Diagnosis and Management of Crohn's Disease

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Crohn's disease is a chronic inflammatory condition affecting the gastrointestinal tract at any point from the mouth to the rectum. Patients may experience diarrhea, abdominal pain, fever, weight loss, abdominal masses, and anemia. Extraintestinal manifestations of Crohn's disease include osteoporosis, inflammatory arthropathies, scleritis, nephrolithiasis, cholelithiasis, and erythema nodosum. Acute phase reactants, such as C-reactive protein level and erythrocyte sedimentation rate, are often increased with inflammation and may correlate with disease activity. Levels of vitamin B_{12}, folate, albumin, prealbumin, and vitamin D can help assess nutritional status. Colonoscopy with ileoscopy, capsule endoscopy, computed tomography enterography, and small bowel follow-through are often used to diagnose Crohn's disease. Ultrasonography, computed axial tomography, scintigraphy, and magnetic resonance imaging can assess for extraintestinal manifestations or complications (e.g., abscess, perforation). Mesalamine products are often used for the medical management of mild to moderate colonic Crohn's disease. Antibiotics (e.g., metronidazole, fluoroquinolones) are often used for treatment. Patients with moderate to severe Crohn's disease are treated with corticosteroids, azathioprine, 6-mercaptopurine, or anti–tumor necrosis factor agents (e.g., infliximab, adalimumab). Severe disease may require emergent hospitalization and a multidisciplinary approach with a family physician, gastroenterologist, and surgeon. (*Am Fam Physician.* 2011;84(12):1365-1375. Copyright © 2011 American Academy of Family Physicians.)

▶ **Patient information:** A handout on Crohn's disease, written by the authors of this article, is provided on page 1379.

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract characterized by inflammation at any point from the mouth to the rectum *(Table 1)*. The prevalence in the United States is 201 per 100,000 adults.[1] Patients with Crohn's disease often present in adolescence, and the median age at diagnosis is 20 to 30 years.[2] Crohn's disease is more prevalent in women than men, in developed countries, and in the northern hemisphere.[1,2] The annual U.S. economic burden of Crohn's disease is estimated to be $10.9 to 15.5 billion in 2006 U.S. dollars.[3]

Although the etiology of Crohn's disease is unknown, it is associated with a mutation on the *NOD2* gene.[4] Smoking and use of oral contraceptives and nonselective nonsteroidal anti-inflammatory drugs are associated with exacerbation of symptoms.[5-7]

Table 1. Location of Crohn's Disease and Associated Symptoms

Location	*Symptoms*	*Comments*	*Frequency (%)*	*Common diagnostic testing*
Ileum and colon	Diarrhea, cramping, abdominal pain, weight loss	Most common form	35	Colonoscopy with ileoscopy, CT enterography, biopsy
Colon only	Diarrhea, rectal bleeding, perirectal abscess, fistula, perirectal ulcer	Skin lesions and arthralgias more common	32	Colonoscopy with ileoscopy, CT enterography, biopsy
Small bowel only	Diarrhea, cramping, abdominal pain, weight loss	Complications may include fistula or abscess formation	28	Colonoscopy with ileoscopy, CT enterography, capsule endoscopy, small bowel follow-through, enteroscopy, biopsy, magnetic resonance enterography
Gastroduodenal region	Anorexia, weight loss, nausea, vomiting	Rare form May cause bowel obstruction	5	Esophagogastroduodenoscopy, small bowel follow-through, enteroscopy

CT = computed tomography.

Clinical Features

Inflammatory bowel disease includes two distinct chronic conditions (i.e., Crohn's disease and ulcerative colitis) that have significant clinical and pathologic differences *(Table 2)*.

HISTORY AND PHYSICAL EXAMINATION

Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, fever, gastrointestinal bleeding, and weight loss. The history should address the onset, severity, and pattern of symptoms, especially frequency and consistency of bowel movements. History targeting risk factors and possible alternative diagnoses includes recent travel, exposure to antibiotics, food intolerance, medications, smoking, and family history of inflammatory bowel disease[8] *(Table 3[9])*. Specific questions addressing extraintestinal manifestations include eye and joint problems and symptoms of anemia *(Table 4)*.[10] Questions about the impact of symptoms should include time missed from school or work.

