



RSim General & Colorectal Surgery
1 Farrer Park Station Road,
#13-10, Farrer Park Medical Centre,
Singapore 217562.
Tel: (65) 6636 3493 Fax: (65) 6636 3494

Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

What Is Inflammatory Bowel Disease?

The Gastrointestinal Tract

The gastrointestinal (GI) tract (the digestive system) is a tube that extends from the mouth to the anus. It is a complex organ system that first carries food from the mouth down the esophagus to the stomach. There, acids and stomach motion break food down into particles small enough so that nutrients can be absorbed by the small intestine, which is, despite its name, the longest part, about 20 feet, of the GI tract. Food passes from the stomach into the small intestine, first entering the duodenum, then the jejunum, and finally the ileum. Next, residual material passes in liquid form into the large intestine, which consists of the colon and rectum and is about six feet long. The waste matter travels through the colon, forming into solid feces as the water is slowly absorbed. The first portion of the colon, which is located in the lower right quadrant of the abdomen, is called the cecum. From here, the large intestine travels to the upper right quadrant (where it is called the ascending colon), then across the abdomen to the upper left quadrant (the transverse colon), then down (the descending and sigmoid colon) to the rectum, which stores the feces until the sphincter muscles in the anus relax, allowing the solid waste matter to pass from the body.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a general term that covers the specific disorders ulcerative colitis and Crohn's disease.

Ulcerative Colitis.

Ulcerative colitis is an inflammatory disease of the large intestine. Ulcers form in the inner lining, or mucosa, of the colon or rectum, often resulting in diarrhea, blood, and pus. The inflammation is usually most severe in the sigmoid and rectum and usually diminishes higher in the colon. The disease develops uniformly and consistently until, in some cases, the colon becomes rigid and foreshortened.



Crohn's Disease

Crohn's disease is an inflammation that extends into the deeper layers of the intestinal wall. It is found most often in the ileum and the lower right part of the large intestine (cecum), known as the ileocecal region. The disorder, however, can develop in any part of the gastrointestinal tract, including the anus, stomach, esophagus, and even the mouth. It may affect the entire colon or form a string of contiguous ulcers in one part of the colon or develop as multiple scattered clusters of ulcers skipping healthy tissue in between.

What Causes Inflammatory Bowel Disease?

Although the causes of inflammatory bowel disease are not yet known, genetic factors certainly play some role. Up to 25% of people with IBD also have family members with the disease. The inherited risk is highest if a mother has the condition, followed by a sibling. A father with IBD poses the least inherited risk to his children. Although different genes play weaker or stronger roles in ulcerative colitis and Crohn's disease, some experts believe that genetic mapping will allow detection of the genes responsible for both diseases, most likely on chromosomes 6, 12, and 16.

Some researchers believe that the disease develops in people who have a genetic susceptibility that enables an agent such as a virus or bacteria to trigger an abnormal immune response. If such organisms or other factors injure the lining of a healthy intestine, the immune system reduces inflammation and injury with white blood cells called suppressor T cells. In IBD, however, there appears to be an increase in white blood cells called helper-T cells, which produce damaging proteins known as cytokines. These proteins, particularly those known as tumor necrosis factor, interferon-gamma, and interleukin-1 beta, cause intestinal inflammation and damage, which, in a vicious cycle, attract even more helper-T cells. A protein on the surface of intestinal cells called ICAM-1 also plays a role. White blood cells are activated by increased levels of ICAM-1, which occur in IBD. Recent research on Crohn's disease suggests that a natural mechanism called apoptosis, a process whereby cells self-destruct, may be faulty. In the case of Crohn's disease T



cells may lack this property and so they proliferate faster than they die, causing an excessively strong immune response.

Some research indicates that infectious organisms, either viruses or mycobacteria, may be responsible for triggering the inflammatory process leading to either Crohn's disease or ulcerative colitis. Studies have found that children with IBD are likely to have more and earlier childhood infections; one study found a higher risk for both diseases in children who had the measles and mumps in the same year. One study indicates that exposure to measles during pregnancy puts the baby at risk for developing Crohn's disease, but a major follow-up analysis found no evidence for this association. While a link between IBD and vaccination for measles, mumps, and rubella has been suggested, a recent study has strongly refuted this association. A stronger, but still speculative, suspect for Crohn's disease may be mycobacteria that cause a form of tuberculosis.

Because inflammatory bowel disease is much more prevalent in industrialized nations, experts believe environmental factors, such as diet, must play some role, although studies have been conflicting. One study found that high fat intake (particularly animal fat) was associated with later development of ulcerative colitis. A high sugar intake (from non-fruit sources) was related to both inflammatory bowel disorders. A high intake of fluids and diets rich in fruits, vitamin C, and magnesium were associated with a lower risk for both disorders, and a high intake of potassium and vegetables was associated with a lower risk for Crohn's only.

What Are The Symptoms Of Inflammatory Bowel Disease?

Ulcerative colitis and Crohn's disease share many symptoms, although they also differ in important ways. Both are chronic diseases and symptoms usually appear in young adults. In many patients, symptoms flare up (relapse) after symptom-free periods (remission); other patients have continuous symptoms, although medical treatments can bring about remissions even in many of these patients. Symptoms can be mild or very severe and disabling. They can



develop gradually or have a sudden onset. The severity of symptoms and relapse rates also vary with seasons, with highest risk in the winter and autumn and lowest in summer.

Diarrhea

The most common symptom of both ulcerative colitis and Crohn's disease is diarrhea. Blood may appear in the stools, especially with ulcerative colitis. The blood may be readily visible or visible only using a microscope, in which case it is called occult blood.

Constipation

Constipation may develop during active flare-ups of both Crohn's disease and ulcerative colitis. Constipation from Crohn's disease usually occurs from an obstruction in the small intestine. In ulcerative colitis, constipation may occur when the inflamed rectum triggers a reflex response in the colon that causes it to retain the stool.

Abdominal Pain

Cramps can occur from intestinal contractions caused by inflammation. The severity of the pain usually depends on the severity of diarrhea. Intestinal pain may also be an indication of a serious condition, such as an abscess, or a perforation of the intestinal wall.

