Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), is a common cause of adult and childhood morbidity throughout the world. Approximately 1 million people in the United States have UC and CD. Over the past 10 years, clinicians and researchers have vastly expanded the diagnostic and therapeutic options available for patients with UC and CD. It is important that clinicians understand these options when evaluating patients with suspected IBD and when discussing treatment with them. This article reviews the definition, diagnosis, and treatment of these complex diseases and discusses recently developed diagnostic modalities and therapies for IBD.

**Epidemiology**

Epidemiologic studies have shown that the incidence of CD has increased over the past 40 years, while the incidence of UC has leveled off. In separate studies from Olmsted County, MN, and northern Norway, the incidence of UC was 15 and 12.8 cases per 100,000 persons, respectively. The incidence of CD ranges from 3.1 to 14.6 cases per 100,000 person years. The Ashkenazi Jewish population has the highest prevalence rates of disease of any group in the world. Patients with IBD typically develop symptoms between 15 and 40 years of age. However, a second peak between 50 and 80 years is also suggested in some studies. There appears to be no difference in risk between men and women.

**Factors Underlying the Development of IBD**

IBD is a chronic inflammatory disorder of the gastrointestinal system. UC and CD are immunologically mediated disorders whose underlying pathophysiology is multifactorial and involves an abnormal immune response in genetically susceptible individuals to an environmental stimulus. The cause of the inflammatory response is multifactorial and is thought to be a combination of defective mucosal barriers and altered mucosal immunity.

**Family History**

Studies have shown that a positive family history is the strongest risk factor for future development of IBD. There appears to be a closer relationship between family history and disease development in CD than in UC. Concordance rates in identical twins are 60% in CD and 15% in UC. If both parents have IBD, the chance that their child will develop disease by age 28 years is 33%.

**Environmental Factors**

Environmental factors are important in the manifestation of IBD, and smoking seems to have the most profound effect. Smoking is protective against UC but may increase a person’s risk of CD. Smoking has also been shown to increase CD-related symptoms and is an independent risk factor for disease recurrence after surgery. It has also been suggested that non-steroidal anti-inflammatory drugs may lead to or worsen disease flares. Some studies have shown that an appendectomy early in life will reduce one's chance of developing UC. Initial studies pointed to a relationship between IBD and various psychosocial abnormalities, although this has not been borne out. Although studies suggested that stress may lead to disease exacerbations from enteric activation and proinflammatory cytokines, recent findings from Li and colleagues do not support an association between psychological stress and the development of IBD in young to middle-aged adults.

**Genetic Susceptibility**

With the development of new genetic technologies, physicians are beginning to understand the basic pathogenesis of IBD. Multiple studies have confirmed the significant role that individual gene loci have on disease development. In 1996, Hugot and colleagues confirmed the role of the NOD2/CARD15 gene in CD. Multiple genes have now been identified that are associated with susceptibility to both UC and CD. These include the NOD2/CARD15 gene, as well as the ATG16L1, TNFAIP3, and IRGM genes. The identification of these genes has provided new insights into the pathogenesis of IBD and has led to the development of new therapeutic targets.

**Conclusion**

Inflammatory bowel disease is a complex disorder with multiple risk factors and underlying pathophysiologic mechanisms. Advances in our understanding of the disease have led to improved diagnostic and therapeutic options for patients with IBD. Further research is needed to better understand the genetic and environmental factors that contribute to the development of IBD and to develop new targeted therapies for the treatment of this disease.
described a region spanning the centromere on chromosome 16, the IBD 1 locus, as a gene that predisposes to CD. This linkage to CD has since been confirmed by multiple investigators. The IBD 1 gene is a nucleotide oligomerization domain (NOD). NOD 2, later renamed caspase activation and recruitment domain (CARD) 15, has been linked to early onset of severe disease. NOD 2/CARD 15 is an intracellular pattern recognition receptor that upon sensing the bacterial cell wall component muramyl dipeptide activates the transcription factor nuclear factor-κ B (NF-κB), which leads to the transcription of inflammatory response genes. Mutations in regions of the NOD 2/CARD 15 gene result in failure of NF-κB activation, resulting in dysfunction in the innate immunity and stimulation of a proinflammatory state. Individuals with mutations in NOD 2/CARD 15 have increased susceptibility to CD involving the ileum. Patients with CD who have these mutations are more likely to develop strictures than patients without the gene. Moreover, NOD-2 mutations do not predispose and may, in fact, be protective against the development of UC.