During the physical evaluation, heart rate, blood pressure, temperature, and body weight should be measured.[8] Abdominal examination may reveal tenderness, distention, or masses.[8] An anorectal examination should be performed because one-third of patients have a perirectal abscess, fissure, or fistula at some time during the illness.[11]

EXTRAINTESTINAL MANIFESTATIONS

Extraintestinal manifestations of Crohn's disease are common and include anemia, cholelithiasis, erythema nodosum, inflammatory arthropathies, nephrolithiasis, osteoporosis, uveitis, scleritis, and venous thromboembolism *(Table 4)*.[10] Ultrasonography, computed axial tomography, scintigraphy, and magnetic resonance imaging are helpful for excluding extramural complications.[8,12] The diagnostic accuracy of these tests is provided in *Table 5*.[12]

Diagnostic Studies

LABORATORY TESTING

Laboratory tests are useful for diagnosing Crohn's disease, assessing disease activity, identifying complications, and monitoring response to therapy. Initial testing often includes white blood cell count; platelet count; measurement of hemoglobin, hematocrit, blood urea nitrogen, creatinine, liver enzymes, and C-reactive protein; and erythrocyte sedimentation rate. Stool culture and testing for *Clostridium difficile* toxin should be considered.[8] Presence of antibodies to *Escherichia coli* outer membrane porin and *Saccharomyces cerevisiae* is suggestive of Crohn's disease, whereas perinuclear antineutrophil cytoplasmic antibody is more suggestive of ulcerative colitis.[13]

Table 2. Features of Crohn's Disease and Ulcerative Colitis

Feature	*Crohn's disease*	*Ulcerative colitis*
Location	Any area of gastrointestinal tract	Continuous lesions starting in rectum Generally only occurs in the colon
Thickness	Transmural involvement	Mucosa and submucosa only
Colonoscopy findings	Skip lesions, cobblestoning, ulcerations, strictures	Pseudopolyps, continuous areas of inflammation
Anemia	+	+ +
Abdominal pain	+ +	+
Rectal bleeding	+	+ +
Colon cancer risk	+ +	+ + + +

+ = more common or prevalent.

Table 3. Differential Diagnosis of Crohn's Disease

Celiac disease	Irritable bowel syndrome
Chronic pancreatitis	Ischemic colitis
Colorectal cancer	Lymphoma of small bowel
Diverticulitis	Sarcoidosis
Infection (e.g., *Yersinia, Mycobacterium*)	Ulcerative colitis

Information from reference 9.

Table 4. Prevalence of Extraintestinal Manifestations of Crohn's Disease

Extraintestinal manifestation	*Prevalence (%)*
Anemia	9 to 74
Anterior uveitis	17
Aphthous stomatitis	4 to 20
Cholelithiasis	13 to 34
Episcleritis	29
Erythema nodosum	2 to 20
Inflammatory arthropathies	10 to 35
Nephrolithiasis	8 to 19
Osteoporosis	2 to 30
Pyoderma gangrenosum	0.5 to 2
Scleritis	18
Venous thromboembolism	10 to 30

Information from reference 10.

Table 5. Accuracy of Common Radiologic Tests in the Diagnosis of Inflammatory Bowel Disease*

Test	*Sensitivity (%)*	*Specificity (%)*	*Positive likelihood ratio†‡*	*Negative likelihood ratio†‡*	*Positive predictive value (%)†*	*Negative predictive value (%)†*
Computed axial tomography	84.3	95.1	3.8	0.03	79.0	96.5
Magnetic resonance imaging	93.0	92.8	2.8	0.02	73.9	98.3
Scintigraphy	87.8	84.5	1.2	0.03	55.4	96.9
Ultrasonography	89.7	95.6	4.4	0.02	81.6	97.5

NOTE: *Assume a prevalence of 0.18 percent, or approximately one in 556.*

**—Includes Crohn's disease and ulcerative colitis.*
†—*Calculated from sensitivity and specificity.*
‡—*Weighted for prevalence.*

Information from reference 12.

Table 6. Laboratory Tests to Assess Disease Activity and Complications in Patients with Crohn's Disease

