To understand fully how Crohn disease develops and progresses, it is essential to recognize that the gastrointestinal (GI) tract of a healthy individual is in a state of dynamic immune homeostasis, or persistent naturally occurring inflammation. The immune system is responsible for balancing factors that activate its defense system and induce inflammation while simultaneously down-regulating the inflammation to maintain mucosal integrity. Because the mucosal surfaces that line the gut are the physical interfaces of the body’s immune system with the outside world and the GI tract consists of a large portion of the body’s mucosal lymphoid tissue, it is crucial that mucosal integrity be maintained. Because the mucosal surfaces that line the gut are the physical interfaces of the body’s immune system with the outside world and the GI tract consists of a large portion of the body’s mucosal lymphoid tissue, it is crucial that mucosal integrity be maintained. Because the mucosal surfaces that line the gut are the physical interfaces of the body’s immune system with the outside world and the GI tract consists of a large portion of the body’s mucosal lymphoid tissue, it is crucial that mucosal integrity be maintained.

Pathogenesis

Crohn disease, often seen in the literature as “Crohn’s disease,” is a progressive, systemic autoimmune disorder marked by abnormal inflammation of the GI tract. Any part of the GI tract can be affected, from the mouth to the

After completing this article, the reader should be able to:
- Describe the pathogenesis of Crohn disease.
- List predisposing factors for Crohn disease.
- Summarize the signs, symptoms, and comorbidities associated with the disease.
- Discuss the diagnosis of Crohn disease, including the patient history, physical examination, laboratory tests, medical imaging, and endoscopic procedures.
- Explain treatment options for Crohn disease and their effectiveness.

Crohn disease (often seen in the literature as “Crohn’s disease”), an autoimmune disease with debilitating gastrointestinal and extragastrointestinal manifestations, is on the rise in the United States and Europe. This article discusses the disease process, clinical presentation, diagnostic tools, and treatment options for Crohn disease. Statistics regarding disease prevalence and epidemiology also are reported.


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Crohn Disease: Pathophysiology, Diagnosis, and Treatment

Crohn disease is characterized by chronic, recurrent inflammation of the gastrointestinal tract. Symptoms may include diarrhea, abdominal pain, fever, and weight loss. The disease can affect any part of the gastrointestinal tract, including the mouth, esophagus, stomach, small intestine, and colon. Several subtypes of Crohn disease are recognized, depending on the area of the GI tract most affected.

It is now widely accepted that IBD results from an inappropriate response of a defective mucosal immune system to the indigenous flora and other luminal antigens. Experimental evidence suggests that impairment of a variety of immune pathways might result in the initiation of potentially destructive inflammatory cascades. Compelling evidence that supports this hypothesis comes from the use of animal models of IBD, in which genes for varying inflammatory cells and receptors were individually deleted, with all cases resulting in the development of inflammation of the intestinal tract similar to IBD.

One potential area of mucosal malfunction relates to the epithelial wall’s role as a barrier. The wall of the intestinal lumen consists of 5 layers: epithelial-lined mucosal layer, submucosal layer, 2 muscular layers (inner circular and outer longitudinal), and the outer serosal layer (see Figure 1). In patients with Crohn disease, the epithelial layer often increases in permeability, allowing pathogens to leak through to the mucosal layers beneath with less resistance. This defect often precedes the clinical onset of Crohn disease in individuals with a familial risk. In fact, this “leaky bowel” impairment has even been found in healthy first-degree relatives of patients with IBD, implicating its origin as a genetic defect.

As a result of microbial pathogens’ increased access to the mucosal layer and the submucosa’s numerous embedded antigen receptors, an immune response may be triggered and the inflammatory cascade initiated.

The mucosa’s role in antigen recognition, a second potential reason for immune malfunction, is a variation in the distribution of its toll-like pattern recognition receptors (TLRs). TLRs can be found throughout the luminal epithelium, and they vary in both concentration and type. TLRs are individually specialized receptors. Each TLR recognizes specific commensal microorganisms. When working in unison, they recognize the majority of intestinal microbes that make up the gut’s natural bacterial flora. Typically, the cells of a healthy patient will express TLR-3 and TLR-5 primarily, with subsequent down-regulation of the immune response due to constant receptor activation by recognized and expected commensal bacteria. However, in patients with Crohn disease, fewer TLR-3 and TLR-5 receptors are present. This results in hypersensitivity to commensal exposure, inducing an unsuppressed, aggressive inflammatory response.

A third potential complication is the mucosa’s inability to suppress an inappropriately triggered immune response. T-cells, members of a group of white blood cells (WBCs) known as lymphocytes, play a central role in cell-mediated immunity. When immune cells are not properly controlled and cleared from the body, they persist and remain activated rather than undergoing apoptosis (programmed cell death). These potential malfunctions of the intestinal mucosa and the subsequent impairment of the normal immune response are closely linked to 2 primary risk factors: genetic predisposition and exposure to various environmental antigens.

Genetic Predisposition

Genetic predisposition—especially familial aggregation—seems to be the strongest independent indicator of which individuals will develop Crohn disease.
Current research shows that among those with Crohn disease, 2.2% to 16.2% have a first-degree relative who also has the disease. Furthermore, for a first-degree relative of a patient with Crohn disease, the estimated lifetime risk of developing Crohn disease ranges from 4.8% to 5.2%, making first-degree relatives 3 to 20 times more likely to develop the disease than those without the familial connection. Furthermore, the risk for a sibling of a patient with Crohn disease is even higher than the average risk for a first-degree relative.

Regarding ethnicity, similar data have shown that for an individual of European Jewish (Ashkenazi) descent, the estimated lifetime risk for those with a first-degree relative who has Crohn disease increases to 7.8%, making them 3 to 5 times more likely to develop the disease than non-Ashkenazi Jews who also have a first-degree relative with Crohn disease. In fact, Crohn disease is more prevalent in Ashkenazi Jews than in any other ethnic group.

Crohn disease has been characterized as a polygenic disease process. Genome-wide scans show susceptibility loci for Crohn disease on multiple chromosomes that play a potential role in development of the disease. Regions on chromosomes 16q, 12, 6, 14, 5, 19, 1, 16p, and 10 have been renamed IBD1 to IBD9, respectively, indicating their involvement in the IBD process. Mutations to several of these loci have been found to affect an individual’s systemic immune response directly. For example, the product of a mutation on the IBD1 locus of chromosome 16q has been found to influence the regulation of macrophages, and in essence the immune-inflammatory response. Another example can be found on chromosome 6 (IBD3), a region that plays an important role in autoimmunity.

Because a mutation on any 1 or several of the IBD loci can activate specific immunologic response pathways, certain mutations in these loci might be associated with certain Crohn disease courses. For instance, the IBD1 locus, which is associated exclusively with the disease in white populations, has been associated with the stricturing form of Crohn ileitis (inflammation in the small intestine), and IBD3 has been linked to Crohn colitis (inflammation in the large intestine). Furthermore, extraintestinal disease complications have been linked to other Crohn-related genetic mutations. Conversely, some mutations recently have been described as possibly protecting against Crohn disease.

When considering the effect of genetic predisposition for Crohn disease, it is important to note that the relative risk of developing the disease for an individual with a mutation in one of the IBD gene loci is fairly low (approximately 1:200). This data supports the understanding that environmental factors also must be involved as a trigger for the expression of the genetic mutation.

**Environmental Risk Factors**

Geographical data indicate that, although rates of Crohn disease incidence are stabilizing in high-incidence regions, low-incidence regions are showing an increase in the number of diagnosed cases. The highest incidence rates and prevalence of reported Crohn disease cases are in the northern hemisphere, particularly Northern Europe (27-48 cases per 100 000); the United States has 3 to 5 cases per 100 000. In contrast, the countries with the lowest incidence rates and prevalence of reported cases are in the southern hemisphere, specifically South America, Southeast Asia, Africa (with the exception of South Africa), and Australia. For example, rates measured at a hospital in Argentina were 0.03 per 100 000. Although the data suggest that a gradient exists between northern and southern continents, they also suggest that other factors are involved. Socioeconomic status, including access to and quality of health care, sanitation standards and hygiene practices, and dietary habits, likely play a role, although not in the way one might expect.

Rural communities in developing regions of China suffer from limited access to and lower quality of health care facilities and related services. However, a study showed increasing incidence rates of Crohn disease among immigrants from low-incidence regions of China who moved to more developed regions of the country. Furthermore, a lower risk of developing Crohn disease has been associated with factors such as an absence of tap water, absence of hot water, large or poor families, crowded living conditions, and consumption of contaminated foods—all factors related to a low socioeconomic status. The theory behind this counterintuitive phenomenon is that excessive sanitation might limit exposure to environmental antigens and impair the functional development of the mucosal immune system, followed by subsequent immune intolerance to...
some environmental antigens. Although there is no evidence that Crohn disease is directly caused by luminal microbes, it is quite likely that these microbes indirectly provide the antigenic trigger to a fundamentally dysregulated immune system. This concept is strengthened by the observations in animal experiments that have shown IBD to develop in the presence of normal gut flora but not in germ-free mice.²

A third possible factor in the correlation between decreased incidences of Crohn disease and socioeconomic status is diet. A positive correlation between the disease incidence and increased intake of meat protein, milk protein, and polyunsaturated fatty acids has been reported. A negative correlation between disease incidence and consumption of vegetable protein also was reported, with no correlation determined regarding consumption of fish-based protein.³ Numerous diet-focused studies have shown a strong link between a country’s socioeconomic status (ie, industrialized vs developing) and an increased prevalence of animal-based proteins in the standard diet of economically prosperous communities. However, it is important to note that dietary studies often have weaker research methods because of poor patient compliance or recall, making interpretation of the findings difficult.⁴

**Manifestations and Complications**

The Vienna classification was developed to describe the distinct clinical phenotypes of Crohn disease with respect to disease location and potential complications (see Table 1). According to the data, at diagnosis the disease is located at the:

- Terminal ileum (Crohn ileitis) in 47% of patients.
- Colon (Crohn or granulomatous colitis) in 28%.
- Ileo colon (Crohn ileocolitis) in 21%.
- Upper gastrointestinal tract (Crohn jejunitis, gastroduodenal Crohn disease, or Crohn disease of the esophagus) in 3% of the cases.

In addition, the disease can be further classified as stricture in 17% of patients, penetrating (fistulae, abscesses, or both) in 13%, and nonstricturing and nonpenetrating in 70% of all patients at diagnosis.⁵ It is important to note that Crohn disease is a chronic, progressive disease, and patients often develop complications as the inflammation reaches additional segments of bowel.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Vienna Classification of Crohn Disease Phenotypes</th>
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<tbody>
<tr>
<td>Variables</td>
<td>Subgroups</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>&lt; 40 years</td>
</tr>
<tr>
<td></td>
<td>≥ 40 years</td>
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<tr>
<td>Location of disease</td>
<td>Terminal ileum</td>
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<tr>
<td></td>
<td>Colon</td>
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<td></td>
<td>Ileo colon</td>
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<td>Upper gastrointestinal</td>
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<td>Behavior</td>
<td>Nonstricturing nonpenetrating</td>
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<td></td>
<td>Stricture</td>
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Regardless of the inflammatory pathway triggered, there are general initial features of the inflammatory process that are common to the development of inflammatory bowel disorders. Upon activation of the body’s immune-response system by commensal bacteria, migration of inflammatory cells from the vasculature system flood into the intestinal mucosa at the site of the inflammatory trigger. A multitude of aggressive metabolites and mediators accumulates in the mucosal tissue, resulting in tissue damage. Such metabolites include nitric oxide, oxygen radicals, prostaglandins, leukotrienes, and histamines, all released at the site of inflammation and subsequently promoting fibroblast growth, collagen secretion, and varying degrees of luminal stricture formation.⁶

When there is narrowing of the intestinal lumen, patients with Crohn disease are in danger of developing a mechanical intestinal obstruction, a complication of the disease in which the intestinal pathway becomes occluded. A bowel obstruction can occur at any level distal to the duodenum and is considered to be a medical emergency. In rare cases, intestinal inflammation and obstruction can result in toxic megacolon, an acute form of colonic distention in which the colon becomes grossly dilated. This condition can cause decreased tissue perfusion with subsequent septic shock if the bowel is perforated. About 27% of patients who do not display evidence of stricture at the time of Crohn disease diagnosis develop luminal stricture as their disease progresses.⁷

The focal infiltration of inflammatory neutrophilic cells into the intestinal epithelium typically occurs at
areas overlying lymphoid aggregates called Peyer patches, usually found in the ileal segment of the small intestine. In addition, neutrophils can infiltrate the intestinal crypts (glands in the intestinal wall responsible for generation of new epithelium) and with chronic irritation lead to cryptitis. If the inflammation is not suppressed, the inflamed crypt cells can progress into ulcers, an outcome seen in highly active disease states. A characteristic more specific to Crohn disease and often used to differentiate it from other inflammatory bowel pathologies is the abrupt transition between the unaffected and the ulcerated tissues. Known as skip lesions, these can develop throughout the diseased segments of bowel, with some segments being affected but not others. In addition, one side of the intestinal wall can be affected but not the other.1,2

A second Crohn disease-specific manifestation is a transmural pattern of inflammation, with evidence of inflammation spanning the entire depth of the intestinal wall.1 The inflammation begins in the submucosa and spreads to the mucosa and serosa. With the development of serositis, the serosa becomes granular and dull gray in appearance, with the intestinal wall taking on a rubbery texture. Furthermore, serosal extension of mesenteric fat (creeping fat) might wrap around the bowel surface and often is used for staging the disease’s progression.2

In early stages, focal mucosal ulcers might develop and can resemble canker sores (aphthous ulcers) (see Figure 2). As the disease progresses, multiple ulcers can unite into longitudinal or transverse linear serpentine fissures that can extend into the intestinal lymphoid tissue. In some cases, a disease complication can arise when these ulcerations in the bowel wall traverse the entire thickness of the organ’s tissue and form fistulæ between an inflamed segment of bowel and an adjacent anatomical structure.

Fistulæ can form between the diseased bowel segment and another loop of bowel (enteroenteric), the bladder (enterovesicular), the vagina (rectovaginal), skin (enterocutaneous), or the peritoneal cavity (see Figure 3). With the development of multiple fistulæ, chronic blood loss often results in anemia. In addition, proliferation of commensal bacteria within the peritoneal cavity can result in peritonitis, inducing further inflammation in the form of abdominal ascites. The location of fistula development depends on the Crohn disease phenotype, with formation occurring at sites of excessive inflammation throughout the GI tract. In cases of penetrating Crohn disease, about 29% of patients who have received a Crohn disease diagnosis but who do not display evidence of fistulæ will develop luminal fistulæ as their disease progresses.3

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**Figure 2.** Double-contrast barium enema examination in Crohn colitis demonstrates numerous aphthous ulcers. Image reprinted with permission from David I Weltman, MD, published by Medscape Reference.

**Figure 3.** Double-contrast barium enema study demonstrates multiple fistulous tracts between the terminal ileum and the right colon adjacent to the ileocecal valve, the so-called double-tracking of the ileocecal valve. Image reprinted with permission from David I Weltman, MD, published by Medscape Reference.
Another finding associated with chronic Crohn disease–related inflammation is the presence of granulomas. These occur in about 50% of all Crohn disease types and consist of spherical aggregations of immune cells (specifically, giant cells) that develop when the immune system is attempting to wall off substances recognized as foreign. Granulomas can occur anywhere in the alimentary tract. In patients with Crohn disease limited to one bowel segment, they typically are found within the large intestine. The granulomas that form with Crohn disease are the noncaseated type, meaning they do not exhibit a “cheeselike” appearance of tissue necrosis. Often, the intestinal lining takes on a cobblestone appearance as a result of granulomatous projections of inflamed tissue surrounded by areas of ulceration (see Figures 4 and 5).2,10

One last potential disease complication is related to the chronic inflammatory aggravation of the mucosal tissue that often can lead to architectural distortion, atrophy, and even metaplastic cellular changes. If left untreated, the persistent activation of the inflammatory response associated with Crohn disease leads to a 5- to 6-fold increase in the risk of developing cancer. Depending on the location of the inflammation, patients with Crohn disease can be at risk for developing lymphoma or cancer of the small bowel and colon.3

Although Crohn disease exhibits primarily GI-specific manifestations, it is important to remember that it is a systemic autoimmune disorder, and Crohn disease patients often present with an array of extragastrointestinal manifestations. Crohn disease can be associated with comorbidities involving almost all organ systems (see Box).1 Individuals with Crohn disease also are at risk of developing other disease complications as a result of malnutrition due to decreased food intake associated with painful digestion and impairment of epithelial cell absorption of dietary nutrients.

After the first year following diagnosis, 10% to 30% of patients with Crohn disease have an exacerbation of symptoms, 15% to 25% maintain low disease activity, and 55% to 65% have disease remission. Furthermore, 13% to 20% of patients with Crohn disease have chronic activity, 67% to 73% have a chronic-intermittent course, and 10% to 13% remain in remission for several years.13 The life expectancy of patients with Crohn disease is reduced slightly, and quality of life can be greatly impaired.
Diagnosis

Crohn disease diagnosis is based on many clinical features. The initial step is a thorough investigation of the patient’s presenting symptoms, including any related medical, social, and family history. This is followed by a focused physical examination of the abdomen and any other symptom-related body systems. If, based on the history and physical examination, Crohn disease is a potential diagnosis, most clinicians check for non-specific inflammatory activity with a variety of simple laboratory tests, including an erythrocyte sedimentary rate (ESR), C-reactive protein (CRP), and leukocyte and platelet count. Finally, medical imaging can be used to confirm diagnosis and monitor disease activity.

Patient History

Crucial information can be garnered prior to meeting the patient by reviewing his or her demographic information such as age, sex, and race. This information can be used to determine whether the patient falls into groups associated with increased incidence of Crohn disease. The disease presents typically in a bimodal distribution, with the highest occurrence initially in individuals between the second and third decades of life and a minor incidence peak between the sixth and seventh decades. As for sex, incidence is slightly higher among women than men. Lastly, race also has been shown to play a role in the development of Crohn disease in North America, with prevalence rates for Hispanic (4.1 per 100 000) and Asian (5.6 per 100 000) individuals being much lower than those for white (43.6 per 100 000) and African American (29.8 per 100 000) individuals.

The chief complaints with inflammatory bowel disorders are diarrhea, abdominal pain, malaise, low-grade fever, and unintended weight loss. When assessing the onset of potential IBD symptoms, it is important to note that the disease often is present for months or even years before the symptoms manifest and a diagnosis can be made. Because of the intermittent nature of these diseases, it is possible that the patient has been experiencing the symptoms for some time, and only as they have increased in severity has he or she decided to seek medical intervention.

The location of symptomatic pain is often one of the strongest indicators of Crohn disease type. If the patient complains of pain in the right lower quadrant of the abdomen, this could indicate a case of ileocecal Crohn disease. However, pain in the right lower quadrant, especially when associated with a high fever, also can indicate acute appendicitis, which should be ruled out with confidence because it can lead to a life-threatening emergency.

When the patient suffers from a Crohn flare-up, symptoms usually occur simultaneously. The length of time between symptom relapses often is noted, and a progressive decrease in time between Crohn flare-ups can indicate progression of the disease.

The pain associated with Crohn disease typically is crampy and colicky in nature, consistent with most forms of bowel inflammation. The patient reporting blood in his or her stool can be a strong indicator of whether the disease has colonic involvement. The more proximal the inflammatory disease is within the GI tract, the less likely the patient’s stool will be noticeably red. Instead, it will appear dark, almost black. This is known as melena. Blood from the lower GI tract appears brighter red and is known as hematochezia. Melena is present in approximately 50% of Crohn disease cases, with Crohn ileitis rarely being associated with bloody stool and Crohn colitis presenting with only minor amounts of blood. It also is important to question the presence of any genitourinary symptoms because fistulae that form between the intestinal tract and the bladder can exhibit either blood or fecal matter in the urine, as well as urinary tract infections.

Box

Comorbidities Associated With Crohn Disease

- Migratory polyarthritis.
- Erythema nodosum.
- Pyoderma gangrenosum.
- Pleuritis.
- Myocarditis.
- Hepatic pericholangitis and sclerosing cholangitis.
- Obstructive uropathy with kidney stones (with associated predisposition to urinary tract infections).
- Pancreatitis.
- Ankylosing spondylitis.
- Sacroilitis.
- Various neurological conditions.
A few possible aggravating factors can hasten the progression of Crohn disease and magnify the presenting symptoms. Often, eating exacerbates abdominal pain because of the passage of food through the inflamed portion of colon. Because of the fairly common presence of lactose intolerance, dairy products can be problematic foods. If the patient is suffering from a bowel obstruction, high-fiber foods such as raw fruits, vegetables, and nuts can enhance abdominal pain. If the location of the bowel inflammation is localized to the terminal ileum—the site at which the body absorbs most dietary fat—fat malabsorption can result, often leading to worsening diarrhea. In addition, cigarette smoking is strongly associated with the development of Crohn disease, resistance to medical therapy, and early disease relapse. Use of nonsteroidal antiinflammatory drugs (NSAIDs) also can exacerbate IBD, possibly leading to NSAID-induced colitis characterized by small bowel and colonic ulcers, erosion, or strictures.

When evaluating the patient’s diet, it is important to note that a positive correlation has been reported between Crohn disease and intake of meat protein, milk protein, and polyunsaturated fatty acids.

A subjective evaluation of the severity of the patient’s symptoms, such as asking the patient to rate his or her pain on a 10-point scale, can be useful. The higher the pain ranking, the more likely the inflammation is transmural in nature, potentially structuring and obstructing abdominal contents or fistulizing to nearby organs. The number of liquid bowel movements per day also can be used to measure the severity of the disease course.

A final symptom that might be reported is unintended weight loss. There are multiple potential contributing factors for a sudden and unexpected decrease in weight. The most obvious reason is severe, watery diarrhea, which results in decreased water-specific weight as well as dehydration. Another cause is pain associated with digestion that discourages the patient from eating. In addition, a subset of patients could develop sinus tracts that penetrate the bowel and form fistulae from the colon to the small intestine or stomach, which can result in bacterial overgrowth and subsequent diarrhea, weight loss, and malnutrition. Depending on the location of the involved bowel segment, various nutrient deficiencies can develop, including 

and hypoalbuminemia. Nutrient deficiencies are most common when the ileum is affected. Furthermore, a thorough medical history also should include immunizations the patient has received. There is a hypothesis that the attenuated live measles, mumps, and rubella vaccine might increase the risk of IBD, and although evidence to support this view is relatively weak, knowledge of the hypothesis might be useful.

Physical Examination

The physical examination should capture the following vital signs: blood pressure, respiratory rate, heart rate, and temperature. Mild elevation in temperature often signifies the presence of an underlying inflammatory process such as Crohn disease.

During the abdominal examination, patients with the penetrating form of Crohn disease might present with fistulae that form between the intestinal tract and the overlying dermal layer (enterocutaneous fistulae). These occur most often at the site of surgical scars. Abdominal distention due to prolonged bloating might be visible and can indicate intestinal obstruction, a characteristic complication of Crohn disease. Movement of the abdomen from peristalsis of the intestinal tract usually is not visible; rippling movements indicate possible intestinal obstruction.

Auscultation (listening to bowel sounds) should precede percussion because the maneuvers associated with percussion might alter the frequency and intensity of the bowel sounds. Adequate auscultation of bowel sounds requires a minimum of 5 minutes of listening, incorporating all 4 quadrants of the abdomen (right upper, right lower, left upper, and left lower). Although the sounds usually are generalized for the entire abdomen, areas that exhibit high-pitched tinkling sounds suggest fluid and air under pressure, and thus an early bowel obstruction. Often, loud prolonged gurgles, called borborygmi, can be heard. These also are a potential sign of intestinal obstruction.

When performing percussion of the abdominal cavity, the degree of percussion tone will vary depending on the size and density of the organs within the abdomen. The percussion tone is loud over air, less loud over fluid, and soft over solid areas. Typically
when assessing the abdomen, tympany will be the predominant sound because air is present within the intestines. Dull sounds indicate the location and size of the abdominal organs or potential masses associated with intestinal obstruction.

With Crohn disease, palpation might reveal focal tenderness with palpable masses that represent thickened or matted bowel loops, usually in the lower abdomen. In addition, generalized abdominal tenderness might be due to fistula formation.

If a differential diagnosis of IBD still is supported after the abdominal examination, a rectal examination should be completed. Approximately one-third of patients who have Crohn disease with either large or small bowel involvement exhibit signs of perianal disease, including perianal skin tags, fistulae, or anal fissures that can cause patient discomfort.

**Laboratory Tests**

The patient history and physical examination should yield enough information to provide a short list of potential differential diagnoses. However, often the subjective information garnered from the patient interview and the limited objective information obtained from the physical examination are not enough to make a confident final diagnosis. When Crohn disease is the most likely diagnosis, clinicians often use a variety of laboratory tests and medical imaging procedures to help provide concrete evidence of the disease.

Several laboratory tests can confirm the presence of nonspecific inflammatory activity, including ESR, CRP, and leukocyte and platelet counts. Caution should be exercised when evaluating the results of these lab tests, however, because some medications can increase or decrease lab values.

A total WBC count is part of most routine laboratory diagnostic evaluations. This test consists of 2 components. The first is a count of the leukocytes in 1 mm³ of peripheral venous blood. The other component, the differential count, measures the percentage of each type of leukocyte present in the same specimen. Neutrophils and lymphocytes make up 75% to 90% of the total leukocytes; the remaining WBCs include monocytes, eosinophils, and basophils.

Although the total leukocyte count has a wide range of normal values, many diseases can induce abnormal values. An increased total WBC count (leukocytosis ≥ 10 000) usually indicates infection, inflammation, or tissue necrosis. Emotional stress also can increase the value. It is important to note that patients who have had a splenectomy often also have persistent mildly to moderately elevated WBC counts. A decreased total WBC count (leukopenia ≤ 4000) occurs in many forms of bone marrow failure and can be a result of dietary deficiencies and autoimmune disorders. In addition, values tend to be lower in the morning and higher in the late afternoon. Serial WBC counts have both a diagnostic and prognostic value.

CRP is an acute, phase-reactant protein that indicates the presence of an inflammatory process. Under normal circumstances, it is produced by hepatocytes in low quantities, with average values ranging from 1.0 to 3.0 mg/L. The synthesis of CRP is initiated by antigen-immune complexes, bacteria, fungi, and trauma. Measuring a patient’s CRP levels provides the clinician with a nonspecific confirmation of both infections and inflammatory disorders; elevated CRP levels often are seen with tissue necrosis. Table 2 summarizes the diagnostic significance of elevated CRP by level.

In the presence of inflammatory changes, the CRP shows an earlier and more intense increase than ESR and, conversely, with recovery, CRP returns to a normal level preceding the subsequent return of ESR to a normal level as well. The CRP decreases when the inflammatory process is suppressed by antiinflammatory agents, salicylates, or steroids. Elevated test results can be due to hypertension, elevated body mass index, metabolic syndrome/diabetes mellitus, chronic infection (eg, gingivitis, bronchitis), chronic inflammation (eg, rheumatoid arthritis), and low levels of high-density lipoprotein/high triglycerides. Cigarette smoking also can increase CRP levels, whereas moderate alcohol consumption, weight loss, and increased activity or endurance exercise can decrease levels.

### Table 2

<table>
<thead>
<tr>
<th>CRP Level (mg/L)</th>
<th>Probable Cause</th>
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<tbody>
<tr>
<td>10-50</td>
<td>Viral infection</td>
</tr>
<tr>
<td>50-200</td>
<td>Bacterial infection</td>
</tr>
<tr>
<td>200-250</td>
<td>Burns</td>
</tr>
</tbody>
</table>

Abbreviation: CRP, C-reactive protein.
ESR is another nonspecific test used to detect illnesses associated with acute and chronic infection, inflammation, advanced neoplasms, and tissue necrosis or infarction. ESR is a measurement of the rate at which the red blood cells settle in a saline solution or plasma over a specified period. It is not diagnostic for any particular disease or injury. Because inflammatory, neoplastic, infectious, and necrotic diseases increase the protein (mainly fibrinogen) content of plasma, red blood cells have a tendency to stack up on one another, increasing their weight and causing them to descend faster. Therefore, the ESR is increased in these diseases. Compared with CRP, ESR peaks more slowly and can take several days to decrease, even if the clinical condition is ameliorated.

The ESR is a fairly reliable indicator of the course of disease and therefore can be used to monitor disease progression, especially for inflammatory autoimmune diseases such as Crohn disease. In general, as the disease worsens, the ESR increases, and as the disease improves, the ESR decreases. If the ESR results are equivocal or inconsistent with clinical impressions, the CRP test is then performed. The Westergren method for interpreting normal ESR lab values is both age- and sex-dependent, with normal values for men being 15 mm/hr and up to 20 mm/hr for women. For children, a normal ESR level is typically no higher than 10 mm/hr, with the levels of infants being no higher than 2 mm/hr.

One other laboratory test that is usually ordered to aid in GI-related diagnoses is a guaiac test, in which a stool sample is obtained during the rectal examination to check for occult blood. To rule out other potential causes of abdominal pain and diarrhea, a stool sample also might be checked for bacterial pathogens, parasites, leukocytes, and *Clostridium difficile* infection.

**Imaging Examinations**

**Radiography**

After laboratory testing, the next step is to perform imaging examinations that can confirm a Crohn disease diagnosis. No single imaging procedure uniformly confirms Crohn disease, and often a variety of procedures must be used to make up for limitations associated with each examination.

The typical approach to conducting an imaging work-up for potential Crohn disease is to first conduct generalized imaging of the patient’s abdominal-related symptoms. Obtaining abdominal radiographs (including upright, supine, and lateral decubitus images using standard x-ray equipment without the use of contrast agents) can reveal evidence for several patient complaints. Dilated bowel loops, air-fluid levels, excessive amounts of stool, or bowel loop displacement often can be indicative of possible bowel perforation, obstruction, or organomegaly. For this reason, abdominal radiographs are most useful in the initial evaluation of abdominal pain or nausea and vomiting. In addition, static radiographic images identify extraintestinal calcifications related to gallbladder or kidney stone formation that occasionally accompany Crohn disease in patients with severe malabsorption issues.

Further imaging specifically related to small bowel radiography includes contrast-enhanced upper GI and small bowel follow-through procedures. Contrast agents such as barium or water-soluble diatrizoic acid (Gastrografin) can be administered by mouth or rectum to detect mucosal abnormalities such as ulceration and masses, strictures, and abnormal peristalsis. The contrast can be used alone as a single contrast agent or in combination with air- or gas-forming crystals as part of a double-contrast technique. Single-contrast examinations usually are used to detect obstructing lesions or motility disturbances, while the double-contrast examination aids in detecting more subtle ulcerations in the mucosal wall. During the upper GI series, serial radiographic images are obtained as the contrast is ingested, providing information about abnormalities of the esophagus, stomach, and duodenum.

Current data suggest that 70% of all patients with Crohn disease have some involvement of the small bowel during the course of their disease, with 30% of those having Crohn manifestations limited to the small bowel. Therefore, the small bowel follow-through examination in which the contrast is visualized as it passes into the jejunum and ileum is highly important. During this procedure, the radiologic technologist or radiologist assistant obtains multiple close-up views (often referred to as *spot films*) of areas that seem abnormal. This might require some external, manual compression of the patient’s abdomen to help better position the intestinal area of interest and reveal any concealed pathology. A variation of the examination might include placement of a nasal enteric tube for a technique called...
enteroclysis in which contrast material is introduced rapidly into the intestinal tract below the duodenojejunal junction. The goal is to bypass the stomach and introduce a large bolus into the small bowel, resulting in optimal filling, dilation, and visualization of the intestinal tract.

Attention should be paid to structural abnormalities as well as the length of time required for contrast to reach and traverse the various segments of the colon. Prolonged digestion of the contrast often indicates a potential bowel obstruction due to bowel wall thickening and subsequent stricture. When a bowel stricture is present, the GI “string” sign should be as well (see Figure 6). This radiographic finding resembles a thin string of frayed cotton and is caused by a thin stream of contrast working its way through the narrowed GI pathway.

Computed Tomography

Computed tomography (CT) also can be useful for diagnosing Crohn disease. CT provides computer-aided reconstruction of multiple radiographic images collected in a helical course around a supine patient. Contrast agents can be used to opacify the bowel lumen, revealing the caliber and contour of the GI tract and allowing diagnosis of inflammatory lesions. CT’s ability to visualize the entire abdominal cavity also allows for detection of parenchymal lesions such as abscesses and granulomas in the bowel wall, as well as defining the size, shape, and characteristics of extraintestinal abdominal organs. In some cases, splenomegaly occurs as a sign of liver destruction related to Crohn disease. Furthermore, a CT scan can provide a differential diagnosis when Crohn disease–related pain in the right lower quadrant mimics appendicitis by isolating and evaluating the appendix for signs of inflammation.

CT enteroclysis can offer visualization of the extraluminal bowel wall that endoscopy using a wireless capsule cannot. Using the enteroclysis technique of injecting a contrast bolus through a nasojejunal tube, CT enteroclysis can detect segmental bowel thickening, extraluminal lesions, fistulae, and abscesses, all within a relatively short time. The modality’s ability to detect fistulae, often associated with the transmural inflammation characteristic of Crohn disease, is of greatest value because this information often leads to a change in the patient’s pharmacologic treatment. Early data suggest that CT enteroclysis studies are at least equivalent, if not better than, the current small bowel follow-through.4

However, CT scanning does have drawbacks. During an abdominal CT, patients are exposed to a considerable amount of radiation, with a mean cumulative effective dose of 36.1 mSv, although doses of more than 75 mSv are possible. This is far more than the dose received during a routine small bowel radiography procedure. Because Crohn disease has an initial peak during the second and third decades of life and the body is at a heightened sensitivity to the effects of radiation at this time, imaging techniques that use less radiation or no radiation should be considered. Another limitation of the CT examination is that collapsed loops of bowel often create artifacts that distort pathology, and the lack of dynamic imaging capabilities makes it difficult to differentiate between peristalsis
and skip lesions, a prime distinguishing manifestation of Crohn disease. The inability to identify skip lesions can lead to misdiagnosis.

**Magnetic Resonance Imaging**

Similar to CT, magnetic resonance (MR) imaging can provide multiple cross-sectional images of the abdomen and pelvis. However, unlike CT, MR can be performed with respiratory compensatory tools and faster pulse sequences to reduce artifacts caused by breathing or peristalsis, allowing differentiation between peristalsis and Crohn disease–related skip lesions. Because of its multiplanar capabilities and ability to distinguish inflammatory damage, MR can affect disease management and the decision to perform surgery vs a pharmacologic approach only.18

As with fluoroscopic and CT imaging examinations, an enterolysis technique can be used with MR to better visualize the intestinal walls; however, because of the difference in image collection methods, a polyethylene glycol solution is used as the contrast material. Furthermore, MR can visualize parenchymal lesions such as masses and cysts and might better characterize abnormalities seen on CT. MR imaging also is considered to be better at characterizing perirectal abscesses and fistulae related to Crohn disease. Perhaps most important, especially considering younger patient populations, MR avoids the radiation exposure associated with most other imaging modalities.

Two potential limitations of the MR imaging examination, however, are the relatively small bore in which the patient must fit during the imaging procedure, as well as the hour-long examination time during which absolute stillness is required to attain images free of motion artifacts. Often these testing requirements prove challenging to patients who suffer from even mild forms of claustrophobia, as well as those who are in critical condition and require constant monitoring of vital signs.

**Ultrasonography**

Ultrasonography often is the first imaging study obtained when suspected extraintestinal manifestations of Crohn disease involving the liver require evaluation. Through the use of sound waves, radiation-free images can be created to detect abnormalities such as cirrhosis or gallstone formation. However, ultrasonography has proven limited in its ability to image the GI tract because of decreased visibility in obese patients, an inability to penetrate the skeletal ribs that partially cover the abdomen, and the air found within the bowel loops. However, endoscopic ultrasonography has proven useful for evaluating fistula healing or recurrence in the perianal region. Furthermore, Doppler ultrasonography can be beneficial when evaluating the role of vasculature, specifically the superior mesenteric artery in correlation with the inflamed bowel segment this artery perfuses.18

**Endoscopic Techniques**

Small bowel radiography mostly has been superseded by endoscopic examination for Crohn disease diagnosis because the endoscope is more sensitive for detecting mucosal abnormalities and also allows clinicians to obtain mucosal biopsies and resect lesions. Endoscopy can be performed either in an anterograde fashion using a gastroscope, push enteroscope, or double balloon enteroscope, or retrograde via a colonoscope. Although the gastroscope is useful for assessing upper GI-related issues, it is limited to the third and sometimes fourth portions of the duodenum. Furthermore, examination of the small intestine past the ligament of Treitz is not feasible with a standard gastroscope, and thus push enteroscopy with a long (≥200 cm) endoscope can be used. However, advancing this instrument beyond the first 50 cm of jejunum can prove difficult.

In such cases operative enteroscopy can be used, in which a surgeon makes a small incision in a patient’s abdomen and pleats the small bowel onto the enteroscope while the endoscopist examines the luminal surface. This procedure usually is selected only when the surgeon intends to proceed directly to a resection of the affected intestine.

A traditional nonradiographic method for assessing Crohn disease is colonoscopy with ileoscopy. Colonoscopy is an endoscopic examination of the colon with a fiber-optic camera on a flexible tube passed retrograde through the anus. In addition, the distal part of the small bowel can be examined through techniques known as ileal intubation and ileoscopy in which the scope is passed through the cecum. Anterograde intubation through the esophagus also can be conducted, reaching as far as the third and fourth portion of the duodenum via use of a gastroscope. The goal of the procedure is to provide visual confirmation of luminal destruction as
endoscopy, in which the patient swallows a pill-sized camera measuring 11 mm by 26 mm, and pictures are taken remotely for review by a clinician without the need for patient sedation (see Figure 8). However, even this relatively noninvasive examination has contraindications, specifically in patients with bowel strictures identified with abdominal imaging. Because of concern about possible capsule entrapment and the need for subsequent surgical intervention to remove the device in cases involving intestinal stricture, a recently developed capsule shell dissolves, allowing the intracapsular fragments to disassemble and pass through the stricture. However, because of the procedure’s high cost, which ranges between $20 000 and $30 000, use in the general population is far from routine, especially when other more cost-efficient imaging methods can provide similar information.

### Treatment

#### Pharmacologic Approaches

Traditionally, treatment for Crohn disease primarily depended on pharmacologic therapies, with surgical intervention when necessary. Medications are prescribed based on the stage of disease process (active disease or remission), level of disease activity (mild to moderate, moderate to severe, or severe to fulminant), and evidence of penetrating behavior (fistulae). In clinical practice, a patient has mild-to-moderate disease activity when he well as an opportunity for biopsy of abnormal tissue or therapeutic intervention. Collected tissue can be analyzed histologically for microscopic evidence of Crohn disease. These examinations rarely allow visualization of the entire small bowel; thus, the true extent of disease must be examined using an alternate procedure.

Two variations of the traditional colonoscopy procedure include the push enteroscope and double-balloon enteroscopy. The push enteroscope is simply an elongated version of the gastroscope used to visualize as far as the jejunum. To assess as far as the ileum, however, use of the double-balloon enteroscope is necessary (see Figure 7). In this procedure, 2 balloons spaced several centimeters apart on an enteroscope device are systematically inflated and deflated in sequence, allowing the enteroscope to be advanced through long stretches of small intestine, barring any impassable strictures. This procedure avoids the problem of stretching or looping of the small bowel that is associated with traditional endoscopy. In fact, by combining an anterograde and retrograde approach, the entire small bowel can be investigated in more than 86% of patients. Adequate access to the small intestine enables successful therapeutic interventions, including cauterization of lesions and treatment of GI bleeding.

Complications of endoscopy include bleeding after biopsy (0.3%-1%), perforation (0.05%-0.5%), and sedation-associated hypotension and hypoxia (1%-5%). As a result, the patient population for this procedure is somewhat limited.

The desire to visualize the GI lumen in the least invasive way prompted development of wireless capsule endoscopy, in which the patient swallows a pill-sized camera measuring 11 mm by 26 mm, and pictures are taken remotely for review by a clinician without the need for patient sedation (see Figure 8). However, even this relatively noninvasive examination has contraindications, specifically in patients with bowel strictures identified with abdominal imaging. Because of concern about possible capsule entrapment and the need for subsequent surgical intervention to remove the device in cases involving intestinal stricture, a recently developed capsule shell dissolves, allowing the intracapsular fragments to disassemble and pass through the stricture. However, because of the procedure’s high cost, which ranges between $20 000 and $30 000, use in the general population is far from routine, especially when other more cost-efficient imaging methods can provide similar information.

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**Figure 8.** A wireless endoscopy capsule. Image courtesy of Euchiasmus and Wikimedia Commons.
or she is ambulatory and can tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, or a painful mass or obstruction. In addition, these patients have lost less than 10% of their body weight. Moderate-to-severe disease activity is characterized by failed treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain or tenderness, intermittent nausea and vomiting without obstruction, or significant anemia. Finally, severe-to-fulminant disease activity is characterized by persistent symptoms while on corticosteroids, high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

Patients achieve remission when they are asymptomatic or without inflammatory sequelae, including patients who responded to medical or surgical intervention without evidence of residual disease. Steroid-dependent patients, however, are not considered to be in remission. Many pharmacologic therapies for Crohn disease are associated with serious adverse effects, and patients must be monitored carefully for changes in their condition. Adverse effects for commonly used drugs are summarized in Table 3.

Sulfasalazine

When treating a patient with active disease, the primary goal is to induce a state of remission, accomplished by reducing the presence of focal mucosal inflammation while simultaneously controlling the immune system’s inflammatory response, thus preventing further inflammatory destruction. In general, the first-line therapy for patients with mild-to-moderate disease activity is the antibiotic drug sulfasalazine. A derivative of mesalazine, sulfasalazine is used to induce remission in active disease, especially for those with colonic involvement. As a sulfonamide, it is a synthetic analog of p-aminobenzoic acid. Because of this structural similarity to p-aminobenzoic acid, sulfonamides compete with the substrate for the bacterial enzyme dihydropteroate synthetase (found in local intestinal flora), which synthesizes p-aminobenzoic acid into folic acid. By inhibiting the synthesis of folic acid available to enterobacteria, they are left without the nucleic acids needed to create DNA and RNA and thus cannot divide and proliferate. However, sulfasalazine is contraindicated in patients who have sulfa-related intolerance. In such cases, mesalazine would be prescribed instead. Although mesalazine is a widely prescribed antiinflammatory agent, a meta-analysis of the 3 largest trials evaluating the drug failed to show a clinically significant improvement. Thus, its routine use is controversial.

Corticosteroids

Another class of antiinflammatory agents often used to aid induction of remission in Crohn disease patients is corticosteroids. Used particularly for patients with moderate-to-severe disease, these drugs dramatically reduce inflammation by redistributing leukocytes to other body compartments, thereby lowering their blood concentration and function. A recent population-based study reported that 44% of patients with Crohn disease needed corticosteroids to achieve remission. After 4 weeks of use, 58% of patients achieved complete remission and an additional 26% achieved a partial remission.

Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic corticosteroids</td>
<td>Acne, infection, ecchymoses, hypertension, hirsutism, petechial bleeding, striae, diabetes mellitus, osteonecrosis, osteoporosis, myopathy, psychosis, cataracts, and glaucoma</td>
</tr>
<tr>
<td>Azathioprine and 6-MP</td>
<td>Panreatitis, fever, rash, arthralgia, malaise, nausea, diarrhea, thrombocytopenia, hepatitis, veno-occlusive disease, leukopenia, infection, and lymphoma</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Rash, nausea, diarrhea, mucositis, hypersensitivity pneumonitis, bone marrow suppression, infection, and hepatic fibrosis or cirrhosis</td>
</tr>
<tr>
<td>Anti–TNF-α antibodies</td>
<td>Infusion reactions, delayed hypersensitivity reactions, formulation of autoantibodies, demyelination, drug-induced lupus, worsening of congestive heart failure, reactivation of latent tuberculosis, infections, non-Hodgkin lymphoma, and possibly solid tumor malignancies</td>
</tr>
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response. In addition, after 1 year of corticosteroid use, 32% achieved a prolonged response. However, at the 1-year benchmark, 28% of the patients became steroid dependent, and 40% still required surgical intervention. Corticosteroids work by inhibiting fibrin deposition, leukocyte migration, fibroblast proliferation, and scar formation that can occur with persistent mucosal inflammation. More specifically, corticosteroids enter cells and combine with steroid receptors in the cytoplasm. Upon making this link, they enter the cell nucleus where they modify the synthesis of proteins, forming a protein that inhibits the enzyme phospholipase A2, which is needed to supply arachidonic acid, essential for the formation of inflammatory mediators.  

In patients requiring treatment for Crohn ileitis or ileocolitis, budesonide is the corticosteroid of choice because of its targeted delivery to the ileum and right colon via a formulation that is pH and time dependent. Budesonide has markedly reduced systemic adverse effects compared with other corticosteroids, and budesonide trials have shown the drug to be more effective when concomitantly with mesalazine than when mesalazine is used alone. Furthermore, it has similar efficacy to prednisolone (a derivative of prednisone) for inducing remission of active Crohn disease. Prednisone, a more potent corticosteroid, is used primarily for patients who do not respond to sulfasalazine, mesalazine, or budesonide, or outpatients with severe disease. Prednisone itself is inactive until it is converted in the liver into prednisolone.

Caution must be used with these drugs. After approximately 7 days of corticosteroid use, the ability of the adrenal cortex to produce natural corticosteroids is suppressed, and the patient is at risk for steroid dependency. For this reason, as well as the various short-term and long-term adverse effects associated with the use of corticosteroids, prolonged use is not recommended. Instead, substitution with an immunosuppressive drug is the standard of care whenever possible.  

Immunomodulators  
Immunomodulatory agents, particularly immunosuppressors, often are used concomitantly with antibiotic and antiinflammatory therapy to down-regulate the body’s overactive immune response and prevent prolonged distribution of inflammatory cytokines.

Classified as cytokine antagonists, drugs such as infliximab and adalimumab specifically target the production of tumor necrosis factor-alpha (TNF-α). TNF-α is a cytokine involved in systemic inflammation. An acute-phase protein, it belongs to a class of proteins whose plasma concentrations increase or decrease in response to inflammation. The primary role of TNF-α is regulation of immune cells and induction of programmed cell death, thus initiating inflammation. Hence, the goal of using immunomodulation therapy is to block TNF-α release and prevent apoptosis as well as subsequent activation of the inflammatory cascade.

Infliximab is a biological therapy drug, meaning that it is derived from living sources, specifically murine (mouse) protein. It is prescribed as a complementary drug for patients with moderate-to-severe Crohn disease in combination with an antiinflammatory medication. Administered as an infusion, infliximab acts as an antibody that binds to TNF-α and neutralizes the cytokine. However, because infliximab must be given by infusion, and some patients might have difficulty with the infusion process, adalimumab can be prescribed as an alternative. An anti–TNF-α antibody constructed similarly to infliximab, this drug differs only in that it consists of a fully human protein component and can be administered subcutaneously.

One other immunomodulatory drug that often is prescribed in combination with other TNF-α suppressants is methotrexate. Methotrexate is a folate antimetabolite that is structurally related to folic acid and acts as an antagonist to the vitamin. By inhibiting dihydrofolate reductase—the enzyme that converts folic acid to its active form, tetrahydrofolic acid—methotrexate deprives lymphocyte cells of folate and leads to decreased production of the compounds that these cells depend on for replication. Inhibition of dihydrofolate reductase indirectly leads to depressed DNA, RNA, and protein synthesis, and ultimately cell death. Furthermore, methotrexate prolongs the efficacy of infliximab by preventing the development of antiinfliximab antibodies.

Through a combination of drug therapies, patients with Crohn disease should manage to reach a state of disease remission, a decrease in disease symptoms, and an increase in their quality of life. However, it is crucial to manage patients with a drug therapy protocol that will help them maintain their remission. Two structurally
Surgical Interventions

More than 50% of patients with Crohn disease will require at least 1 surgical procedure during the course of their disease. Surgical intervention for the treatment of Crohn disease–related complications typically is reserved for patients who have not responded to pharmacologic therapies or are in an acute, life-threatening state, specifically those who have luminal strictures leading to bowel obstruction or fistulae complicated by abscess formation and significant blood loss.

Bowel Resection

The traditional surgical method used for fistulizing segments of bowel is resection of the affected segments of the GI tract, followed by anastomosis of the proximal and distal ends of the unaffected bowel. The rate of recurrence with bowel resection procedures is relatively high, with 70% of patients having an endoscopically confirmed recurrence within 1 year of surgery and 50% having a symptomatic recurrence within 4 years. Furthermore, patients who require a second resection surgery usually receive such treatment within 5 years, with the recurrence presenting at the previous site of anastomosis. Furthermore, scars related to bowel surgery can form adhesions and become a potential cause of bowel obstruction.

Stricturoplasty

Another option for treating bowel obstruction is stricturoplasty. This surgery restores free flow through the bowel without removing narrowed segments. Stricturoplasty involves widening a narrowed segment of bowel lumen by making an incision lengthwise along 1 side of the bowel, pushing the 2 ends of the cut together, and then suturing the bowel transversely (see Figure 9). This process can be repeated at multiple sites of strictureting along the bowel in a single surgical session and can be particularly helpful for those who already have had extensive bowel resection and are at risk for short bowel syndrome.

Other Antibiotics

An additional treatment protocol is followed when managing a patient with complications related to the penetrating form of Crohn disease. The first line of therapy for these patients is antibiotic drugs such as ciprofloxacin and metronidazole, which are specifically used for their primary effects on the colonic and perianal enterobacteria. The goal is to prevent the bacteria that are native to the intestinal tract from traveling through the fistulous tracts that have developed and proliferating outside the GI system, where they are likely to induce sepsis. Ciprofloxacin, a second-generation fluoroquinolone, works by entering the bacterium by passive diffusion through water-filled protein channels in the outer cell membrane. Once inside the cell, ciprofloxacin inhibits the replication of bacterial DNA, and thus leads to bacterial cell death. Metronidazole has a different mechanism of action. Its metabolites break down into compounds that enter the bacterial cells, binding to intracellular macromolecules and inducing a bactericidal effect. When needed, the second line of treatment consists of the introduction of an immunosuppressant, either azathioprine or mercaptopurine, in combination with infliximab or adalimumab, assuming these drugs are not already prescribed as part of the primary Crohn disease treatment.

related immunomodulatory drugs given to aid in the withdrawal of remission-inducing corticosteroids while maintaining disease remission are azathioprine and its analog, 6-mercaptopurine. Azathioprine exhibits its effects after it is converted into 6-mercaptopurine, in which it then penetrates target cells and is converted into the nucleotide TIMP1. TIMP1 then inhibits the biosynthesis of purine, resulting in decreased RNA and DNA production within lymphocytes and thus an overall decrease in lymphocyte production. Because of the delayed onset of treatment efficacy associated with remission-maintenance drugs, ranging from 6 to 17 weeks, they often are given in combination with the remission-inducing agents at the beginning of the remission maintenance protocol. Once the dedicated maintenance therapy is in full effect, the remission-inducing agents can be discontinued. However, the remission-maintenance therapy usually is continued for the remainder of the patient’s life.
syndrome usually is treated with a change in diet, intravenous feeding, vitamin and mineral supplements, and medications. Severe cases might require intestinal transplant surgery, which has high risks related to infection or rejection of the transplanted organ. In addition, postoperative maintenance of remission still requires the use of antibiotics and antiinflammatory and immunomodulatory agents.

Complementary and Alternative Treatments

Complementary and alternative medicine is defined as a group of diverse medical and health care systems, practices, and products that are not generally considered part of Western conventional medicine. Despite a lack of scientific data in the form of controlled trials for either the efficacy or safety of complementary and alternative medicine treatments, its use by patients with IBD is widespread and increasing. Several complementary and alternative medicine methods have been used specifically to treat symptoms related to Crohn disease. These treatment methods include prebiotics and probiotics, acupuncture, botanical extracts, smoking cessation education, stress reduction techniques, and diet modification.

Probiotics are living microbes commonly consumed as part of fermented foods with specially added active live cultures. Specific probiotic organisms include Lactobacilli, Bifidobacteria, gram-positive cocci, Enterococci, and yeast species such as Saccharomyces boulardii. Evidence from animal models of IBD suggests that probiotics can alter the intestinal microbiota and ameliorate disease, treating symptoms of flatulence, diarrhea, and abdominal pain. The suggested mechanism of action is related to their potential to improve immune function by protecting against pathogens by means of competitive inhibition.

Prebiotics differ from probiotics in that they are nondigestible food ingredients that stimulate the growth and activity of commensal bacteria in the digestive system that are beneficial to the body. Prebiotics most often are made up of soluble fiber, such as fermented short-chain carbohydrates, and allow specific changes in both composition and activity of the GI flora. Similar to probiotics, prebiotics can enhance luminal immunoregulatory bacteria, reduce the activity of proinflammatory factors, and decrease inflammation. However, when evaluated in human trials, neither pre- nor probiotics proved efficacious except in a few trials consisting of only a few subjects. Further research is required before this treatment method will be used routinely.

A second alternative therapy suggested for use in treating Crohn disease is acupuncture. Acupuncture involves inserting and manipulating needles into various points on the body to induce a controlled inflammatory response. It has been hypothesized that acupuncture potentially activates the body’s immune system, influencing nonspecific cellular influx, activation of cell proliferation, and regulation of subsequently involved cells, resulting in transport, breakdown, and clearance of bioactive mediators of inflammation. Although peer-reviewed research is limited, the data seem to indicate that acupuncture could contribute to recovery in patients with IBD.

Another alternative therapy for IBD patients being researched is the use of botanical extracts. The gum resin extract of Boswellia has been reported to have antiinflammatory and immunomodulatory activity, and Scutellaria’s active flavanoid compounds reportedly have potent antifibrotic effects. The use of natural products to aid in Crohn disease treatment is thought to reduce the risk of toxicity associated with pharmacologic treatment while maintaining the drugs’ therapeutic effectiveness. In addition, recent investigations into the role of...
the endocannabinoid system in the GI tract have shown that Cannabis sativa extracts also might aid in reducing intestinal inflammation by activating CB1 receptors present in enteric nervous system neurons, which results in protective modulation of functions such as gastric secretion, gastric emptying, and intestinal motility.24

Lifestyle changes also have been suggested to aid in recovery for patients with Crohn disease who have managed to reach disease remission. One such lifestyle change is smoking cessation. Research has shown that cigarette smoking is strongly associated with the development of Crohn disease, resistance to medical therapy, and early relapse of the disease.7 By developing a therapeutic strategy based on the individual patient’s degree of motivation, degree of tobacco dependency, history of depression, prior attempts to quit, and his or her specific Crohn disease course, the clinician can combine pharmacologic and group cognitive behavior therapy to suit the patient’s particular needs.27

Psychological stress also has been reported to increase activity of IBD. Adverse life events, chronic stress, and depression seem to increase the likelihood of relapse in patients who have achieved disease remission.28 Furthermore, studies have shown a strong correlation between patients with active IBD and reports of significantly prolonged sleep latency (difficulty falling asleep), frequent sleep fragmentation (difficulty staying asleep), higher rates of sleeping pill use, decreased daytime energy, and poor overall sleep quality.29 Therefore, it is important for the treating physician to approach patient care holistically and consider the need for assessment and management of depression or sleep disorders that might be associated with Crohn disease.

Finally, as mentioned previously, certain foods can aggravate Crohn disease symptoms. Because of lactose intolerance, dairy products might be a problematic food that encourages diarrhea.30 Conversely, if a patient suffers from bowel obstruction, high-fiber foods such as raw fruits, vegetables, and nuts might contribute to abdominal pain.31 For this reason, customized dietary modifications, specifically exclusion diets, can reduce aggravation of the injured intestinal tract and expedite disease remission.