Other Symptoms

Fever, fatigue, and loss of appetite are often present, and the patient may lose weight. Tenesmus (a painful urge for a bowel movement even if the rectum is empty) can occur in response to inflammation. Neurologic or psychiatric symptoms may be early signs of Crohn's disease when accompanied by gastrointestinal problems.

How Serious Is Inflammatory Bowel Disease?

Outlook for Ulcerative Colitis.

Surgical removal of the colon is the only cure for ulcerative colitis, but the disease varies greatly in severity. In one 10-year study, 87% of patients went into complete remission after a single



attack and only 8% developed a chronic persistent condition. Mortality rates were generally the same as in the general population, although they were higher in UC patients with severe initial attacks or extensive disease.

Outlook for Crohn's Disease.

The outlook for Crohn's disease varies widely. At the extreme ends, some patients may experience only one episode and others suffer continuously. Although recurrences tend to be the norm, disease-free periods can be years to decades-long in some patients. Crohn's disease cannot be cured even with surgery but treatments are now available that can offer significant help to most patients. Crohn's disease is rarely a direct cause of death and most people can live a normal lifespan with this condition.

Determining Severity of Inflammatory Bowel Disease

Ulcerative Colitis. Ulcerative colitis is considered mild if a patient has the following symptoms: four or less movements a day; only occasional blood in the stool; a normal temperature, pulse rate, and hemoglobin or red blood cell count; and no abnormalities observed on x-rays of the colon.

Ulcerative colitis is considered serious if the following symptoms are present: more than six movements a day; frequent to persistent blood in the stool; fever; a rapid pulse; anemia; abnormal x-rays of the colon; and tenderness in the abdomen when pressed, with possible distention.

Determining Severity of Crohn's Disease.

Crohn's disease can range from being benign (such as when limited Crohn's disease occurs only around the anus in older people) or it can be very severe. As with ulcerative colitis, the fewer movements, the milder the disease. In mild disease, abdominal pain is absent or minimal. The patient has a sense of well-being that is normal or close to normal. There are few, if any,



complications outside the intestinal tract. The physician does not detect any mass when pressing the abdomen. The red blood cell count is normal or close to normal, and the patient is not underweight.

In severe Crohn's disease, the patient has movements frequent enough to require opiates or other potent anti-diarrheal medication. Abdominal pain is severe and usually located in the lower right quadrant of the abdomen. (It should be noted, however, that the location of the pain might not indicate the site of the actual problem, a phenomenon known as referred pain.) The red blood cell count is low. The patient has a poor sense of well-being and experiences complications that may include weight loss, joint pain, inflammation in the eyes, reddened or ulcerated skin, fistulas, abscesses, and fever.

Complications of Inflammatory Bowel Disease

Toxic Megacolon.

Toxic megacolon is a serious complication that can occur if inflammation spreads into the deeper layers of the colon. In such cases, the colon enlarges and becomes paralyzed. In severe cases, it may rupture, a surgical emergency that carries a 30% mortality rate. Symptoms include weakness and abdominal pain and bloating; the patient may be disoriented or groggy. X-rays are needed to confirm the diagnosis, but

barium enemas and colonoscopies should not be performed. Toxic megacolon is more likely to occur with ulcerative colitis, but it can also develop in Crohn's disease. Unfortunately, medications used for pain and diarrhea, such as opiates, and drugs that reduce spasms of the colon may increase the risk of toxic megacolon, although its incidence is decreasing as more effective treatments are developed.



Fistulas.

The deep ulcers of Crohn's disease frequently result in the development of fistulas, channels that can burrow between organs, loops of the intestine, or between the intestines and skin. If fistulas develop between the loops of the small and large intestines, they can interfere with absorption of nutrients. They often form pockets of infection or abscesses, which may become life threatening without treatment. Fistulas are rare in ulcerative colitis.

Intestinal Blockage.

Inflammation from Crohn's disease produces segments of scar tissue known as strictures that can constrict the passages of the intestines, causing bowel obstruction with severe cramps and vomiting. Strictures usually occur in the small intestine but can also occur in the large intestine.

Cancer.

Chronic ulcerative colitis increases the risk for colon cancer. In different studies, this risk has been estimated to be 5% to 10% after 10 years and 15% to 40% after 30 years. People with ulcerative colitis should consider annual screening with colonoscopy beginning as early as age 25, depending on other risk factors, particularly any evidence of precancerous tissue (dysplasia). Individuals should discuss with their physician the risks and benefits of these screening procedures. It should be noted that inflammation can produce changes in tissue that resemble precancerous or cancerous changes, increasing the chance for a false diagnosis of cancer. Inflammatory bowel disease in the rectum and lower (sigmoid) colon does not significantly increase the risk for cancer. [For more information, see , Colon and Rectal Cancers.]

Patients with Crohn's disease of the colon have a similar risk for colon cancers. Other cancers, such as lymphoma or carcinoma of the small intestine or anus, may also be more common in patients with Crohn's disease, but the risk is not high.



Complications Occurring Outside the Gastrointestinal Tract.

Inflammation may occur in tissues beyond the gastrointestinal tract, most commonly in the joints, which can cause stiffness and arthritic-like symptoms. Inflammation in other sites can also cause skin ulcers, mouth sores, problems in the eyes, hepatitis, and complications in the kidneys. Sometimes the large airways in the lungs are impaired. Gallbladder disease and gallstones are common complications of IBD. The pancreas may be more often affected than previously thought in IBD, since the symptoms of these conditions are similar. Internal blood loss from ulcers in the intestine can cause anemia; it is a particular problem in Crohn's disease, because of the impaired ability of the small intestine to absorb vitamins and minerals necessary for blood production. People with IBD are at higher risk for forming blood clots (thromboembolism). Women with inflammatory bowel disease have a higher risk for menstrual abnormalities, with 25% reporting problems in fertility. Half of women with Crohn's disease report pain during sexual intercourse. Almost 40% of them have ovarian cysts and 18% have had a hysterectomy, about half of these patients before age 35, mostly to relieve pain. People with Crohn's disease tend to have an increased incidence of psoriasis, and one study has found a genetic link between the two disorders. About 30% of children with Crohn's disease and significantly fewer children with ulcerative colitis have impaired physical growth, probably mostly due to malnutrition caused by IBD. Such children may reach puberty later but, once it occurs, hormonal cycles tend to be normal.