Category	*Test*	*Initial testing*	*Subsequent testing*	*Comments*
General	White blood cell count	✓	✓	Elevated with inflammation or infection, or secondary to glucocorticoid use Decreased with 6-mercaptopurine and azathioprine (Imuran) use
	Hemoglobin and hematocrit level	✓	✓	Anemia
Acute phase reactants	Platelet count	✓	✓	Increased with inflammation or decreased with treatment (e.g., azathioprine)
	C-reactive protein level and erythrocyte sedimentation rate	✓	✓	If elevated, may correlate with disease activity
Stool studies	Stool for culture, ova and parasites, and *Clostridium difficile* toxin	✓	✓	To rule out major infectious cause of diarrhea
Nutritional status	Iron, ferritin, vitamin B_{12}, and folate levels; total iron-binding capacity		✓	Decreased absorption or increased iron loss leading to anemia
	Albumin and prealbumin levels		✓	Decreased with poor nutritional status and with protein-losing enteropathy
	Vitamin D and calcium levels		✓	Decreased secondary to malabsorption, small bowel resection, or corticosteroid impairment of vitamin D metabolism Measure when initiating corticosteroid therapy
Complications	Liver function testing	✓	✓	Performed to rule out sclerosing cholangitis, screen for adverse effects of therapies
	Blood urea nitrogen and creatinine levels	✓	✓	Monitor renal function
Diagnosis	Fecal lactoferrin and calprotectin levels		✓	Surrogate marker for bowel inflammation May distinguish between flare-up of Crohn's disease and symptoms of irritable bowel syndrome
	Antibodies to *Escherichia coli* outer membrane porin and *Saccharomyces cerevisiae*; perinuclear antineutrophil cytoplasmic antibody		✓	Distinguish between Crohn's disease and ulcerative colitis

Information from references 8, 14, and 15.

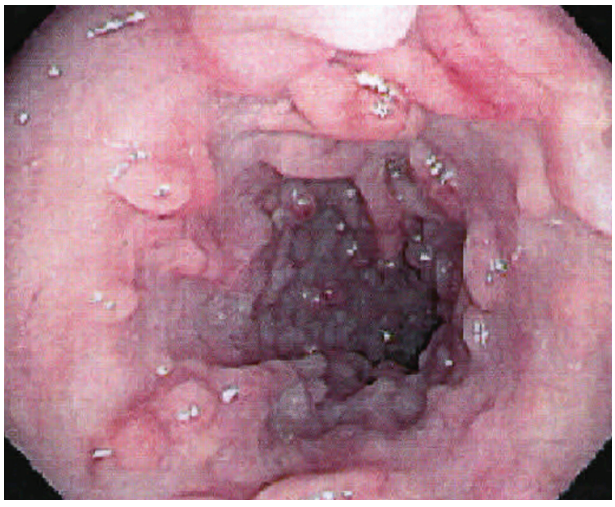

Figure 1. Colonoscopic image showing erythematous and friable mucosa with numerous pseudopolyps in a patient with Crohn's disease.

Subsequent testing may include measurement of iron, ferritin, total iron-binding capacity, vitamin B_{12}, folate, albumin, prealbumin, calcium, and vitamin D to monitor common complications. Fecal lactoferrin and calprotectin are surrogate markers for bowel inflammation and may help distinguish between inflammatory conditions and irritable bowel syndrome.[14,15] An elevated fecal calprotectin level reliably indicates relapse in patients with Crohn's disease (sensitivity of 80 percent; specificity of 90.7 percent; positive likelihood ratio = 1.9; negative likelihood ratio = 0.04).[14] *Table 6* lists laboratory tests to assess disease activity and complications in patients with Crohn's disease.[8,14,15]

ENDOSCOPY AND RELATED INVESTIGATIONS

Colonoscopy with ileoscopy and biopsy is valuable in the diagnosis of Crohn's disease at the junction of the ileum and colon[8] *(Figure 1)*. Characteristic endoscopic findings include skip lesions, cobblestoning *(Figure 2)*, ulcerations, and strictures. Histology may show neutrophilic inflammation, noncaseating granulomas, Paneth cell metaplasia, and intestinal villi blunting. Other diagnostic tests useful in the diagnosis of small bowel Crohn's disease include capsule endoscopy, computed tomography enterography *(Figure 3)*, magnetic resonance enterography, and small bowel follow-through *(Tables 7*[16] *and 8)*. Capsule endoscopy should be avoided in patients with small bowel strictures because capsule retention may occur. Esophagogastroduodenoscopy is recommended in patients with upper gastrointestinal symptoms; asymptomatic patients with iron deficiency anemia; and patients with active Crohn's disease who have a normal colonoscopy.[8]

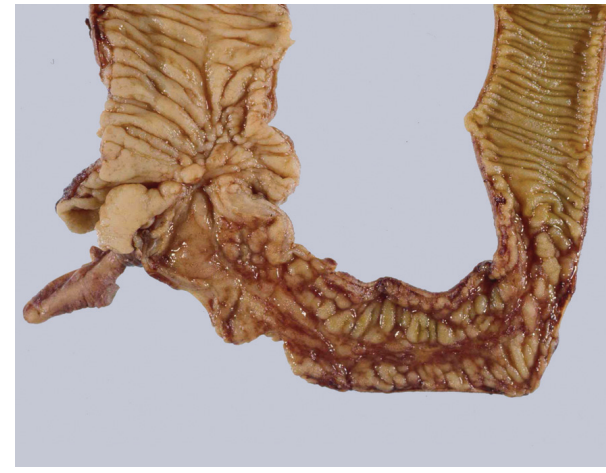

Figure 2. Gross anatomical specimen from a patient with ileocolonic Crohn's disease. Note the sharp demarcation between the cobblestone mucosa of the involved segment and the grossly normal ileal and colonic mucosae.

Active Treatment

Therapeutic recommendations are determined by disease location, activity, and severity, and by disease-associated complications. The goals of therapy are control of symptoms, induction of clinical remission, and maintenance of remission with minimal adverse effects.[17] Two principal strategies are currently used for Crohn's disease management. A traditional "step-up"

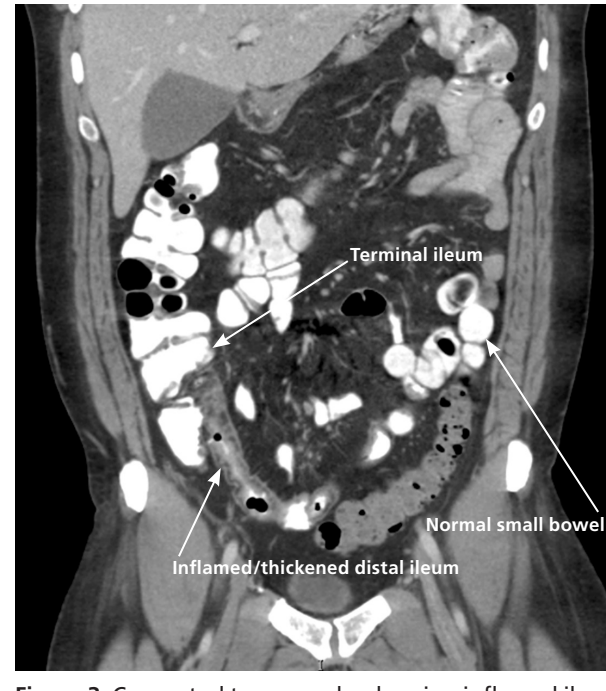

Figure 3. Computed tomography showing inflamed ileum in a patient with Crohn's disease.

Table 7. Accuracy of Common Endoscopic Diagnostic Tests for Active Small Bowel Crohn's Disease*

Test	*Sensitivity (%)*[16]	*Specificity (%)*[16]	*Positive likelihood ratio*†‡	*Negative likelihood ratio*†‡	*Positive predictive value (%)*†	*Negative predictive value (%)*†
Individual test						
Capsule endoscopy	83	53	0.38	0.07	27.9	93.4
Colonoscopy with ileoscopy	74	100	∞	0.06	100	94.6
CT enterography	82	89	1.6	0.04	62.0	95.7
Small bowel follow-through	65	94	2.4	0.08	70.4	92.4
Pairs of tests						
Capsule endoscopy plus colonoscopy with ileoscopy	100	57	0.51	0.00	33.8	100
Capsule endoscopy plus CT enterography	92	53	0.43	0.03	30.0	96.8
Capsule endoscopy plus small bowel follow-through	92	53	0.43	0.03	30.0	96.8
CT enterography plus colonoscopy with ileoscopy	84	94	3.0	0.03	75.4	96.4
CT enterography plus small bowel follow-through	85	94	3.1	0.04	75.6	96.6
Small bowel follow-through plus colonoscopy with ileoscopy	78	100	∞	0.05	100	95.4

NOTE: *Assume a prevalence of 0.18 percent, or approximately one in 556.*

∞ = an infinite amount; CT = computed tomography.

**—Involves 28 percent of all patients with Crohn's disease.*

†—*Calculated from sensitivity and specificity.*

‡—*Weighted for prevalence.*

Information from reference 16.

Table 8. Comparison of Various Diagnostic Tests for Crohn's Disease

Test	*Comment*
Capsule endoscopy	Better yield for nonstricturing small bowel Crohn's disease than small bowel follow-through and colonoscopy with ileoscopy; capsule retention possible with small bowel stricture
Colonoscopy with ileoscopy	Direct visualization of inflammation, fistula, or stricture of terminal ileum and colon; ability to obtain biopsies from the ileum and colon
Computed tomography enterography	Permits visualization of the bowel wall and lumen; exposes patient to ionizing radiation
Computed tomography	Reveals intraintestinal inflammation and extraintestinal manifestations; exposes patient to ionizing radiation
Magnetic resonance enterography	Permits visualization of the bowel and lumen; expensive; no ionizing radiation
Magnetic resonance imaging	Reveals intraintestinal inflammation and extraintestinal manifestations without radiation
Scintigraphy	Uses radiolabeled leukocytes to diagnose bowel inflammation and to estimate disease extent and activity; role in clinical practice is limited
Small bowel follow-through	Radiographic examination of small bowel after ingestion of contrast medium (barium)
Ultrasonography	Detects increase in vascular flow, abscess, sinus tracts, and lymphadenopathy

approach begins with corticosteroids or mesalamine products and advances to immunomodulators or anti–tumor necrosis factor (TNF) agents based on severity of disease *(Table 9)*. A "top-down" approach begins with anti-TNF agents. The optimal treatment strategy remains controversial.

A Cochrane review did not find a significant difference between elemental and nonelemental diets (odds ratio [OR] = 1.10; 95% confidence interval [CI], 0.64 to 1.75) in inducing remission in patients with Crohn's disease.[18] Preventive and supportive therapies are summarized in *Table 10.*

Table 9. Immunomodulator Therapy for Crohn's Disease

Drug	*Dosage*	*Common adverse effects*
6-mercaptopurine	50 mg by mouth per day (maximum: 1.5 mg per kg per day)	Myelosuppression, hepatic toxicity, immunosuppression, hepatic encephalopathy, pancreatitis, rash, hyperpigmentation, lymphoma, fever
Azathioprine (Imuran)	50 mg by mouth per day (maximum: 2.5 mg per kg per day)	Gastritis, nausea, vomiting, lymphoma, fever May cause pancreatitis, leukopenia, anemia, thrombocytopenia
Budesonide (Entocort EC)	9 mg by mouth every morning for up to eight weeks (induction)	Diarrhea, nausea, arthralgias, headache, respiratory tract infection, sinusitis
Methotrexate	25 mg subcutaneously or intramuscularly per week	Alopecia, photosensitivity, rash, diarrhea, anorexia, nausea, vomiting, stomatitis, leukopenia, pneumonitis May also cause hyperuricemia, gastrointestinal hemorrhage, myelosuppression, hepatotoxicity, lung fibrosis, renal failure
Prednisone	20 to 40 mg by mouth per day	Hypertension, fluid retention, hypernatremia, osteoporosis, depression, increased risk of infection
Anti–tumor necrosis factor agents		
Adalimumab (Humira)	160 mg subcutaneously once at week 0, then 80 mg once at week 2, then 40 mg every two weeks	Injection site reactions (e.g., erythema, itching, hemorrhage, pain, swelling), infection, tuberculosis, malignancies (e.g., lymphoma), autoantibodies/lupus-like syndrome
Certolizumab pegol (Cimzia)	400 mg subcutaneously once at weeks 0, 2, and 4, then 400 mg every four weeks	Injection site reactions, upper respiratory tract infection, headache, hypertension, rash, infections
Infliximab (Remicade)	5 mg per kg intravenously once at weeks 0, 2, and 6, then 5 mg per kg every eight weeks	Infusion-related reactions (e.g., dyspnea, flushing, headache, rash, chest pain, hypotension, pruritus, urticaria, anaphylaxis), delayed reaction (e.g., serum sickness, myalgia, arthralgia), infections, pneumonia, cellulitis, abscess, skin ulceration, sepsis, bacterial infection, autoantibodies/lupus-like syndrome, lymphoma

FDA = U.S. Food and Drug Administration; NA = not available.

**—Estimated retail price of one month's treatment based on information obtained at http://www.drugstore.com (accessed July 18, 2011). Generic price listed first; brand price listed in parentheses.*

MILD DISEASE ACTIVITY

Patients with mild disease activity and no systemic symptoms are ambulatory and able to tolerate oral diet and medications.[8]

Mesalamine Products. Sulfasalazine (Azulfidine) and 5-aminosalicylic acid (5-ASA) are often used in the medical management of mild to moderate colonic Crohn's disease *(Table 11)*. Sulfasalazine can cause nausea, headache, fever, rash, male infertility, and rarely agranulocytosis, which usually occurs within the first two months of therapy. 5-ASA is believed to have anti-inflammatory and immunosuppressive properties. 5-ASA products are well tolerated and are preferred to sulfasalazine because they have fewer adverse effects. Headache, nausea, diarrhea, and abdominal pain may occur with 5-ASA. Pancreatitis or pneumonitis may occur with sulfasalazine and mesalamine.

Antibiotics. Antibiotics, especially metronidazole (Flagyl) and ciprofloxacin (Cipro), are widely used and can have both anti-inflammatory and anti-infectious

FDA boxed warning	Monitoring	Cost of generic (brand)*
None	Creatinine level at baseline Complete blood count with differential weekly during induction Liver enzyme tests weekly during induction White blood cell count, platelet count, hemoglobin level	$93 ($207)
Chronic immunosuppression increases risk of neoplasia	Creatinine level at baseline Complete blood count weekly for one month, then every two weeks for two months, then monthly and when dose changes Liver enzyme tests White blood cell count, platelet count, hemoglobin level	$28 ($160)
None	Signs and symptoms of hypercorticism and adrenal suppression with long-term therapy	NA ($1,560)†
Fetal death and congenital abnormalities (not recommended for use in women of childbearing age), hepatotoxicity Fibrosis and cirrhosis with prolonged use Malignant lymphoma may occur	Chest radiography at baseline Complete blood count with differential and platelet count at baseline then monthly Blood urea nitrogen measurement, creatinine level, and liver enzyme tests at baseline then every four to eight weeks	$32 (NA)
None	Blood pressure, electrolyte panel, blood glucose level, mental status, ophthalmic examination (with prolonged therapy), dual energy x-ray absorptiometry	$12 (NA)
Active tuberculosis, reactivation of latent tuberculosis, invasive fungal infections‡	Purified protein derivative test and chest radiography at baseline Monitor for signs and symptoms of tuberculosis and active hepatitis B (in those who are carriers of hepatitis B virus)	NA (more than $2,000) for 80 mg
Active tuberculosis, reactivation of latent tuberculosis, invasive fungal infections‡, lymphoma and other malignancies	Purified protein derivative test and chest radiography at baseline Monitor for signs and symptoms of tuberculosis and active hepatitis B (in those who are carriers of hepatitis B virus)	NA ($1,755) for 200 mg§
Active tuberculosis, reactivation of latent tuberculosis, invasive fungal infections‡, hepatosplenic T-cell lymphoma	Purified protein derivative test and chest radiography at baseline Monitor for signs and symptoms of tuberculosis and active hepatitis B (in those who are carriers of hepatitis B virus) Dermatologic examination in patients with psoriasis	NA ($753) for 100 mg

†—*Four-week course of therapy.*

‡—*Invasive fungal infections include histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis.*

§—*Wholesale prices based on* Red Book. *Montvale, N.J.: Medical Economics Data; 2010.*

properties. Controlled trials have not consistently demonstrated effectiveness.[19,20]

Budesonide. Budesonide (Entocort EC) is an oral, controlled-release glucocorticoid that is useful for treating Crohn's disease at the junction of the ileum and colon or ascending colon. A Cochrane review found that budesonide was more effective than placebo (relative risk [RR] = 1.96; 95% CI, 1.2 to 3.2) or mesalamine (RR = 1.63; 95% CI, 1.2 to 2.2) for induction of remission in patients with Crohn's disease.[21]

MODERATE DISEASE ACTIVITY

Outpatients with moderate disease activity are defined by failed treatment for mild disease or by fever, weight loss, abdominal pain, nausea or vomiting without obstruction, or anemia.[8] Many of these patients are treated by gastroenterologists.

Corticosteroid Therapy. Patients with moderate to severe Crohn's disease are treated with prednisone until improvement of symptoms. Corticosteroids are more effective than placebo (RR = 1.99; 95% CI, 1.51 to 2.64;

Table 10. Supportive and Preventive Measures in Patients with Crohn's Disease

Treatment modality	*Preventive measure*
All therapies	Stop smoking
	Avoid nonsteroidal anti-inflammatory drugs and oral contraceptives (associated with symptom exacerbation)
	Ensure routine immunizations are current (e.g., influenza, pneumococcal vaccination)
	Avoid pregnancy in women of childbearing age
Anti–tumor necrosis factor therapy	Obtain purified protein derivative test and chest radiography before initiating therapy
	Update immunizations, including hepatitis B
Corticosteroids	Baseline dual energy x-ray absorptiometry; calcium and vitamin D supplementation; consider bisphosphonate therapy
Sulfasalazine (Azulfidine) and methotrexate	Folic acid supplementation

$P < .00001$) and 5-ASA products (RR =1.65; 95% CI, 1.33 to 2.03; $P < .00001$) at inducing remission in patients with Crohn's disease.[22] If symptoms are not controlled with adequate doses of prednisone, urgent gastroenterology consultation is warranted. No standards have been established for corticosteroid tapering; however, reduction by 5 to 10 mg per week to 20 mg and then by 2.5 to 5 mg per week until discontinuation is reasonable.

Azathioprine and 6-Mercaptopurine. Azathioprine (Imuran) and 6-mercaptopurine can effectively induce remission in patients with active Crohn's disease within three to six months of achieving the maximal dose (OR = 2.5; 95% CI, 1.6 to 3.9; number needed to treat [NNT] = 5).[23] These agents are primarily used for long-term maintenance of remission and are typically combined with corticosteroids or occasionally with anti-TNF preparations. Routine monitoring of white blood cell count, platelet count, and hemoglobin and creatinine levels is recommended.[24] Adverse effects of azathioprine and 6-mercaptopurine include leukopenia, thrombocytopenia, bone marrow suppression, immunosuppression, pancreatitis, hypersensitivity reaction, lymphoma, nausea, vomiting, elevated liver enzymes, and fever.

Methotrexate. Methotrexate is an alternative therapy for patients intolerant of azathioprine or 6-mercaptopurine. It effectively induces remission and enables withdrawal from corticosteroids in patients with refractory Crohn's disease (NNT = 5).[25] Potential adverse effects include bone marrow suppression, leukopenia, nausea, vomiting, hepatic fibrosis, and pneumonitis. Chest radiography, complete blood count, and liver enzyme tests are recommended before initiating treatment.[24] Risk factors for hepatotoxicity include obesity, diabetes mellitus, chronic alcohol use, abnormal liver chemistries, and a cumulative dose of methotrexate exceeding 1.5 g.[26]

Anti-TNF Agents. Three TNF antagonist (anti-TNF) therapies (infliximab [Remicade], adalimumab [Humira], and certolizumab pegol [Cimzia]) are approved by the U.S. Food and Drug Administration for moderate to severe Crohn's disease. Anti-TNF therapy may be considered in patients with moderate to severe active Crohn's disease that does not respond to corticosteroids or immunosuppressive therapy. It is also used for patients in whom corticosteroids are contraindicated or not desired. Relative or absolute contraindications to anti-TNF therapy include sepsis, tuberculosis, optic neuritis, infusion reaction, and cancer. A negative purified protein derivative test and chest radiography before treatment with anti-TNF agents are important because this therapy is associated with reactivation of tuberculosis.[27] Anti-TNF therapy has been shown to effectively induce and maintain remission in patients with moderate to severe Crohn's disease.[24,28,29]

SEVERE DISEASE ACTIVITY

Patients with severe disease activity have persistent symptoms despite therapy, or they present with fever, vomiting, evidence of intestinal obstruction, involuntary guarding or rebound tenderness, cachexia, or evidence of abscess. These patients require emergent hospitalization and gastroenterology consultation.[8] Evaluation often includes abdominal imaging and laboratory tests, including a complete blood count, complete metabolic panel, blood cultures, urinalysis, urine culture, stool culture, and *C. difficile* stool antigen test. Computed tomography or magnetic resonance enterography may differentiate inflammatory from fibrotic strictures. Urgent surgical evaluation is recommended for patients with symptoms of intestinal obstruction or abdominal mass. An abscess requires percutaneous or open surgical drainage. Fluid resuscitation, parenteral corticosteroids, and broad-spectrum antibiotics should be administered, and nutritional support should be provided using elemental feeding or parenteral hyperalimentation.[30] Use of anti-TNF agents is controversial in the treatment of severe Crohn's disease. Failure to respond or worsening symptoms may require surgical intervention.

PERIANAL AND FISTULIZING DISEASE

Suppurative conditions (abscess) are treated with drainage and should be jointly managed by gastroenterologists and surgeons. Chronic fistulae and perianal fissures are treated with antibiotics (metronidazole alone or in

combination with ciprofloxacin), immunosuppressives, or anti-TNF agents.[31] A placebo-controlled trial suggested benefits with infliximab in the closure of cutaneous Crohn's disease fistulae that had not responded to previous therapy with antibiotics, corticosteroids, or immunomodulators.[11] No data are available from controlled trials concerning treatment by internal fistulae closure (enteroenteric, enterocolic, enterovesicular, and enterovaginal) with alternative immunomodulatory agents. Surgery may be considered.

Maintenance Therapy

Azathioprine is effective for maintenance of remission in patients with Crohn's disease (OR = 2.1; 95% CI, 1.4 to 3.5; NNT = 7).[32] In a randomized controlled trial with 24 weeks of follow-up, 65 percent of patients maintained remission with methotrexate.[33] Increasing evidence supports that "top-down" therapy beginning with infliximab and azathioprine may offer corticosteroid-sparing benefits for corticosteroid-naive patients.[34] Evidence demonstrates that low-dose conventional corticosteroids and 5-ASA preparations are ineffective in maintaining remission in patients with Crohn's disease, and high-dose corticosteroids have not been evaluated as maintenance therapy.[35,36] No published studies have evaluated antibiotics in the maintenance of remission. Budesonide is no more effective than placebo for maintenance of remission in patients with Crohn's disease at 12 months (RR = 1.13; 95% CI, 0.94 to 1.35; $P = .19$).[37]

Surgical Therapy

The most common indications for surgery include refractory disease, intractable hemorrhage, perforation, obstruction, abscess, dysplasia, cancer, and unresponsive

Table 11. Mesalamine Products Commonly Used for Treating Crohn's Disease

Brand name	*Generic name*	*Location of action*	*Formulation*	*Dosage*	*Cost**
Apriso	Mesalamine	Colon	0.375-g extended-release capsule	1.5 g orally every morning	NA ($271)
Asacol Asacol HD	Mesalamine	Colon and terminal ileum	400- and 800-mg delayed-release tablets	800 mg orally three times per day	NA ($390)
Canasa	Mesalamine	Rectum	1,000-mg rectal suppository	1,000 mg rectally at bedtime	NA ($522)†
Lialda (multimatrix system)	Mesalamine	Colon	1.2-g delayed-release tablet	2.4 to 4.8 g orally once per day	NA ($512)
Pentasa (pH controlled)	Mesalamine	Small bowel, ileum, colon	250- and 500-mg extended-release capsules	1,000 mg orally four times per day	NA ($635)
Rowasa	Mesalamine	Descending colon	4 g per 60 mL rectal enema suspension	4 g rectally at bedtime	$36 ($95‡) for 60-mL bottle†
Colazal (5-aminosalicylic acid plus inert carrier)	Balsalazide	Colon	750-mg capsule	2.25 g orally three times per day	$103 ($400)
Dipentum (two molecules of 5-aminosalicylic acid)	Olsalazine	Colon	250-mg capsule	500 mg orally twice per day	NA ($347)
Azulfidine	Sulfasalazine	Colon	500-mg tablet	500 mg orally four times per day	$23 ($79)

NOTE: *The products in this table are not approved by the U.S. Food and Drug Administration for treatment of Crohn's disease.*

NA = not available in generic form.

**—Estimated retail price of one month's treatment based on information obtained at http://www.drugstore.com (accessed July 18, 2011). Generic price listed first; brand price listed in parentheses.*

†—Usually only prescribed for short duration (eight to 12 weeks).

‡—Price based on information obtained at http://www.pillbot.com (accessed July 18, 2011).

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Ultrasonography, computed axial tomography, scintigraphy, and magnetic resonance imaging are helpful for excluding extramural complications in persons with Crohn's disease.	C	8, 12
Colonoscopy with ileoscopy and biopsy is a valuable initial test in the diagnosis of ileocolonic Crohn's disease.	C	8
Esophagogastroduodenoscopy is recommended in patients with Crohn's disease who have upper gastrointestinal symptoms.	C	8
There is no difference between elemental and nonelemental diets in inducing remission in patients with Crohn's disease.	A	18
Budesonide (Entocort EC) is effective in inducing, but not maintaining, remission in patients with Crohn's disease.	B	21, 37
Corticosteroids are more effective than placebo and 5-aminosalicylic acid products in inducing remission in patients with Crohn's disease.	A	22
Azathioprine (Imuran) and 6-mercaptopurine are effective in inducing remission in patients with active Crohn's disease.	A	23
Methotrexate is effective in inducing and maintaining remission in patients with Crohn's disease.	B	25, 33

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

fulminant disease. Patients with active luminal Crohn's disease that fails to improve within seven to 10 days of intensive inpatient medical management should be considered for surgery. The most common surgical procedures for Crohn's disease include surgical resection, stricturoplasty, and drainage of abscess. In a recent review of six population-based studies involving 25,870 patients with an average follow-up of 11.1 years, surgery was required in one-third of patients after corticosteroids were initiated, and the risk of postoperative recurrence over 10 years was 44 to 55 percent.[38] In this study, one-half of all patients required surgery within 10 years of the diagnosis of Crohn's disease, and only 10 percent of patients had a prolonged clinical remission.[38]

Limited segmental resection is superior to subtotal colectomy in terms of fewer symptoms ($P = .039$), fewer loose stools ($P = .002$), and better anorectal function ($P = .027$).[39] Postoperative infections are not associated with azathioprine, 6-mercaptopurine, or infliximab, but are associated with corticosteroid therapy.[40] Stricturoplasty has been recommended in selected patients with small bowel disease to avoid impaired nutrient absorption, bile salt diarrhea, steatorrhea, bacterial overgrowth, and short bowel syndrome, but is not recommended for colonic disease.

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Author disclosure: No relevant financial affiliations to disclose.

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