**Conclusion**

Crohn disease is an IBD that results from an inappropriate response of a defective mucosal immune system to the indigenous flora and other luminal antigens. An increase in the permeability of the intestinal epithelial layer allows pathogens to leak through with less resistance, and the mucosa’s inability to suppress an inappropriately triggered immune response compounds the pathogenic process.

Data suggest that those with first-degree family members who have the disease are predisposed to Crohn disease. Furthermore, individuals of Ashkenazi Jewish descent also are at an increased risk for developing Crohn disease. Geographic data indicate an increased risk of developing the disease for those living in the northern hemisphere, particularly the United States and Northern Europe.

The primary manifestations of the disease include intramural inflammatory lesions that can occur at any section of the GI tract, although more typically in the small and large intestine, as well as structuring and abscess formation. These initial disease manifestations can lead to further complications such as stenotic bowel lumen with potential for intestinal obstruction as well as metaplastic cell changes that lead to cancer. Crohn disease can be misdiagnosed as ulcerative colitis; the presence of skip lesions, in which inflammatory lesions develop in more distal aspects of the bowel, usually helps differentiate between the 2 diseases. Because Crohn disease is a systemic autoimmune disease, there is potential for extraintestinal manifestations.

There is no gold standard for the diagnosis of Crohn disease. Instead, a combination of laboratory analysis, comprehensive patient history and physical examination, and various medical imaging examinations are used to confirm the disease and track its progression. Static radiographs and dynamic fluoroscopic imaging can aid in identifying bowel strictures, adhesions, fistulae, and obstructions. CT imaging, another method for assessing the entirety of the GI tract, often is used to differentiate between Crohn disease and appendicitis. However, radiation dose should be considered when serial imaging is required. MR imaging offers a radiation-free option and is especially useful for assessing the presence and extent of perianal disease, as well as for evaluating bowel wall thickening. The role of ultrasonography is limited primarily to evaluation of extraintestinal disease manifestations related to the gallbladder and liver. Endoscopic imaging, often performed with both an antegrade
and retrograde approach to visualize the entire GI tract, or via a pill camera, has largely taken precedence over radiographic imaging, although these approaches come with procedural risks.

Traditional treatments for Crohn disease primarily depend on pharmacologic therapies, with surgical intervention being used when necessary. Decisions regarding which drugs to prescribe are determined based on the stage of the disease, level of disease activity, and evidence of penetrating behavior. A regimen of various antibiotics, corticosteroids, immunomodulatory drugs, and antiinflammatory medications can be prescribed to help bring the disease into a state of remission and prevent future flare-ups. However, no cure for Crohn disease currently is available. Surgical intervention for the treatment of Crohn-related complications typically is reserved for patients who have not responded to pharmacologic therapies or who are in an acute, life-threatening state. Commonly, surgery consists of resection of the diseased bowel with an anastomosis of the 2 remaining bowel ends. Complementary and alternative medical approaches also are used as part of the treatment plan and consist of acupuncture, pre- and probiotics, botanical extracts, and dietary restrictions.

References
Crohn Disease: Pathophysiology, Diagnosis, and Treatment


Crohn Disease: Pathophysiology, Diagnosis, and Treatment

1. The human intestine harbors the largest and most diverse collection of microbial flora within the body, consisting of more than ______ species of commensal bacteria.
   a. 50
   b. 100
   c. 500
   d. 1000

2. To maintain a healthy relationship between the intestinal mucosa and its natural flora, immune homeostasis depends on 3 key mucosal functions.
   a. true
   b. false

3. Results of increased access of microbial pathogens to the submucosa's numerous embedded antigen receptors include:
   1. triggering of an immune response.
   2. initiating the inflammatory cascade.
   3. suppressing the immune response.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

4. Data has shown that for an individual of ______ descent with a first-degree relative who has Crohn disease, the estimated lifetime risk of developing Crohn disease increases to 7.8%.
   a. Native American
   b. Middle Eastern Jewish (Sephardi)
   c. European Jewish (Ashkenazi)
   d. Asian

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5. For a person with a mutation in one of the inflammatory bowel disease (IBD) gene loci, the relative risk of developing the disease is approximately:
   a. 1:5.
   b. 1:50.
   c. 1:100.
   d. 1:200.

6. Which global hemisphere has the highest reported incidence rates and prevalence of Crohn disease cases?
   a. northern
   b. southern
   c. eastern
   d. western

7. The Vienna classification was developed to describe the distinct clinical phenotypes of Crohn disease with respect to:
   1. disease location.
   2. potential complications.
   3. duration of symptoms.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

8. When there is narrowing of the intestinal lumen, patients with Crohn disease are in danger of developing a(n) ______, a complication of the disease in which the intestinal pathway becomes occluded.
   a. hiatal hernia
   b. ileus
   c. mechanical intestinal obstruction
   d. intestinal perforation

9. One manifestation of Crohn disease is a transmural pattern of inflammation, with evidence of inflammation spanning ______ of the intestinal wall.
   a. through the mucosal layer
   b. slightly into the submucosal layer
   c. through the muscular layer
   d. the entire depth

10. Which of the following is not a potential comorbidity associated with Crohn disease?
    a. migratory polyarthritis
    b. pericarditis
    c. sclerosing cholangitis
    d. ankylosing spondylitis

11. Which Crohn disease course is most common?
    a. chronic intermittent
    b. chronic active
    c. remission for several years at a time
    d. complete recovery

12. Race has been shown to play a role in the development of Crohn disease in North America, with prevalence rates for Hispanics and Asians being ______ compared with rates for whites and African Americans.
    a. similar
    b. much lower
    c. slightly higher
    d. much higher

13. The administration of the attenuated live measles, mumps, and rubella vaccine is hypothesized to ______ the risk of IBD.
    a. decrease
    b. increase
    c. both increase and decrease
    d. have no effect on

continued on next page
14. Approximately ______ of patients who have Crohn disease with either large or small bowel involvement exhibit signs of perianal disease.
   a. two-thirds
   b. one-half
   c. one-third
   d. one-quarter

15. Laboratory tests that can confirm the presence of nonspecific inflammatory activity include:
   1. erythrocyte sedimentary rate.
   2. C-reactive protein.
   3. leukocyte and platelet counts.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

16. Enteroclysis is a technique in which contrast material is introduced rapidly into the intestinal tract below the ________ junction.
   a. gastroesophageal
   b. gastroduodenal
   c. duodenoojunal
   d. ileocecal

17. Which of the following are benefits of magnetic resonance imaging over computed tomography for patients with Crohn disease?
   1. characterizing perirectal abscesses and fistulae
   2. it is a radiation-free exam
   3. ability to differentiate between peristalsis and skip lesions
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

18. Medications are prescribed to patients who have Crohn disease based on:
   1. stage of disease process.
   2. level of disease activity.
   3. evidence of penetrating behavior.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

19. Which medication typically is prescribed in place of sulfasalazine for patients with sulfa-related intolerance?
   a. corticosteroids
   b. arachidonic acid
   c. mesalazine
   d. methotrexate

20. The goal of immunomodulation therapy is to ________ TNF-α release and ________ apoptosis as well as subsequent activation of the inflammatory cascade.
   a. block; prevent
   b. activate; permit
   c. block; permit
   d. activate; prevent

21. ________ prolongs the efficacy of infliximab by preventing the development of antiinfliximab antibodies.
   a. Mesalazine
   b. Arachidonic acid
   c. Corticosteroids
   d. Methotrexate

continued on next page
22. More than ______ % of patients with Crohn disease will require at least 1 surgical procedure during the course of their disease.
   a. 10  
   b. 25  
   c. 50  
   d. 75

23. Which surgical procedure involves widening a narrowed segment of bowel lumen by making an incision lengthwise along 1 side of the bowel, pushing the 2 ends of the cut together, and then suturing the bowel transversely?
   a. Whipple procedure  
   b. stricturoplasty  
   c. bowel resection  
   d. bowel diversion

24. Which of the following complementary and alternative medicine–related treatments is not specifically used to treat patients with Crohn disease?
   a. prebiotics and probiotics  
   b. acupuncture  
   c. raw foods diet  
   d. botanical extracts

25. Which of the following does not seem to increase the likelihood of relapse in patients with disease remission?
   a. adverse life events  
   b. chronic stress  
   c. depression  
   d. extended hunger