Emotional and Neurologic Factors

Neurologic and psychiatric complications occur with Crohn's disease, and some experts believe that an autoimmune response affects the central nervous system. In any case, the emotional consequences of IBD cannot be overestimated, particularly in children. Eating becomes associated with fear of abdominal pain before the end of the meal. Frequent attacks of diarrhea can cause such a strong sense of humiliation that social isolation and low self-esteem may result. Adolescents with IBD may have added problems that increase emotional distress, including weight gain from steroid treatments and delayed puberty. Sexual function may be impaired, not



only because of the emotional impact, but also by treatment side effects and complications of the diseases, such as fistulas. Strong support from family, friends, and health professionals is very important.

Who Gets Inflammatory Bowel Disease?

An estimated one to two million Americans suffer from inflammatory bowel disease. (This wide statistical variation is due to the difficulty in diagnosing these disorders and because people in remission may not be identified.) It was thought that Crohn's disease was far less common than ulcerative colitis, but currently they are estimated to have about the same incidence. The number of people with Crohn's disease also appears to be increasing. Women may be slightly more at risk than men for Crohn's disease while the risk in both genders is equal for ulcerative colitis. The diseases are diagnosed most often between the ages of 15 and 40, but another lesser peak onset occurs between 50 and 80. About 2% of IBD cases appear in children below age 10; 30% occur in young people between the ages of 10 and 19. IBD often runs in families, and men and women are equally affected. It occurs four times more in people of Northern European descent than in African Americans. Jewish people of European descent have an even higher risk: five times than of the general population. Scandinavia has the highest rate of Crohn's disease in the world. IBD seems to be more common among city than country dwellers and occurs more frequently in developed than in less developed nations, indicating that both genetic factors and environmental conditions, such as diet, may be involved in its development.

How Is Inflammatory Bowel Disease Diagnosed?

Preliminary Examination and Tests

The physician will take a history and give a thorough physical examination. Blood tests that show an increased number of white blood cells may indicate the presence of inflammation. A stool sample is taken and examined for blood or infections. The disease is particularly difficult to



diagnose in children, in whom IBD may be mistaken for an infection or even depression if other characteristic symptoms, such as bloody diarrhea and weight loss, are not present. Slow growth may be a key feature in making a diagnosis, particularly of Crohn's disease, in children. New blood tests that measure certain antibodies may make it easier to differentiate Crohn's disease from ulcerative colitis in this young population.

Procedures Used for Diagnosis

- Endoscopic Procedures. Flexible sigmoidoscopy and colonoscopy are procedures that involve snaking a fiberoptic tube called an endoscope through the rectum to view the lining of the colon. The physician can also insert instruments through it to remove tissue sample. Sigmoidoscopy, which is used to examine the rectum and left (sigmoid) colon, lasts about 10 minutes and is done without sedation. It may be mildly uncomfortable, but it is not painful. Colonoscopy allows a view of the entire colon and requires a sedative, but it is still performed on an outpatient basis.
- The procedures may help the physician to distinguish between ulcerative colitis and Crohn's disease, as well as other diseases. Ulcerative colitis almost always involves the lower left colon and rectum and is diagnosed using sigmoidoscopy. The physician usually observes an evenly distributed inflamed surface lining the intestine, and the bowel wall bleeds easily when touched with a swab. The pattern observed in Crohn's disease is usually one of scattered patches of ulcers that are deeper, thicker, and larger than those found in ulcerative colitis.
- Under a microscope, tissue samples obtained from a patient with Crohn's disease may reveal granulomas, small collections of inflammatory cells; granulomas may also be present in other conditions, however. Tissue samples should also be examined for the presence of cancerous cells.
- Upper and Lower Gastrointestinal Barium X-Ray. An upper gastrointestinal barium x-ray may be used if Crohn's disease is suspected in the small intestine. Swallowed barium passes into the small intestine and shows up on an x-ray image, which may reveal inflammation, ulcers, and other abnormalities. A barium enema is usually required to view the whole colon. This procedure



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should not be done during active periods of disease, because it increases the risk for toxic megacolon.

- Computed Tomography (CT) Scans. Computed tomography (CT) scans are proving to be useful in evaluating active IBD.

Diseases Resembling Inflammatory Bowel Disease

Irritable Bowel Syndrome.

Irritable bowel syndrome (IBS), also known as spastic colon, functional bowel disease, and spastic colitis causes many of the same symptoms as inflammatory bowel disease. Bloating, diarrhea, constipation, and abdominal cramps are all symptoms of IBS. Irritable bowel syndrome is not caused by inflammation, however, and no fever or bleeding occurs. Behavioral therapy may be helpful in treating IBS. (No psychologic therapy improves inflammatory bowel disease.)

Infections.

If endoscopy reveals inflammation, a physician must always rule out possible infections before a diagnosis of inflammatory bowel disease can be confirmed

Cancer.

Colon or rectal cancers must always be ruled out when symptoms of IBD occur.

What Are The Dietary And Lifestyle Recommendations For Inflammatory Bowel Disease?

Foods

Children with inflammatory bowel disease may suffer from malnutrition, probably the major factor in growth retardation. Some experts recommend that children with IBD increase their calorie and protein intake by 150% of the daily recommended allowance for their specific ages



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and heights. Studies indicate that nutritional support in children is as important as medications for achieving remission.

