Diagnosis and management of Crohn's disease

Abstract word count: 192

Manuscript word count: 2000

Abbreviations:
Capsule endoscopy (CE)
Crohn's disease (CD)
Crohn's Disease Activity Index (CDAI)
Odds ratio (OR)
Confidence interval (CI)
Azathioprine (AZA)
6-mercaptopurine (6-MP)
5-aminosalicylic acid (5-ASA)
Food and Drug Administration (FDA)
Perinuclear antineutrophil cytoplasmic antibody (p-ANCA)
Anti-tumor necrosis factor (Anti-TNF)
Complete blood count (CBC)
White blood cell (WBC)
Anti-Saccharomyces cerevisiae antibodies (ASCA)
Escherichia coli outer membrane porin (anti-OmpC)

Abstract

Crohn's disease (CD) is a chronic inflammatory condition affecting the gastrointestinal tract at any point from the mouth to the rectum. Patients with CD may experience diarrhea, abdominal pain, fever, weight loss, abdominal masses, and anemia. Extraintestinal manifestations of CD include osteopenia, inflammatory arthropathies, episcleritis, nephrolithiasis, cholelithiasis, and pyoderma gangrenosa. Acute phase reactants such as C-reactive protein and sedimentation rate are often increased with inflammation and may correlate with disease activity. Levels of vitamin B12, folate, albumin, prealbumin, calcium, and vitamin D can help assess nutritional status. Colonoscopy with ileoscopy, capsule endoscopy, CT enterography, and small bowel follow-through are often used to diagnose CD. Ultrasound, CT scan, scintigraphy, and MRI can assess for extraintestinal manifestations or complications, e.g., abscess, fistula, or perforation. Mesalamine products are first-line agents used to treat patients with mild to moderate colonic CD. Antibiotics, e.g., metronidazole and fluoroquinolones, are often used in clinical practice for the treatment of CD. Patients with moderate to severe CD are treated with corticosteroids, azathioprine, 6-mercaptopurine, or anti-tumor necrosis factor agents, e.g. infliximab and adalimumab. Severe CD may require emergent hospitalization and a multidisciplinary approach with the family physician, gastroenterologist, surgeon, and dietitian.

<LH>**Background**

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract characterized by inflammation at any point from the mouth to the rectum (see Table 1). Inflammatory bowel disease encompasses two distinct chronic conditions: CD and ulcerative colitis (see Table 2). The prevalence of CD in the US is 201 per 100,000 in individuals 20 years and older (1). Patients with CD often present in adolescence, and the median age of diagnosis for CD is in their 20's (2). CD is more prevalent in women than men, in developed countries, and in the northern hemisphere (1, 2). The annual economic burden of CD is estimated at $10.9 to 15.5 billion for the US in 2006 US dollars (3). While the etiology of CD is unknown; it is associated with a mutation on the NOD2 gene (4). Smoking, oral contraceptives, and non-selective NSAIDs are associated with exacerbation of symptoms (5-7). This review article focuses on CD in adults and excludes special groups such as children and pregnant females.

<SH> **History and physical examination**

Symptoms of CD include abdominal pain, diarrhea, fatigue, fever, gastrointestinal bleeding, and weight loss (see table 3 for differential diagnosis of CD). The history should include the onset of symptoms, recent travel, exposure to antibiotics, food intolerance, medications, smoking, family history of inflammatory bowel disease, and frequency and consistency of bowel movements (8). The physician should inquire about eye and joint symptoms, time missed from school or work, and symptoms of anemia. Heart rate, blood pressure, temperature, and body weight should be measured (8). An abdominal exam may reveal tenderness, distention, or mass (8). An ano-rectal exam should be performed because one third of patients have perirectal abscess, fissure, or fistula at some time during the course of their illness.

<SH>**Extraintestinal manifestations**

Extraintestinal manifestations of CD occur commonly and include anemia, cholelithiasis, erythema nodosum, inflammatory arthropathies, nephrolithiasis, osteoporosis, uveitis, scleritis, and venous thromboembolism (9). (see Table 4).

<LH>**Laboratory tests**

Laboratory tests are useful to diagnose CD, assess disease activity, and determine complications. Initial testing often includes white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, BUN, creatinine, liver enzymes, C-reactive protein, and sedimentation rate. A stool culture and testing for *Clostridium difficile* toxin should be considered (8). Presence of antibodies to *Escherichia coli* outer membrane porin and *Saccharomyces cerevisiae* are suggestive of CD while perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is more suggestive of ulcerative colitis (10). Subsequent testing may also include iron, ferritin, TIBC, vitamin B12, folate, albumin, prealbumin, calcium, and vitamin D levels. Fecal lactoferrin and calprotectin are surrogate markers for bowel inflammation and may be helpful in distinguishing between inflammatory conditions and irritable bowel syndrome (11, 12). In addition, an elevated fecal calprotectin level is a reliable marker of relapse in patients with CD (sensitivity 80%, specificity 90.7%, +LR 1.9,-LR 0.04) (11) (see Table 5).