Certain genetic variations have been shown to be associated with phenotypic subgroups. CARD 15/NOD 2 defects are linked to ileal CD and more severe complications such as fistulas and fibrostenotic CD. The HLA-DRB1*0103 allele is associated with severe UC and colonic CD. This loci is also linked to an increased likelihood that colectomy will be needed. These data suggest that understanding the genetics of UC and CD will allow physicians to not only predict disease presentation and severity but also to select more appropriate therapeutic options.

### Table 1. Differences Between Ulcerative Colitis and Crohn’s Disease

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Mucus</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Rare</td>
<td>+++</td>
</tr>
<tr>
<td>Perianal fistulas</td>
<td>Rare</td>
<td>+++</td>
</tr>
<tr>
<td>Effect of smoking</td>
<td>Improves symptoms</td>
<td>Exacerbates symptoms</td>
</tr>
</tbody>
</table>


### CLINICAL FEATURES

#### Ulcerative Colitis

UC is characterized by recurrent episodes of inflammation limited to the mucosal layer of the colon. At initial presentation, approximately 50% of patients will have pan-colitis, 25% to 33% will have isolated proctitis, and the remaining 25% will have left-sided disease. At any one time, approximately 50% of patients with UC will be in remission. After 10 years of disease, 24% of patients have had a colectomy. UC always involves the rectum and spreads proximally in a continuous fashion.

UC and CD have unique clinical manifestations that enable clinicians to distinguish between the two in most cases (Table 1). Symptoms related to UC can be divided into mild, moderate, or severe. Most patients at initial presentation will have moderate symptoms (71%), 9% will have severe symptoms, and the remaining 20% will have mild symptoms. Those with mild disease have fewer than 4 stools per day with minimal blood at most, whereas those with severe disease have more than 6 stools per day as well as fever and possibly anemia. Symptom severity can be independent of how much of the colon is involved with colitis. Occasionally, patients will present with severe bloody diarrhea (> 10 stools/d) and have signs of systemic toxicity. Severe UC can involve the muscle layers of the colon, which impairs motility and may lead to toxic megacolon and resultant perforation. This condition is termed fulminant colitis and can lead to the need to perform a colectomy in a large percentage of these patients.

#### Crohn’s Disease

CD is distinguished by its transmural mucosal inflammation and may involve the entire gastrointestinal tract, with up to 70% of patients having small bowel involvement. The disease course tends to be more aggressive than UC. Approximately 90% of patients with ileal or cecal disease will eventually require surgery. The transmural inflammation that is typical of CD can lead to fibrosis, obstruction, and fistula formation.

The clinical manifestations of CD are more variable than those in UC. The anatomic distribution of lesions is key in determining symptoms, clinical course, and prognosis. Disease is confined to the colon in 27% of patients, and 29% of patients have only small bowel disease. As many as 41% have both small and large bowel involvement, with one-half of patients having rectal sparing disease. CD may involve any region of the gastrointestinal tract. Typically diarrhea, abdominal pain, fever, and weight loss are the initial symptoms. Crampy abdominal pain occurs frequently, but gross bleeding is...
less common than in UC. These patients may present with peritonitis, fever, and abdominal pain. Sinus tracts may lead to enterovesical, enterovaginal, and enterocutaneous fistulas or fistulas to the retroperitoneum.

**Indeterminate Disease**

Although UC and CD are distinct pathologic entities, differentiating between the two is often difficult in patients with isolated colitis. In approximately 10% to 15% of patients with IBD, physicians will not be able to differentiate between UC and CD. These patients are termed “indeterminate.” The inability to definitely distinguish between the 2 diseases can have a tremendous impact on the medical and surgical options available to the patient.

**Extraintestinal Manifestations**

Extraintestinal manifestations are common in both UC and CD and occur in 21% to 36% of these patients (Table 2). Extraintestinal manifestations can affect any organ system, but the typical sites of involvement are the eyes, skin, and musculoskeletal system. Uveitis and episcleritis are common in both disorders. Erythema nodosum is more common in patients with CD, with a prevalence between 10% and 20%. The presence of erythema nodosum usually parallels the activity of the patient’s CD. Conversely, pyoderma gangrenosum is found in 1% to 10% of patients and is more common in UC. The activity of pyoderma can be independent of a patient’s luminal disease. Arthritides typically involve the large joints in an asymmetric pattern and may be the presenting manifestation of IBD in approximately 20% of patients. The course of ankylosing spondylitis and biliary manifestations such as primary sclerosing cholangitis is independent of the course of the patient’s bowel disease.

