective; infliximab was studied in controlled trials specifically for this purpose. Corticosteroids, methotrexate, and the 5-ASA agents do not heal fistulas.

**OTHER MANAGEMENT CONSIDERATIONS**

**Relapse.** Despite treatment, IBD is a relapsing and remitting disease. Within 6 months, 70% to 80% of patients with UC will have a relapse if they stop maintenance therapy. Only about 5% of patients will have just one attack in their lifetime. About 20% to 25% of patients with severe UC will require a colectomy.

Relapses in CD tend to be less predictable. About 54% to 78% of patients with CD relapse within 18 to 24 months. At the site of surgical anastomosis, 73% to 93% of patients will have new CD lesions in previously uninvolved bowel. Clinical re-

### Table 2 – Therapies used to establish remission in Crohn’s disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylates*</td>
<td>Mild to moderate disease; target to disease location</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Mild to moderate disease; perianal, infectious complications</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Moderate to severe disease</td>
</tr>
<tr>
<td>Immunomodulators* (azathioprine, 6-mercaptopurine, methotrexate)</td>
<td>Moderate to severe disease</td>
</tr>
<tr>
<td>Biologics (infliximab, adalimumab, certolizumab pegol)</td>
<td>Moderate to severe disease</td>
</tr>
</tbody>
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*Off-label use.

### Table 3 – Systemic complications of IBD

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
<tr>
<td>Eye inflammation</td>
</tr>
<tr>
<td>Lower bone density*</td>
</tr>
<tr>
<td>Liver and bile duct inflammation</td>
</tr>
<tr>
<td>Gallstones</td>
</tr>
<tr>
<td>Kidney stones</td>
</tr>
<tr>
<td>Subfertility*</td>
</tr>
<tr>
<td>Skin lesions*</td>
</tr>
<tr>
<td>Arthritis and joint pain</td>
</tr>
<tr>
<td>Growth failure in children</td>
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</tbody>
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*Increased incidence in women. IBD, inflammatory bowel disease.
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The best outcomes occur if a woman is in remission before pregnancy and continues maintenance therapy throughout pregnancy. Risk of malignancy. Patients with IBD, particularly those with pancolitis UC or extensive CD, have a much higher risk (20-fold greater) than the general population of developing cancer of the colon or rectum. The risk increases after 10 years of disease; thus, these cancers tend to occur at a younger age than do those in the general population. Surveillance colonoscopy with dedicated biopsies to detect dysplasia is recommended starting 8 to 10 years after diagnosis and occurring every 1 to 2 years; after 20 years, the procedure should be performed every year.

REFERENCES: