



# UPDATE ON CROHN'S DISEASE

With the prevalence of this disease on the rise, research is ongoing to understand how to better treat its symptoms that greatly affect patients' quality of life.

By Ronale Tucker Rhodes, MS

**IN 2014, THE** Crohn's and Colitis Foundation of America estimated 1.6 percent of Americans (more than five million) have inflammatory bowel disease (IBD), which includes Crohn's disease (780,000) and ulcerative colitis (907,000). Researchers estimate six to 15 new cases of Crohn's are diagnosed per 100,000 people each year.<sup>1</sup>

Crohn's is a chronic IBD characterized by inflammation of any part of the gastrointestinal (GI) tract, from the mouth to the anus; however, it more commonly affects the small intestine where it joins the beginning of the large intestine (or colon).<sup>2</sup> Crohn's can also affect the eyes, skin and joints.<sup>1</sup>

The disease affects both adults and children. The prevalence of Crohn's in 2014 was approximately 241.3 per 100,000 adults 20 years and older, and 57.8 per 100,000 in children and adolescents under 20 years old. Sadly, these numbers have continued to increase. In 2004 and 2005, 43 children and 214 adults per 100,000 people had Crohn's. In 2008 and 2009, these estimates rose to 48 children and 236 adults per 100,000 people.<sup>1</sup>

Crohn's is more common in females, and Caucasians and Ashkenazi Jews develop it at a higher rate than other ethnicities; however, the rate of diagnosis for African Americans is approaching that in whites.<sup>1,3</sup> Interestingly, children are twice as likely to be diagnosed with Crohn's than ulcerative colitis.<sup>3</sup> Crohn's is also more common in the North than in the South, and the number of people diagnosed is higher in the Northeast

and Midwest than in the South or West.<sup>1</sup>

Crohn's can be treated, but it cannot be cured. And, it can significantly degrade a patient's quality of life and may have a high financial burden. In a 2008 review, direct medical costs in the U.S. were \$18,022 to \$18,932 per patient per year<sup>3</sup> at an annual cost of \$3.6 billion. More than one-third of expenses are due to medications (with biologicals generally the most expensive) and hospitalizations (31.4 percent of cost).<sup>1</sup>

## Causes of Crohn's Disease

The cause of Crohn's is not definitively known. It is believed to be an autoimmune disease, but recent research suggests that rather than the immune system attacking the body itself, thus causing chronic inflammation, the immune system may instead be attacking a harmless virus, bacteria or food in the gut.<sup>4</sup>

There are several known risk factors for Crohn's. One is genetics. Approximately 20 percent of people with IBD have another family member with IBD, and families frequently share a similar pattern of disease. In fact, between 5 percent and 20 percent of people with IBD have a first-degree relative with IBD. When both parents have IBD, the risk of their children developing Crohn's is 35 percent.<sup>3</sup>

Age is also a risk factor, primarily affecting young people, with most people diagnosed before age 30. A diet high in fat and/or processed foods increases the odds of getting Crohn's. And, the

environment may play a role. For instance, rates of Crohn's are higher in developed countries, urban areas and northern climates. Finally, the bacteria *Mycobacterium avium paratuberculosis* and a type of *E. coli* are linked to Crohn's.<sup>3,4</sup>

A risk factor easy to control is smoking. While smoking doesn't cause Crohn's, it can make the disease more severe and raises the odds of needing surgery. Nonsteroidal anti-inflammatory drugs such as ibuprofen and naproxen can also make Crohn's worse.<sup>4</sup>

## Symptoms of Crohn's

Symptoms of Crohn's can range from mild to severe and can even be followed by periods of no symptoms that can last weeks to years. Common Crohn's symptoms include frequent and recurring diarrhea, rectal bleeding, unexplained weight loss, fever, abdominal pain and cramping, fatigue and a feeling of low energy, and reduced appetite. Other symptoms can include mouth sores, pain or drainage near or around the anus due to inflammation from a tunnel into the skin (fistula), constipation and an interruption in menstrual cycle in women.<sup>3</sup> In addition, as mentioned previously, Crohn's can also cause inflammation in areas outside the GI tract such as the eyes, skin and joints. Such symptoms are called extraintestinal.<sup>5</sup>

For those with mild-to-moderate Crohn's, symptoms mostly include frequent diarrhea, abdominal pain (with the ability to walk and eat normally), and no signs of dehydration, high fever, abdominal tenderness, painful mass, intestinal obstruction or weight loss of more than 10 percent. Moderate-to-severe symptoms include frequent diarrhea, abdominal pain or tenderness, fever, significant weight loss and significant anemia such as fatigue, shortness of breath, dizziness and headache. Very severe symptoms include high fever, persistent vomiting, evidence of intestinal obstruction (blockage) or abscess (localized infection or collection of pus), and more severe weight loss.<sup>5</sup>

Symptoms also depend on the type of Crohn's disease, which is determined by where the disease is located in the GI tract. There are five types of Crohn's:<sup>5</sup>

1) Ileocolitis affects the end of the small intestine (the ileum) and the large intestine (the colon). Symptoms include weight loss, diarrhea and cramping or pain in the middle or right lower abdomen.

2) Ileitis affects the ileum, and symptoms are the same as for ileocolitis.

3) Jejunoileitis is characterized by patchy areas of inflammation in the upper half of the small intestine (the jejunum).

Symptoms include mild to strong abdominal pain and cramps following meals, as well as diarrhea.

4) Gastroduodenal Crohn's disease affects the stomach and the beginning of the small intestine (the duodenum). Symptoms include loss of appetite, weight loss, nausea and vomiting.

5) Crohn's colitis affects the colon. Symptoms include diarrhea, rectal bleeding and disease around the anus (abscess, fistulas, ulcers).

## Complications of Crohn's

Two types of complications can arise due to Crohn's, including local complications that affect just the intestines and systemic complications that affect the whole body (also known as extraintestinal complications).

Local complications include abscess (a pocket of pus that can form on the walls of the intestine or near the anus), bile salt diarrhea (that occurs because the body can't process the fat), fissure (a painful tear in the lining of the anus that can cause bleeding during bowel movements), fistula (sores or ulcers that can turn into openings), malabsorption and malnutrition (that occurs when Crohn's has persisted for a long period and the body is no longer able to make the most of what is eaten), small intestinal bacterial growth (when the bacteria in the gut is higher in the digestive tract) and strictures (narrowed, thickened areas of the intestines).<sup>4</sup>

A host of systemic complications can occur. These include three types of arthritis (peripheral, axial and ankylosing spondylitis), skin problems (pyoderma gangrenosum, skin tags and mouth ulcers), bone loss (most often caused by steroids), vitamin D deficiency, eye problems (episcleritis, scleritis and uveitis), kidney problems (kidney stones, uric acid stones, hydronephrosis and fistulas), liver problems (fatty liver disease, gallstones, hepatitis and pancreatitis) and physical development problems (growth failure and delayed puberty).<sup>4</sup>

People who have Crohn's disease in their large intestine may be more likely to develop colon cancer; however, receiving ongoing treatment to ensure the disease stays in remission reduces the chances of developing colon cancer.<sup>2</sup>

## Managing Crohn's

Crohn's is treated with a combination approach. The goal of treatment is to reduce the inflammation that triggers signs and symptoms using preventive care, including medication, surgical procedures and diet.

Medications include anti-inflammatory drugs such as

## Crohn's Disease vs. Ulcerative Colitis

Both Crohn's disease and ulcerative colitis are inflammatory bowel diseases, but there are some key differences.