**DIAGNOSTIC MODALITIES**

The presumptive diagnosis of IBD is typically made on the basis of a characteristic history provided by the patient. Various diagnostic modalities and histological evidence are used to enhance or confirm a clinical suspicion of IBD and to differentiate between CD and UC. Endoscopy is generally considered the gold standard. The use of computed tomography (CT), magnetic resonance imaging (MRI) technology, and, more recently, capsule endoscopy has provided gastroenterologists with more options in evaluating patients with suspected IBD.

**Endoscopy**

Endoscopy can provide evidence of inflammation and allows for tissue sampling and evaluation of extent of disease. Endoscopic findings in UC typically consist of loss of the typical vascular pattern, ulcerations, and friability (Figure 1). Severe cases may show larger areas of ulceration, profuse bleeding, or exudates involving the colon (Figure 2). Continuous inflammation beginning in the rectum is the hallmark of UC; however, it is possible to see patchy areas of inflammation proximally on endoscopy, especially if the patient has already started treatment. The histology seen on biopsy involves crypt abscesses, gland atrophy, and the loss of goblet cells.

Colonoscopy with intubation of the terminal ileum is important in the diagnosis of CD. Ulcerations adjacent to normal appearing mucosa (ie, skip lesions) that give a cobblestone appearance are characteristic (Figure 3). Noncaseating granulomas can be found on biopsy but are present only approximately one third of the time. Granulomas are nonspecific, and their presence is not pathognomonic for CD. Infectious etiologies, such as tuberculosis, *Clostridium difficile* colitis, or cytomegalovirus colitis, can also be mistaken for CD.

**Imaging Studies**

Barium studies have been used for years to evaluate areas of the bowel, such as the proximal ileum, that is not accessible to colonoscopy. Newer CT and MRI technologies provide more detailed images of these proximal lesions. CT enterography, or CT enteroclysis, incorporates high-resolution CT scanning and infusion of

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**Table 2. Extraintestinal Manifestations of Inflammatory Bowel Disease**

<table>
<thead>
<tr>
<th>Site</th>
<th>Manifestation</th>
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<tbody>
<tr>
<td>Skin</td>
<td>Erythema nodosum</td>
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<tr>
<td></td>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td>Joints</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Eye</td>
<td>Uveitis</td>
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<tr>
<td></td>
<td>Episcleritis</td>
</tr>
<tr>
<td>Blood</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Thromboembolic events (deep vein thrombosis, pulmonary embolism)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Obstructive uropathy</td>
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<tr>
<td></td>
<td>Fistulization to gastrointestinal tract</td>
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<tr>
<td></td>
<td>Secondary amyloidosis</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease</td>
</tr>
</tbody>
</table>

Adapted with permission from Hoffmann RM, Kruis W. Rare extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2004;10:140–7.
water or methylcellulose solution by mouth or by nasoenteric intubation and allows depiction of small bowel disease in those with suspected proximal lesion (Figure 4). In a study of 106 patients, CT enterography had a sensitivity of 100% and a specificity of 95% for small bowel lesions. Similar technologies using MRI have also been shown to be a reliable method of evaluating small bowel pathology in IBD. Evaluation of fistulizing CD has also been improved with the use of MRI and endoscopic ultrasound (EUS). Schwartz et al concluded that MRI and EUS were accurate modalities for assessing fistulas in patients with fistulizing CD.

**Video Capsule Endoscopy**

Video capsule endoscopy, which was first developed for use in detecting obscure GI bleeding, is becoming a widely used and accepted diagnostic tool in IBD as well. The typical capsule costs approximately US $450, is smaller than a dime, and contains a lens, color camera chip, batteries, transmitter, and antenna. Patients ingest the capsule, and the images are transmitted to an external receiver worn around the patient’s waist.
Multiple studies have demonstrated the utility of capsule endoscopy in CD. Fireman et al. showed that 12 of 17 patients with a normal colonoscopy and small bowel follow-through but with a high clinical suspicion of CD had lesions consistent with CD on capsule endoscopy. Recently, Chong et al. compared capsule endoscopy to CT enteroclysis and push enteroscopy in 42 patients (21 with known CD and 21 with suspected CD). Capsule endoscopy detected more erosions than the other modalities in the group of patients with known CD, but there was no difference in yield in the cohort with suspected CD. More importantly, the findings on capsule endoscopy led to a change in management in 70% of these patients. Similarly, Voderholzer et al. compared capsule endoscopy to CT enteroclysis in 41 patients with known CD. In this study, the main difference between capsule and CT scanning was in the detection of proximal lesions (jejunum and proximal ileum). Capsule was able to detect lesions in almost twice as many patients as CT. As with the Chong study, capsule findings led to changes in therapy in 10 patients. All patients improved with the alteration in medications.