Although no evidence exists that any specific foods reduce inflammation, certain foods have been associated with a lower or higher risk for IBD or its symptoms. The foods linked to a lower risk were fruits (for both IBD disorders) and vegetables and green tea (for Crohn's disease). One study found that large doses of fish oil, which is rich in omega-3 fatty acids, improved Crohn's disease. Patients, however, disliked the fishy breath and side effects, including flatulence, heartburn, belching, and diarrhea. Recently, a coated preparation of fish oil was tested and was found to prevent relapse for at least a year in 60% of patients. Omega-3 fatty acids have not proved to be useful for ulcerative colitis. Foods most often blamed for aggravating existing symptoms are milk and milk products, spicy foods, fats, and sugars. When symptoms erupt, physicians recommend a bland, low-fiber diet. Surgery for IBD may increase the risk for absorption of oxalate, a substance that reacts with calcium to form kidney stones. Surgical patients should avoid foods high in oxalates, including spinach, rhubarb, beets, coffee, tea, diet sodas, and chocolate. Patients should drink plenty of fluids. [See also Kidney Stones.]

Vitamin and Mineral Supplements

Crohn's disease and surgical procedures that remove parts of the small intestine can inhibit absorption of vitamins, fats, calcium, and magnesium. Iron supplements and monthly injections of vitamin B-12 may be necessary in such cases. Folic acid supplements may be important, particularly for patients who must restrict fresh fruits and vegetables and for patients taking sulfasalazine. In general, vitamin supplements may be recommended for everyone with IBD, particularly for children to avoid growth retardation; taking large doses of certain vitamins, however, may be harmful.

Elemental Diets

Elemental diets comprise liquids that are fully nutritional. They are sometimes helpful in improving symptoms, reducing relapses, and improving nutrition in Crohn's disease patients.



Included in the nutritional solution is a large amount of glutamine, an amino acid that provides energy for the lining of the small intestine. The solution has an unpleasant metallic taste, and some health professionals recommend adding flavored toppings or instant coffee and drinking the liquid cold to improve its taste. Over-the-counter and less expensive liquid diets, such as Ensure, Sustacal, and others, that meet full nutritional needs and are absorbed in the upper intestine may also be beneficial, but no studies have determined this.

Parenteral Nutrition

Patients with very severe Crohn's disease who cannot tolerate any nutrition by mouth may need total parenteral nutrition (TPN), or hyperalimentation, which is the intravenous administration of nutrients through an indwelling catheter (tube). The procedure carries a risk for infection. Patients with ulcerative colitis may also need TPN if they are malnourished, require surgery, or have very severe symptoms.

Stress Reduction

Although stress is not a cause of inflammatory bowel disease, there are anecdotal reports of an association between stress and symptom flare-ups. Although no evidence exists to confirm that stress reduction techniques, such as relaxation methods, meditation, or cognitive therapy, manage the disease, they might be helpful.

Exercise

The effects of exercise in Crohn's disease are uncertain. Some research indicates that moderate exercise may trigger excess production of chemicals that could cause flare up. One small study, however, reported significant improvement in patients who had been sedentary and who then embarked on a 12-week exercise program. They walked a little over two miles three times a week; during that period there were no flare-ups and they felt physically and emotionally better than before.



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What Are The Drug Treatments For Inflammatory Bowel Disease?

Drugs cannot cure inflammatory bowel disease, but they are effective in reducing the inflammation and accompanying symptoms in up to 80% of patients. Many such drugs are available, including corticosteroids, aspirin-like medications, and drugs that suppress the immune system. The primary goal of drug therapy is to reduce inflammation in the intestine. The success of therapy is determined by its ability to induce and maintain remissions without incurring significant side effects. The patient's condition is generally considered in remission when the intestinal lining has healed and symptoms, such as diarrhea, abdominal cramps and tenesmus, are normal or close to normal. It is more difficult to define remission in Crohn's disease than in ulcerative colitis, because diagnostic test results do not always correlate with a patient's symptoms or complications outside the intestine.

Mesalamine (5-Aminosalicylic Acid) and Its Preparations

Mesalamine is the common name of the compound 5-aminosalicylic acid or 5-ASA, which inhibits substances in the immune system, particularly leukotrienes, that cause inflammation. Mesalamine seems to benefit women more than men. The 5-ASA compound itself is very effective and has few side effects, but it is absorbed so quickly in the upper gastrointestinal tract that it usually fails to reach the colon. Other substances are added to 5-ASA or it is formulated so that it can reach the lower intestine before it is absorbed. The 5-ASA preparations and formulations are generally useful for mild to moderate ulcerative colitis and Crohn's disease and for preventing relapse of ulcerative colitis. They are less useful in maintaining remission of Crohn's disease. The degree of effectiveness for each condition varies depending on the particular drug preparation. Mesalamine has a chemical structure similar to aspirin. People allergic to aspirin, therefore, should not take any of the 5-ASA drugs or preparations, including sulfasalazine, the standard combined preparation. All 5-ASA preparations, including sulfasalazine, appear to be safe for children and for women who are pregnant or nursing. Side



effects vary depending on whether the drug is used alone or in combination with other components. A variant of mesalamine, 4-aminosalicylic acid, is being studied for IBD.

Sulfasalazine.

Sulfasalazine (Azulfidine) has been the standard mesalamine, or 5-ASA, preparation for years. Sulfasalazine is known as a prodrug because it breaks down into mesalamine and sulfapyridine, a sulfa antibiotic that prevents mesalamine from being absorbed until it reaches the colon. There, intestinal bacteria break sulfasalazine into its two components: Mesalamine, the active component, blocks the inflammatory process; the other component, sulfapyridine plays no role in treating the disease.

In ulcerative colitis, sulfasalazine is useful for treating mild to moderate attacks and for maintaining remission. Long-term therapy may even help protect against colon and rectal cancers in patients with ulcerative colitis. It is helpful for some Crohn's disease patients whose active condition occurs in the colon, but it is not effective in the small intestine and does not prevent recurrence there.

The sulfa component of sulfasalazine is responsible for most of its adverse side effects and allergic reactions, which are experienced by up to 30% of patients taking this drug. Some common side effects include heartburn, headache, loss of appetite, abdominal discomfort, dizziness, anemia, fever, and rashes. The drug may temporarily lower sperm count in men and can turn urine a bright orange-yellow color. Rare but serious side effects include a lupus-like disorder, pancreatitis, liver damage, and blood disorders. Some of these blood disorders can become life threatening (although very rarely), so blood counts should be performed regularly, particularly during the first few weeks of treatment. Sulfasalazine can also cause folic acid deficiency, and patients should take supplements of this important B vitamin. As with most major drugs for IBD, withdrawal of sulfasalazine when the disease is still active can trigger a severe relapse.



Rectally-Administered Mesalamine. A rectal form of mesalamine (Rowasa) can be administered using enemas or suppositories. Mesalamine enemas have been reported to help 75% to 90% of patients with ulcerative colitis of the lower colon. Rowasa relieves mild to moderately active UC and prevents relapse. As of the date of this report, this agent was withdrawn from the market because of a failure in its ability to dissolve. A new rectal form gel is proving to be even more effective than the foam enemas.

Other Mesalamine Prodrugs.

Olsalazine (Dipentum) and balsalazide (Colazide) are similar to sulfasalazine, but they are broken down by intestinal bacteria into two components, one of which is mesalamine. Unlike sulfasalazine, however, the other component is a harmless molecule that does not produce sulfapyridine's adverse side effects. Olsalazine causes diarrhea in up to 35% of those taking the drug, which may be minimized by starting out with lower doses and taking the medication with meals.

Delayed Release Mesalamine.

Formulations have been developed that allow mesalamine alone to reach the lower intestine without the need for the sulfa component. A number of oral forms of mesalamine use coatings or time-released formulations to prevent absorption in the upper intestine. Different brands affect different regions in the intestine. Pentasa is released throughout the intestine and so is useful for disease in the small intestine and colon; Asacol is effective in the terminal (last) section of the ileum and the colon. Studies indicate that treatment with delayed-release Asacol has resulted in symptomatic improvement, including remission, in nearly three-quarters of patients with mild to moderate ulcerative colitis. When used alone, it does not appear to be as effective as olsalazine for maintaining remission. For such cases, taking it in higher doses or using it in combination with the rectal form of mesalamine may improve its effectiveness. Some experts believe that maintenance treatment may not be necessary in patients who have been in remission for two years or more. Limited data has also suggested that it produces remission in up to 45% of



patients with active Crohn's disease and prevents relapse in as many as two-thirds of patients for up to a year. A 1999 study reported that Asacol was as effective as corticosteroids and may become the drug of choice for mild to moderate Crohn's disease.

Mesalamine used alone does not adversely affect sperm count fertility, as sulfasalazine does. About 5% or less of patients taking oral mesalamine experience diarrhea. Oral mesalamine, particularly Asacol, may slightly increase the risk for kidney damage. (Olsalazine has a lesser effect on the kidneys.) Other less severe side effects of all oral forms of mesalamine are skin disorders, nausea, cramps, itchiness, anxiety attacks, and inflammation of other organs, although one study reported that mesalamine caused no more side effects than placebos (inactive substances used for comparisons in drug studies).

Corticosteroids

Corticosteroids (also called steroids) are powerful anti-inflammatory drugs. Prednisone, prednisolone, hydrocortisone, and methylprednisolone are the most common steroids. They are used only for active ulcerative colitis and Crohn's disease. Because they have serious long-term effects, they are not useful for maintenance therapy. Corticosteroids are sometimes combined with other drugs to produce more rapid symptom relief and to allow quicker withdrawal, although such combinations do not improve remission time. Some physicians favor corticotropin (ACTH), which stimulates natural production of steroids, but it is effective only in certain patients and is not in common use. Newer steroids, such as budesonide, beclomethasone, and tixocortol, affect only local areas in the intestine and do not circulate throughout the body. Such drugs may avoid the widespread side effects that are a serious problem with long-term treatment using the older steroids. A slow-release oral form of budesonide, for example, is proving to be more effective and safer for mild to moderate Crohn's disease in the ileum and cecum regions than either older steroids or mesalamine. In one study, after eight weeks, 69% of those taking budesonide once a day experienced remission compared to only 45% of those taking mesalamine twice a day. Neither budesonide nor mesalamine were very effective, however, for patients with



severe conditions. Budesonide appears to have less severe side effects than either mesalamine or older steroids.

Steroids can be taken orally, intravenously, by injection, or rectally as a suppository, enema, or foam. In general, oral preparations are used for moderate to severe ulcerative colitis and Crohn's disease. Enemas, suppositories, and, in limited cases, foam preparations may be used for mild to moderate ulcerative colitis located in the left section of the colon, the rectum, and anus. If the patient requires hospitalization, intravenous steroid therapy, with or without rectal steroids, are administered initially. (If these drugs are not effective after a week of intravenous therapy, they are not likely to work.) Once bowel movements are normal and the patient can eat, oral doses replace intravenous and rectal forms, and then they are tapered gradually. Patients who are malnourished are less likely to respond to steroids and those who had an initial inadequate response to steroids are also less likely to do well with repeat therapy. Some patients who have had Crohn's disease for a long-time may have partial or complete resistance to corticosteroids.

Side Effects. Standard steroids can have distressing and sometimes serious long-term side effects, including susceptibility to infection, weight gain (particularly increased fatty tissue on the face and upper trunk and back), acne, excess hair growth, hypertension, accelerated osteoporosis, cataracts, glaucoma, diabetes, wasting of the muscles, and menstrual irregularities. Personality changes can occur, including irritability, insomnia, psychosis, and depression; such emotional changes are sometimes severe enough to produce suicidal thoughts. Growth may be retarded in children. Treatments are available for steroid-induced diabetes, swelling, and hypertension. Vaccines are available to help prevent influenza and pneumonia. Any infection should be treated promptly. Supplemental calcium and vitamin D are important to help to preserve bone mass against osteoporosis. The newer oral steroids, such as budesonide, have far fewer and less severe side effects.



Once the intestinal inflammation has subsided, steroids must be withdrawn very gradually in order to give the body time to recover its own ability to produce natural steroids. Withdrawal symptoms, including fever, malaise, and joint pain may also occur if the dosage is lowered too rapidly. If this happens, the dosage is increased slightly and maintained until symptoms are gone. More gradual withdrawal is then resumed.

Immunosuppressive Drugs

For very active inflammatory bowel disease that does not respond to standard treatments, immunosuppressant drugs are now being used for long-term therapy. Such drugs suppress actions of the immune system and therefore its inflammatory response, which causes ulcerative colitis and Crohn's disease. The two most commonly used immunosuppressants for IBD are azathioprine (Imuran) and mercaptopurine (Purinethol). An immunosuppressant may be combined with a corticosteroid during active attacks; lower doses of the steroid are then needed, resulting in fewer side effects. Corticosteroids may also be withdrawn more quickly.

Immunosuppressants, then, are sometimes referred to as steroid-sparing drugs. They cannot replace steroids for an initial attack, because it takes azathioprine or mercaptopurine three to six months to become effective (although they work more rapidly for subsequent attacks).

Administering azathioprine intravenously (called a loading dose) may speed up the initial response. Immunosuppressants can, in any case, prevent relapse when used alone, and in some studies have proved to be effective for maintaining remissions in ulcerative colitis that have lasted at least two years. They also appear to help maintain remission in Crohn's disease, and appear to heal fistulas and intestinal ulcers caused by this disease.

Other immunosuppressants being investigated for IBD and showing promise include cyclosporine (Sandimmune), mycophenolate mofetil, or MMF (Cellcept), and methotrexate (Folex). Methotrexate or MMF may be effective alternatives for patients with Crohn's disease who have failed other treatments and cannot tolerate the standard immunosuppressant. Cyclosporine may be useful for Crohn's disease accompanied by fistulas, but it does not seem to be beneficial for long-term maintenance.



Initiating treatment with intravenous cyclosporin followed by oral administration of the drug may help patients with acute severe ulcerative colitis. Studies indicate that up to half of patients can avoid surgery for over four years. Serious complications, some life threatening, can occur, however, in patients with ulcerative colitis who have an unfavorable response to both cyclosporine and corticosteroids. Experts recommend that cyclosporine be used only by ulcerative colitis patients who have previously responded favorably to steroids and who can be closely monitored by knowledgeable specialists. Methotrexate does not appear to be effective for ulcerative colitis.

Side Effects.

Although experts have been concerned about dangerous side effects based on experience with immunosuppressants used in transplant operations, the lower doses of the drugs required for IBD and other inflammatory disorders may make them safer for long-term treatments than steroids. One study of Crohn's disease patients, for example, reported that mercaptopurine was safe for long-term use. The most frequent side effects of immunosuppressants include stomach and intestinal distress, rash, numbness or tingling in the hands and feet, mouth sores, and hair loss (or excessive hair growth with cyclosporine). It should be noted, however, that the actions of immunosuppressant damage certain rapidly growing immune system cells, including those that produce antibodies, causing an increased risk for infection. Oversuppression of the immune system can result in low blood cell counts as well and other serious side effects. These include anemia, herpes zoster (shingles), hepatitis, bladder toxicity, and menstrual irregularity with possible sterility. (Administering pulsed doses at the time of menstruation may avert infertility in women.) Some increase in blood cancer has been associated with the use of azathioprine for other disorders, but there appears to be no increased risk when azathioprine is taken as sole therapy. Between 3% and 15% of patients taking immunosuppressants develop pancreatitis; in such cases immunosuppressants should never be used again. Symptoms of pancreatitis usually occur within the first few weeks and include nausea, vomiting, and upper abdominal pain that may radiate to the back.



Antibiotics

The antibiotics ciprofloxacin (Cipro) and metronidazole (Flagyl) used in combination or alone are useful for people with Crohn's disease whose condition is accompanied by bacterial overgrowth, abdominal abscesses, and infections around the anus and genital areas. These antibiotics are used for infections caused by anaerobic bacteria, which are organisms that can exist without oxygen and often cause abscesses and abdominal and gynecologic infections. Either antibiotic alone or in combination is equally effective with remission rates of about 70% that last a year. Ciprofloxacin is the antibiotic of choice. In one study it was as effective as mesalazine for patients with mild to moderate Crohn's disease. In another study, metronidazole helped prevent IBD recurrence after surgery, but side effects were severe. Other antibiotics used for Crohn's disease include trimethoprim/sulfamethoxazole (Bactrim, Cotrim, Septra) and tetracycline. Withdrawal brings on relapse, so long-term therapy is required, carrying a risk for side effects, including numbness and tingling in the hands and feet. Antibiotic therapy has no role in the treatment of ulcerative colitis other than with existing infections or helping prevent complications after surgery.

Biologic Response Modifiers

Biologic response modifiers are drugs that interfere with the inflammatory response. Of special interest are drugs that are genetically engineered to target the immune factors known as cytokines, particularly tumor necrosis factor (TNF) and certain interleukins.

Infliximab.

Infliximab (Remicade) is the first genetically-engineered drug to be approved for Crohn's disease. The drug is made from a specially developed antibody (termed a monoclonal antibody) called cA2, which acts against tumor necrosis factor (TNF), a major player in the inflammatory process that causes IBD. Recent trials of the drug indicate that it may help patients with moderate to severe Crohn's disease that has not responded to other treatments. Infliximab reduces and even eliminates the signs of inflammation and heals ulcers and even fistulas in many patients. The most common side effects to date are headache, abscess, upper respiratory tract infection, and



fatigue. It may also be helpful for patients with ulcerative colitis. Of concern were reports of four cases of lymphomas in people taking the cA2 antibody, but the cancers may have been due to their underlying diseases, not the drug.

Other Biologic Response Modifiers.

Other anti-TNF drugs, including thalidomide and CDP571, are under investigation for IBD. Interleukins and interferon are other immune factors that play a role in the inflammatory response and are being studied. Early studies of an agent called recombinant human interleukin 11 (rhIL-11) reported response rates between 33% and 42% in patient with Crohn's disease. Molecular treatment known as antisense therapy is being used to block the genetic expression of ICAM, a protein that plays an important role in the production of immune factors that cause the inflammatory response.

Nicotine

Some patients with ulcerative colitis have reported that their disorder began after they quit smoking, and many studies have reinforced the association between smoking and protection against ulcerative colitis. Studies are showing that the nicotine patch helps to induce remission and reduce symptoms in almost 40% of patients who use it for four weeks. Another study found, however, that patches are not useful for maintaining remission. Side effects, particularly in nonsmokers, include nausea, lightheadedness, and headache. Investigators are studying methods of applying nicotine directly into the colon. (No one should smoke for relief of ulcerative colitis symptoms; the risks from cigarettes far outweigh the potential benefits of their nicotine.)

It should be noted that smoking has the opposite effect for Crohn's disease; in one study, when smokers with the disease quit, the incidence of relapse was reduced by 40% over a year.

Experimental Therapies

A number of agents, including alternative remedies, are being studied with some degree of success. Disappointing results for UC patients were found in trials of fatty acids (butyrate), fish oil, and leukotriene inhibitors.



Heparin.

Intravenous heparin is an anti-bloodclotting agent that also has anti-inflammatory properties and may have benefits for ulcerative colitis. In one study seven out of 13 patients achieved complete remission after four weeks. (It had few benefits for Crohn's patients.) Because of the risk of bleeding, however, it must be administered only in patients who are hospitalized. Other studies are underway testing low-weight heparins (eg., enoxaparin), other heparin derivatives (GM1892), and inhaled versions of heparin.

Apheresis.

Apheresis is a procedure that cycles a patient's blood and removes specific components before reinfusing the blood back into the patient. Several forms of apheresis are being tested in inflammatory bowel disease, including removal of certain white blood cells (leukocytapheresis or granulocytapheresis) that may contribute to the inflammatory response in either Crohn's disease or ulcerative colitis. A typical treatment is one session per week for five weeks decreasing to one session per month for five months. In one study, half of Crohn's patients attained remission after the initial five-week period. Those with very severe cases tended not to respond. Side effects during the procedure are common but temporary; they include nausea, vomiting, fever, chills, nasal obstruction, palpitations, and respiratory distress.

Anti-Tuberculosis Treatment.

In two small trials, drugs that are used to treat tuberculosis (clofazimine or clofazimine, rifampin, ethambutol, and dapsone) have produced remission in patients with Crohn's disease when used with corticosteroids.

Topical Anesthetics.

Small studies indicate that enemas using topical anesthetics lidocaine and ropivacaine may be helpful for patients with mild to moderate ulcerative colitis.



RSim General & Colorectal Surgery
1 Farrer Park Station Road,
#13-10, Farrer Park Medical Centre,
Singapore 217562.
Tel: (65) 6636 3493 Fax: (65) 6636 3494

Bismuth.

Enemas using bismuth compounds are also showing promise in small studies for mild to moderate ulcerative colitis.

Hyperbaric Oxygen.

Animal studies indicated that hyperbaric oxygen (exposure to pure oxygen at high pressure) may help reduce inflammatory injury in the colon.

Helminths.

In one interesting very small study, patients with Crohn's disease swallowed the eggs of a parasitic worm known as a helminth. The disease went into remission for several weeks in five of the six patients. The parasite does not invade tissue or spread other diseases.

Treatments for Symptoms and Complications

Diarrhea and Constipation.

Mild to moderate diarrhea may be reduced by taking one teaspoon of psyllium hydrophilic colloid (Metamucil) twice a day in a glass of water. Opiates or drugs used to relax muscle spasms may help relieve mild to moderate diarrhea and abdominal cramps, but they should be used for very short periods and not for severe cases. In very ill patients, large doses of certain antidiarrheal drugs can trigger the onset of toxic megacolon. Bulk-type laxatives can help constipation. Cholestyramine (Questran) has been found to be useful for reducing diarrhea in Crohn's patients who have had ileal resections.

Treatment of Anemia.

Iron supplements may be required for anemia. Intravenous iron with or without erythropoietin (a hormone that acts in the bone marrow to increase the production of red blood cells) is effective for severe anemia in IBD that does not respond to iron alone. Crohn's disease patients benefit from the combination; ulcerative colitis patients usually improve on IV iron alone.



Antidepressants.

Antidepressants may help relieve emotional problems. It should be stressed, however, that inflammatory bowel disease is not a psychologic disorder, and such drugs will not affect the basic illness.

Pain-Relievers.

Acetaminophen, sold as Tylenol and other common brands, is the drug of choice for mild pain. Acetaminophen is not one of the nonsteroidal anti-inflammatory drugs (NSAIDs), which include, among dozens of others, aspirin, ibuprofen (Advil, Motrin, Rufen), and naproxen (Anaprox, Naprosyn, Aleve). NSAIDs are often used against other inflammatory disorders, but they have been implicated in triggering inflammatory bowel disease; one study found that they doubled the risk for emergency treatment of gastrointestinal symptoms in patients with colitis. NSAIDs, therefore, should be avoided for IBD.

What Are Surgical Procedures For Inflammatory Bowel Disease?

Surgery for inflammatory bowel disease is usually performed to remove diseased sections of the intestinal tract. It can cure ulcerative colitis, but it is useful only for reducing symptoms in Crohn's disease. Although usually used as a last resort for both conditions, in one study, patients with either condition reported significant improvement in quality of life after surgery. Some experts believe surgery might be considered at an earlier point in the course of the diseases for some patients than is currently standard.

Surgery for Ulcerative Colitis

In 20% of ulcerative colitis patients, drug therapy is not effective and surgery is necessary. Surgery may also be required because of hemorrhage, chronic illness, perforation of the colon, or to prevent colon cancer.



For a complete cure, a procedure called proctocolectomy is performed in which the entire colon and rectum are removed. Since the lower part of the rectum is removed, including the sphincter muscles that control bowel movements, an ileostomy is required. With this procedure, the surgeon makes a small opening in the lower right corner of the abdomen through which the cut ends of the small intestine are brought out. A bag is kept over the opening, which accumulates waste matter and requires emptying several times a day.

Other procedures have been developed so that some patients may not need to use an ileostomy bag. Ileoanal anastomosis takes advantage of the fact that ulcerative colitis does not extend to deeper layers of the colon. The colon is removed but only the superficial diseased inner layer of the rectum is stripped, leaving the sphincter muscles intact. The anus is then attached to the ileum (the final portion of the small intestine leading to the colon), and a pouch is constructed out of the small bowel above the anus to collect waste material. A temporary ileostomy is usually required, which is closed in a second operation three months later. The patient then can pass bowel movements normally through the anus, although they may be watery and more frequent. In about 5% to 10% of cases, complications occur that are severe enough to require conversion to an ileostomy. Some experts stress that the procedure be performed only on patients in whom it is absolutely clear that ulcerative colitis, and not Crohn's disease, is causing the IBD. Discovering underlying Crohn's disease or other problems during the procedure can increase the risk for complications. (The use of infliximab may prove to reduce complications in patients who are found to have Crohn's disease during this procedure.)

Another operation, continent ileostomy, may be used for patients whose rectal muscles are not strong enough for ileoanal anastomosis or who have already had an ileostomy and want a more convenient arrangement. The surgeon forms a pouch for collecting waste from the last few inches of the ileum. A valve is created in the abdominal wall through which a tube is inserted to drain waste material from the pouch. At first the pouch is drained eight to ten times a day, but eventually it needs to be emptied only about half as many times. Usually the procedure is done in two stages, with an ileostomy bag worn for several months before the pouch is made. Recent



advances, however, have allowed surgeons to complete the procedure in one operation unless the patient is very ill. In continent ileostomies, the valve may leak or the catheter may become blocked; in at least 10% of these procedures, the valve needs to be repaired later on.

Complications are common, although in one study, 97% of patients still had functioning pouches after an average of almost six years. The most common complication of both procedures is inflammation of the pouch (pouchitis), which can usually be treated easily. (In one study about 4.5% of patients who had pouchitis developed a chronic form, which causes increased defecation and requires long-term medication.) Severe scarring at the incision occurs in more than half of patients; a recent study found that placing an experimental absorbable membrane made from hyaluronate (a natural lubricating substance) along the incision reduced the rate of scarring to 15%. When the rectum is removed, there is a small danger of injury to the nerves that control erection and bladder function.

Surgery for Crohn's Disease

About 70% of Crohn's patients eventually need surgery to remove damaged areas of the colon. Crohn's disease cannot be cured with surgery because new disease can appear in other areas of the intestine. Surgery, however, may be helpful for relieving symptoms and to correct blockage, perforation, fistulas, or bleeding.

Procedures.

In most cases of Crohn's disease, only a part of the colon needs to be removed, a procedure called resection. Infrequently, the entire colon is removed (total colectomy) and an ileostomy is created. In a study of its effects, surgery improved the quality of life in most patients except for those who continued to have active disease. Minimally invasive surgical techniques known as laparoscopies are now available for many Crohn's procedures that are proving to be effective and allow a speedier recovery than the standard so-called open surgeries. Disease in the upper parts of the small intestine tends to require more extensive surgery than in the lower small intestine. If large segments of the small intestine are removed, short-bowel syndrome may develop, in which



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1 Farrer Park Station Road,
#13-10, Farrer Park Medical Centre,
Singapore 217562.
Tel: (65) 6636 3493 Fax: (65) 6636 3494

there is a problem absorbing nutrients. Some patients requiring small bowel surgery may be candidates for a procedure called strictureplasty, which involves cutting and stitching only the areas obstructing the intestine, so that it widens the intestine without removing sections of it. The procedure is by no means fool-proof and nearly half of patients require reoperation, but stricture in the jejunum and ileum of the small intestine is safe and generally effective over the long term. It may not be useful for Crohn's disease in duodenum (the first section of the small intestine).

Disease Recurrence after Surgery.

Early recurrence of Crohn's disease and the need for repeat surgeries is very common after resection. (If the entire colon is removed there is still a high chance of recurrence in the rectum and a lower risk for recurrence in the small intestine. Younger people are at higher risk.) The antibiotic, metronidazole, may be helpful in preventing recurrence of Crohn's disease after surgery. A study of low-dose budesonide, a steroid, reported little protection against recurrence after surgery. In one study, people at highest risk for early recurrence and a need for a repeat procedure were those who had surgery for perforations or who had Crohn's disease for more than about nine years before the first operation. People with a perforated bowel required a second procedure, on average, three years after the first one. Those with a long disease duration before the first procedure needed a repeat operation on average five years afterward and were also at higher risk for a third procedure. People without perforated bowels or those with a shorter disease duration required a second procedure about seven years after the first one.

Where Else Can Help Be Found For Inflammatory Bowel Disease?

Crohn's & Colitis Foundation of America, Inc., 386 Park Avenue South, 17th Floor, New York, NY 10016-8804. Call (800- 932-2423 or (212-685-3440) or on the Internet (<http://www.ccfa.org/>)

Information books and brochures about inflammatory bowel disease, including the magazine Foundation Focus . Refers people to local support groups in the US and other countries.



RSim General & Colorectal Surgery
1 Farrer Park Station Road,
#13-10, Farrer Park Medical Centre,
Singapore 217562.
Tel: (65) 6636 3493 Fax: (65)6636 3494

United Ostomy Association, 19772 MacArthur Blvd, Suite 200, Irvine, CA 92612-2405. Call (800) 826-0826 or on the Internet (<http://www.uoa.org/>)

This organization refers people to local support group chapters. They offer many free publications about ostomy care and management and have also a subscription to bimonthly magazine Ostomy Quarterly (\$25 in US, higher elsewhere).

National Digestive Diseases Information Clearinghouse, 2 Information Way, Bethesda, MD 20892-3570. Call (301-654-3810) or on the Internet (<http://www.aerie.com/nihdb/nddic/ddtest.html>)
Offers patient information and educational materials.

American Gastroenterological Association, American Digestive Health Foundation, 7910 Woodmont Avenue, 7th Floor, Bethesda, MD 20814. Call (301 654-2055) or on the Internet (<http://www.gastro.org>)

American Society for Gastrointestinal Endoscopy, 13 Elm Street, Manchester, MA 01944. On the Internet (<http://www.asge.org/>)

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