Crohn's Disease	Ulcerative Colitis
<ul style="list-style-type: none"> <li>• Inflammation may develop anywhere in the GI tract, from the mouth to the anus</li> </ul>	<ul style="list-style-type: none"> <li>• Limited to the large intestine (colon and rectum)</li> </ul>
<ul style="list-style-type: none"> <li>• Most commonly occurs at the end of the small intestine</li> </ul>	<ul style="list-style-type: none"> <li>• Occurs in the rectum and colon, involving a part of the entire colon</li> </ul>
<ul style="list-style-type: none"> <li>• May appear in patches</li> </ul>	<ul style="list-style-type: none"> <li>• Appears in a continuous pattern</li> </ul>
<ul style="list-style-type: none"> <li>• May extend through entire thickness of bowel wall</li> </ul>	<ul style="list-style-type: none"> <li>• Inflammation occurs in innermost lining of the intestine</li> </ul>
<ul style="list-style-type: none"> <li>• About 67 percent of people in remission will have at least one relapse over a five-year period</li> </ul>	<ul style="list-style-type: none"> <li>• About 30 percent of people in remission will experience a relapse in a year</li> </ul>

Source: Crohn's & Colitis. Understanding Crohn's Disease. Accessed at [www.crohnsandcolitis.com/crohns?cid=ppc\\_ppd\\_msft\\_cd\\_da\\_crohn%27s\\_disease\\_statistics\\_Exact\\_64Z1867745&msclkid=9a7bb2749d4517211c83eeb929115fe](http://www.crohnsandcolitis.com/crohns?cid=ppc_ppd_msft_cd_da_crohn%27s_disease_statistics_Exact_64Z1867745&msclkid=9a7bb2749d4517211c83eeb929115fe).

mesalamine (Asacol, Lialda, Pentasa), olsalazine (Dipentum) and sulfasalazine (Azulfidine), and immune system modifiers such as azathioprine (Imuran) and methotrexate (Rheumatrex). However, the latter can take up to six months to work, and they have a higher risk of causing infections that can be life-threatening. Antibiotics such as ciprofloxacin (Cipro), metronidazole (Flagyl), vancomycin (Vancocin) and antiprotozoal (Alinia) are also commonly prescribed. In addition, corticosteroids, a more powerful type of anti-inflammatory, such as prednisone (Solu-Medrol) and budesonide (Entocort) can be used in conjunction with other therapies; however, side effects can be severe if used long-term.<sup>4,6</sup>

Moderate to severe Crohn's disease can also be treated with biologics when other treatments haven't worked. Unlike other therapies for Crohn's, biologics aggressively target the particular proteins that cause inflammation in the GI tract. There are three types of biologics to treat Crohn's: TNF (tumor necrosis factor)-alpha inhibitors, integrin blockers and interleukin blockers — and all are costly.

TNF-alpha inhibitors are sold under the brand names Remicade, Humira and Cimzia, and are given in prefilled pens or syringes that can be self-administered. Because these drugs can't solely block the immune system from attacking its own tissue while leaving the natural immune responses intact, they increase susceptibility to other diseases and infections, and they can sometimes increase the risk of developing certain cancers.

Integrin blockers include natalizumab (Tysabri) and vedolizumab (Entyvio), which work by interfering with the process of white blood cells attaching to the lining of the intestines to reduce inflammation and relieve other symptoms. Severe and even fatal side effects have been associated with integrin blockers.

Ustekinumab (Stelera) is the only interleukin inhibitor

approved by the U.S. Food and Drug Administration to treat Crohn's. It works by targeting two specific proteins (interleukin-12 and interleukin-23) that are thought to cause inflammation and are found in high levels in people with Crohn's. Stelera can also increase the risk of infections.<sup>7</sup>

The Crohn's and Colitis Foundation estimates two-thirds of people with Crohn's disease will need surgery to treat complications of the disease or when medications don't help.<sup>4</sup> Surgical procedures include anastomosis (the diseased part of the bowel is removed and the two healthy ends are joined together), ileostomy (connecting the intestine to the skin of the torso, which has an opening where waste products can be collected in a special pouch), small bowel resection (removal of the small bowel), fistulectomy (removal of the fistulous tract), strictureplasty (removal of scar tissue that has built up in the intestinal wall), colectomy (removal of all or part of the colon) and proctocolectomy (removal of the rectum and all or part of the colon).<sup>4,6</sup>

Dietary modifications, especially during flare-ups, can help reduce disease symptoms and replace lost nutrients. Doctors recommend making changes to diet such as avoiding carbonated drinks; avoiding popcorn, vegetable skins, nuts and other high-fiber foods; drinking more liquids; eating smaller meals more often; and keeping a food diary to help identify foods that cause problems.<sup>3</sup>

Preventive care is an essential aspect of lifelong disease management. According to a U.S. population-based study that used 2015 and 2016 National Health Interview Survey results, adults with IBD are more likely than adults without IBD to receive preventive care services such as receiving medical advice about smoking cessation and healthy diet, receiving colon cancer screening in the past year, getting an HIV test, receiving the pneumococcal vaccine and flu vaccine in the past year, and having a tetanus vaccine in the past 10 years.<sup>8</sup>

However, in 2017, the American College of Gastroenterology published clinical guidelines addressing preventive care in patients with IBD in response to data that suggest IBD patients do not receive preventive services at the same rate as general medical patients. According to the guidelines, patients with IBD often consider their gastroenterologist to be the primary provider of care, but to improve care, health maintenance issues need to be co-managed by both the gastroenterologist and primary care team. Therefore, the guidelines recommend gastroenterologists inform primary care providers of the unique needs of IBD patients, especially those on immunomodulators and biologics or being considered for such therapy. In particular, documentation of up-to-date vaccinations are crucial as IBD patients are often treated with long-term immune-suppressive therapies and may be at increased risk for infections, many of which are preventable with vaccinations. Health maintenance issues addressed in the guideline include identification, safety and appropriate timing of vaccinations; screening for osteoporosis, cervical cancer, melanoma and nonmelanoma skin cancer; identification of depression and anxiety; and smoking cessation.<sup>9</sup>

Moderate to severe Crohn's disease can also be treated with biologics when other treatments haven't worked.

### Looking Ahead

Due to the vast and growing numbers of people suffering from Crohn's disease, research to treat and manage the condition is prolific. In fact, there are more than 1,000 studies listed on [ClinicalTrials.gov](https://www.clinicaltrials.gov) researching medications for Crohn's. In addition, many organizations are supporting ongoing research initiatives.

The Crohn's and Colitis Foundation is at the forefront of accelerating research about the disease. Every five years, it convenes leading scientists to update the foundation's IBD research agenda and identify new priorities. The foundation is currently supporting two major initiatives. The Microbiome Initiative seeks to develop greater understanding of the role of gut microbes (bacteria, viruses, etc., normally

found in the intestines) in digestive health and IBDs. And, the Genetics Initiative is a collaborative effort to better understand genes and their functions, and the chain of biological events that result in IBD.<sup>10</sup>

The foundation is also supporting five studies, including:<sup>10</sup>

- The Pediatric Risk Stratification Study, which is looking to identify disease prognosis by identifying measurable risk factors for the complications of severe disease;
- IBD Partners, a comprehensive Internet-based registry designed to study thousands of patients with Crohn's disease or ulcerative colitis under a single research initiative;
- Clinical Research Alliance, a network of major medical centers and smaller facilities collaborating on clinical studies of the management and treatment of IBD;
- The Autoimmune Disease in Pregnancy Study, which is being conducted to learn how Crohn's and other autoimmune diseases affect the outcome of pregnancies; and
- The PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) study, which is investigating whether there is a higher rate of adverse events in a prospective national sample of women from the U.S. with IBD who are being treated with biologic drugs.

Two breaking clinical trials results are showing promise:

- In May, SetPoint Medical released results of its successful proof-of-concept study evaluating its bioelectronic medicine approach to treat Crohn's, which showed clinically meaningful reductions in disease activity in the majority of patients, along with improvements in mucosal healing. The study, which was conducted across five centers in Europe, treated 16 biologic-refractory patients with active Crohn's disease. All 16 patients were implanted with a vagus nerve stimulating (VNS) device to deliver proprietary doses of electricity designed to activate the innate inflammatory reflex to produce a systemic anti-inflammatory effect and help regulate the immune systems. Patients were separated into two cohorts: The first were washed off their biologic drugs and received only VNS monotherapy, and the second continued their biologic drugs, to which they had inadequate clinical response, in addition to adjunctive VNS therapy.

At 16 weeks, enhanced clinical response (with Crohn's Disease Activity Index (CDAI) score improvement of 100 or more points) was observed in eight of 16 patients, with four patients achieving CDAI remission (CDAI below 150). On average, levels of serum biomarkers associated with inflammation were reduced compared to baseline, while an anti-

inflammatory cytokine, IL-10, increased from baseline, indicating pharmacodynamic activation of the inflammatory reflex. Patient-reported outcomes indicated a significant improvement in quality of life for seven of the 16 patients who had previously been refractory to biologic therapy. Over the course of the study, 10 patients had an improvement in their autonomic balance, the ratio of sympathetic to vagal tone as measured by heart rate variability, with the shift toward values typically observed in the healthy population.<sup>11</sup>

• Also in May, results of a study showed people with Crohn's who worked with their gastroenterologists to earlier detect and address worsening symptoms were more likely to stay out of the hospital and reduced their annual medical cost by \$6,500 per person. In the 24-month study conducted by SonarMD and Blue Cross and Blue Shield of Illinois, researchers compared a group of 176 Crohn's disease patients who were enrolled in SonarMD's solution to a matched control group that was not. SonarMD contracts with payers to work directly with subspecialists in their network to provide value-based care for patients with high-beta (symptomatic, chronic and likely to deteriorate rapidly, leading to complications, hospitalizations and highly variable per-capita costs) conditions. Its clinical staff uses technology to connect with patients, calculate risk and coordinate care. "The results of this research study demonstrate how an innovative approach to patient engagement and monitoring can improve access to care, health outcomes and affordability," said Derek Robinson, MD, vice president and chief medical officer at Blue Cross and Blue Shield of Illinois.<sup>12</sup>

## Crohn's Impact on Patients

Crohn's disease takes a toll on patients both physically and mentally. A study conducted to understand the impact of Crohn's on various aspects of daily life from the perspective of patients living with the disease found a need for more patient education and more collaborative relationships between patients and providers regarding treatment decisions. Study participants stated Crohn's caused fear and embarrassment, they were reluctant to share the full impact of the disease with family and providers, and they relied on their provider for treatment decisions. Many participants accepted a new state of normalcy if their current medication helped their most bothersome symptoms without providing sustained remission. Participants receiving biologic therapy generally were more informed, more satisfied and more likely

to adhere to treatment regimens.<sup>13</sup>

More recently, studies have found anxiety and depression are two to three times more likely to occur in IBD patients compared with the general population. In one study, researchers looked at the data of 432 IBD patients within the Intestinal Diseases Natural History Database at the Pennsylvania State College of Medicine in Hershey, Pa. Of these, approximately 44 percent were found to have significant scores on a scale for anxiety or depression, with a majority of them (59 percent) female. About 20 percent had both anxiety and depression. The study also found patients with anxiety and/or depression reported their symptoms to be more severe compared to those who did not have anxiety or depression.<sup>14</sup>

Fortunately, as more is being discovered about how to manage symptoms of Crohn's, the search for the cause of the disease continues. It is understood to be an autoimmune reaction, and treatment of the disease is reliant on medication, surgery and diet. Moreover, the American College of Gastroenterology's recently introduced guidelines for Crohn's now recognize the additional need for screening for depression and anxiety in these patients. Given Crohn's increasing prevalence and profound impact on patients, further studies will hopefully yield a more complete understanding of it, leading to more effective treatment. ■

**RONALE TUCKER RHODES** is the editor of *IG Living* magazine.

## References

1. Crohn's & Colitis Foundation of America. The Facts About Inflammatory Bowel Disease, November 2014. Accessed at [www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf](http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf).
2. National Institute of Diabetes and Digestive and Kidney Diseases. Definition & Facts for Crohn's Disease. Accessed at [www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease/definition-facts](http://www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease/definition-facts).
3. Healthline. Crohn's Disease: Facts, Statistics, and You. Accessed at [www.healthline.com/health/crohns-disease/facts-statistics-infographic#1](http://www.healthline.com/health/crohns-disease/facts-statistics-infographic#1).
4. WebMD. Crohn's Disease Overview. Accessed at [www.webmd.com/ibd-crohns-disease/crohns-disease/digestive-diseases-crohns-disease#1](http://www.webmd.com/ibd-crohns-disease/crohns-disease/digestive-diseases-crohns-disease#1).
5. Crohn's & Colitis Foundation of America. Crohn's Symptoms. Accessed at [www.crohnsandcolitis.com/crohns/disease-symptoms](http://www.crohnsandcolitis.com/crohns/disease-symptoms).
6. Managing Crohn's Disease. Treatments. Accessed at [www.managingcrohnsdisease.com/treatments](http://www.managingcrohnsdisease.com/treatments).
7. Healthline. TNF-Alpha Inhibitors vs. Other Biologic Therapies for Crohn's Disease. Accessed at [www.healthline.com/health/crohns-disease/tumor-necrosis-factor](http://www.healthline.com/health/crohns-disease/tumor-necrosis-factor).
8. Centers for Disease Control and Prevention. Inflammatory Bowel Disease Prevalence in the United States. Accessed at [www.cdc.gov/ibd/data-statistics.htm](http://www.cdc.gov/ibd/data-statistics.htm).
9. IBD Biologics. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease, May 22, 2017. Accessed at [www.ibdbiologics.com/discuss/acg-clinical-guideline-preventive-care-in-inflammatory-bowel-disease](http://www.ibdbiologics.com/discuss/acg-clinical-guideline-preventive-care-in-inflammatory-bowel-disease).
10. Crohn's and Colitis Foundation. Current Research Studies. Accessed at [www.crohnscolitisfoundation.org/research/current-research-studies](http://www.crohnscolitisfoundation.org/research/current-research-studies).
11. SetPoint Medical Reports New Data Demonstrating its Bioelectronic Medicine Effectively Reduces Crohn's Disease Activity. SetPoint press release, May 20, 2019. Accessed at [www.apnews.com/Globe%20NewsWire/3e14944724cd56e5adcd1236358420dbc](http://www.apnews.com/Globe%20NewsWire/3e14944724cd56e5adcd1236358420dbc).
12. DDW 2019: New Study Shows SonarMD Lowers Cost of Managing Crohn's Disease. SonarMD press release, May 19, 2019. Accessed at [www.apnews.com/Business%20Wire/e21a283b38584e8aac031e95ea0dfca4](http://www.apnews.com/Business%20Wire/e21a283b38584e8aac031e95ea0dfca4).
13. Norton, BA, Thomas, R, Lomax, KG, and Dudley-Brown, S. Patient Perspectives on the Impact of Crohn's Disease: Results from Group Interviews. *Patient Preference and Adherence*, 2012; 6: 509-520. Accessed at [www.ncbi.nlm.nih.gov/pmc/articles/PMC3413071](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413071).
14. Soto, C. The Impact of Anxiety and Depression on Patients with Inflammatory Bowel Diseases. Crohn's and Colitis Foundation, Nov. 7, 2018. Accessed at [www.crohnscolitisfoundation.org/research/clinical-trials-community/research-updates/the-impact-of-anxiety-and.html](http://www.crohnscolitisfoundation.org/research/clinical-trials-community/research-updates/the-impact-of-anxiety-and.html).