Contraindications to capsule endoscopy include patients with a history of small bowel obstruction, past strictures, prior major abdominal surgery, or other evidence of gastrointestinal pathology on small bowel series. The primary concern with capsule endoscopy is that the capsule may be retained due to strictures. Capsule endoscopy has several limitations including being able to visualize only mucosal surfaces and not being able to collect biopsy specimens. Overall, capsule endoscopy is a promising new technology that should be beneficial in the diagnostic work-up of patients with IBD. However, its exact role in this setting is still being defined.

Serologic and Fecal Testing

Serological markers, such as perinuclear-staining antineutrophil cytoplasmic antibodies (p-ANCA) and anti-\textit{Saccharomyces cerevisiae} antibodies (ASCA), have been used in evaluation of IBD. Studies have shown that p-ANCA is found predominantly in those with UC, while ASCA is more prevalent in those with CD. A study of 813 patients showed that the prevalence of ASCA in patients with CD was 59.7%, while that of p-ANCA in UC was 49.7%. The specificity of ASCA for differentiating CD from controls was 91%, while the specificity of p-ANCA for separating UC from controls was 95%. Unfortunately, the sensitivity of both ASCA and p-ANCA are too low (60% and 50%, respectively) for these tests to be useful as a sole diagnostic tool in patients with suspected IBD.

As discussed earlier, the inability to distinguish between CD and UC can have a tremendous impact on a patient’s medical and surgical options. Unfortunately, serologic testing does not appear to be helpful in determining a diagnosis (UC or CD) in patients with indeterminate colitis. In a study that prospectively applied ASCA and p-ANCA testing to 97 patients with...
indeterminate colitis, the test was not helpful in nearly half of the patients; 47 (48.5%) were negative for both ASCA and p-ANCA. In addition, in patients whose test suggested UC (ASCA negative/p-ANCA positive), 36% actually had CD. CD was definitively diagnosed in 17 of these patients based on characteristic small bowel involvement, fistula formation, or granulomas found at biopsy. UC was diagnosed in 14 patients by lack of transmural inflammation, characteristic histology, or diffuse, proximally spreading inflammation. In the remaining 66 patients (68%), no conclusive diagnosis was possible. The application of serologic testing in IBD is still evolving. As more markers are discovered, the utility of this type of testing will likely improve.

Recent studies have shown that fecal proteins can help in the evaluation of patients with suspected IBD. Studies by Wassell et al and van den Bergh et al demonstrated that fecal calprotectin, a calcium- and zinc-binding anti-inflammatory protein found in neutrophilic granulocytes and monocytes, can be used as an index of intestinal inflammation. Silberer et al showed that levels of calprotectin and a second fecal protein, PMN-elastase, each correlated with endoscopically classified severity of inflammation. It is thought that these markers may be useful noninvasive tools in the screening of patients with abdominal pain and diarrhea. Moreover, they seem to be helpful in differentiating between active and non-active IBD and possibly also in monitoring disease activity.

**TREATMENT**

With the advent of new biological therapies, clinicians have more treatment options for IBD. The goals of therapy are to not only treat acute disease flares but ultimately to induce and then maintain remission using agents with the least amount of side effects, thus improving a patient’s quality of life. Designing a treatment plan begins with an accurate and complete assessment of the extent of disease. History and physical examination, combined with the endoscopic and radiologic tools described above, allow clinicians to determine which treatment regimen would most benefit a particular patient.

**Ulcerative Colitis**

Therapy for UC is determined by disease activity and location. The mainstay of therapy for mild to moderate UC is aminosalicylate (5-ASA)-based drugs. Mesalamine enemas and suppositories can be used as first-line therapy in distal colitis. Oral 5-ASA preparations can be added for those who do not receive complete benefit or cannot tolerate topical therapy. Oral 5-ASA is available in many forms, including mesalamine (Asacol, Pentasa), sulfasalazine, olsalazine (Dipentum), and balsalazide (Colazal). For patients with distal colitis, combination therapy with topical and oral 5-ASA agents has been shown to be more effective in achieving clinical remission than either alone. The key to utilizing the 5-ASA agents is to maximize the dose and delivery to the area of active colitis. The therapeutic benefit of the drugs is dose dependent; doses less than 2 g typically are ineffective. 5-ASA agents are useful in maintaining remission, and as with acute disease, the dose and delivery need to be optimized once remission is achieved. Topical steroids, such as hydrocortisone foams or enemas, are also effective in acute distal colitis flares. Because the steroids are absorbed from the colon and can cause glucocorticoid side effects, these therapies are typically used only after 5-ASA treatment has failed.

Oral steroids are reserved for patients with more extensive disease or those who are refractory to initial treatment. Oral prednisone at doses of 40 mg/d is used to induce remission. Doses above 40 mg/d increase the side-effect profile in these patients without much increase in efficacy.

Severe UC may require hospitalization and intravenous (IV) corticosteroid therapy. Patients refractory to oral and topical 5-ASA drugs or oral steroids should be hospitalized and begun on IV steroids. Superimposed infections, such as cytomegalovirus or C. difficile, and complications, such as toxic megacolon or perforation, should be ruled out prior to initiation of inpatient therapy. In general, failure of IV steroids after 7 to 10 days is an indication for colectomy. In some circumstances, IV cyclosporine can be used as a salvage therapy; studies have shown that remission can be induced in up to 82% of patients. However, unless cyclosporine is used as a bridge to immunomodulator treatment, more than 50% of patients will need a colectomy within 1 year. Only physicians experienced in the management of systemic immunosuppressive therapy should consider using cyclosporine due to the risk of infection, neoplasm, hepatotoxicity, and nephrotoxicity associated with this drug.

Immunomodulators are not useful for treating acute
UC due to their slow onset of action, typically taking 3 to 6 months to demonstrate their full clinical effect. Side effects of these drugs include increased susceptibility to infection, bone marrow toxicity, lymphoma, hepatits, pancreatitis, and, in some studies, increased risk for lymphoma.

Research has shown that tumor necrosis factor-α (TNF-α) plays an important role in the inflammatory cascade of IBD. TNF-α, a product of active macrophages, plays a key role in those regulatory peptides with altered expression in IBD. Infliximab (Remicade) is a chimeric monoclonal antibody that acts against TNF-α. It possesses a complement-fixing IgG1 constant region and a murine antigen binding region. Each bind to soluble TNF-α, causing apoptosis of activated T cells. Infliximab has recently been shown to be effective for both induction and maintenance of remission in patients with UC. In 2 separate randomized, double-blind placebo controlled trials, 34% to 39% of patients receiving 5 mg/kg of infliximab were in remission by week 8 and 26% to 34% were still in remission at week 30. Infliximab has also been shown to be effective as a rescue therapy in patients experiencing acute severe flares of UC not responding to conventional treatment. Although infliximab is generally safe, a number of important and serious complications can result from infliximab therapy, including hypersensitivity reactions, infusion reactions, drug-induced lupus, infections, malignancies including lymphoma, and rarely death.

UC can be essentially cured by removing the target for the immune system, the colon. Surgical options vary from total proctocolectomy with permanent ileostomy to ileal-pouch anal anastomosis.

**Crohn’s Disease**

Similar to UC, first-line therapy for mild luminal or inflammatory CD is 5-ASA drugs. The agent one chooses depends on the location of the patient’s disease. Pentasa is more effective in large and small bowel CD, whereas Asacol is primarily for patients with isolated Crohn’s colitis. For patients who do not respond to or do not tolerate 5-ASA drugs, antibiotics such as metronidazole and ciprofloxacin have been shown to be effective in mild to moderate disease.

Budesonide (Entocort), a glucocorticoid with extensive first pass metabolism and low systemic activity, has proven to be a suitable alternative to 5-ASA agents and steroids for patients with mild to moderate right-sided (ileum and right colon) disease. Studies comparing budesonide to 5-ASA agents in patients with mild to moderate CD have found it to be superior. Budesonide has fewer side effects than classic steroid preparations. However, it is not as effective in left-sided or more extensive disease. Corticosteroids are typically reserved for patients with CD who do not respond to the above treatments.

Refractory CD may require the use of an immunomodulator agent. Response rates to azathioprine and 6-MP are approximately 60% to 70%. Because of their slow onset of action, azathioprine and 6-MP are primarily used to maintain remission. Methotrexate, a dihydrofolate reductase inhibitor, is also effective in CD and is useful for patients unresponsive or intolerant to azathioprine and 6-MP. Therapy is typically given parenterally.

Initial trials with infliximab in patients with CD showed that up to two thirds of patients responded to treatment, with one third entering clinical remission. The response to treatment in these studies was generally within 2 weeks. The ACCENT I trial demonstrated that infliximab given every 8 weeks was also effective in maintaining remission. Infliximab is indicated for patients with moderate to severe CD.

**CONCLUSION**

Identifying disease location and severity is the most important step in designing individual treatment plans for patients with IBD. It is important that clinicians understand the options available to them when discussing treatment with their patients. As more is understood about the genetics and pathophysiology of IBD, clinicians will be able to offer more individualized therapies that will reduce symptoms, induce remission, and improve the quality of life for those with IBD.

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