<LH>**Diagnostic studies**

Colonoscopy with ileoscopy and biopsy is a valuable initial test in the diagnosis of CD at the junction of the ileum and colon, e.g. ileocolonic (8) (see Figure 1). Characteristic endoscopic findings include skip lesions, cobblestoning, ulcerations, and strictures. Histology may show neutrophilic inflammation, noncaseating granulomas, Paneth cell metaplasia, and intestinal villi blunting (see Figure 2). Other diagnostic tests useful in the diagnosis of small bowel CD include capsule endoscopy (CE), CT or MR enterography, and small bowel follow-through (13). CE should be avoided in patients with small bowel strictures since capsule retention may occur (see Tables 6 and 7). (see Figure 3). The diagnostic accuracy of these tests is listed in Table 8. Esophagogastroduodenoscopy is recommended in patients with upper

gastrointestinal symptoms or in asymptomatic patients with iron deficiency anemia and active CD with a normal colonoscopy (8).

<LH> **Treatment**

Therapeutic recommendations are determined by disease location, disease activity, severity, and disease-associated complications. The goals of therapy are control of symptoms, induction of clinical remission, and maintenance of remission (14). There are 2 approaches to the treatment of CD. A traditional step-up approach begins with steroids or mesalamine products and advances to immunomodulators or anti-TNF agents based on severity of disease. A top-down approach begins with anti-TNF agents. The best approach for the treatment of CD is controversial and is highly debated in the literature. A recent Cochrane review did not find a significant difference between elemental and non-elemental diets [OR 1.10 (95% CI 0.64, 1.75)] in inducing remission of patients with CD (15). Table 9 shows a list of preventative services in patients with CD.

<LH>**Mild disease activity**

Patients with mild disease activity are ambulatory and able to tolerate oral diet without manifestations of systemic toxicity (8).

<SH>**Mesalamine products**

Sulfasalazine and 5-aminosalicylic acid (5-ASA) are frequently used in the medical management of patients with mild to moderate colonic CD. Sulfasalazine can cause nausea, headache, fever, rash, and male infertility, and rarely agranulocytosis, a severe side effect that 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 treatment due to fewer side effects. Headache, nausea, diarrhea, and abdominal pain may occur with 5-ASA. Pancreatitis or pneumonitis may occur with treatment with sulfasalazine and mesalamine. (see Table 9).

<SH>**Antibiotics**

Antibiotics, e.g., metronidazole and ciprofloxacin, are widely used in clinical practice for the treatment of CD and may have anti-inflammatory properties in addition to anti-infectious properties. Controlled trials have not consistently demonstrated efficacy (16, 17).

<SH>**Budesonide**

Budesonide is an oral, controlled-release glucocorticoid which is primarily useful for treating CD at the junction of the ileum and colon or ascending colon (see Table 10). A recent Cochrane review found that budesonide was more effective than placebo (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 CD (18).

<LH>**Moderate disease activity**

Outpatients with moderate disease activity are considered to have failed treatment for mild disease or have fever, weight loss, abdominal pain, nausea or vomiting without obstruction, or anemia (8). Many of these patients are managed by gastroenterologists.

<SH>**Steroid therapy**

Patients with moderate to severe CD are treated with prednisone until improvement of symptoms. Corticosteroids are more effective than placebo (RR 1.99; 95% CI 1.51 to 2.64; $P < 0.00001$) or 5-ASA products (RR 1.65; 95% CI 1.33 to 2.03; $P < 0.00001$) for induction of remission in patients with CD (19). If symptoms are not controlled with adequate doses of prednisone, then urgent gastroenterologist consultation is warranted. There are no standards for steroid tapering; however, reduction of 5-10 mg per week until 20 mg and then by 2.5-5 mg weekly until discontinuation of therapy is reasonable.

<SH>**Azathioprine and 6-Mercaptopurine**

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective in inducing remission in active CD within 3-6 months after achieving maximum dose [OR 2.5 (95% CI, 1.6-3.9, NNT 5)] (20). These agents are primarily utilized for long-term maintenance of remission and are typically combined with steroids or occasionally with anti-TNF preparations. Routine monitoring

of WBC count, hemoglobin, platelets, and creatinine is recommended (21). Side effects of both AZA and 6-MP include leukopenia, thrombocytopenia, bone marrow suppression, immunosuppression, pancreatitis, hypersensitivity reaction, lymphoma, nausea, vomiting, elevated liver enzyme tests, and fever.

<SH>**Methotrexate**

Methotrexate, an alternative for patients intolerant to AZA or 6-MP, is effective at inducing remission and in enabling complete withdrawal from corticosteroids in patients with refractory CD (NNT=5) (22). Potential adverse events include bone marrow suppression, leukopenia, nausea, vomiting, hepatic fibrosis, and pneumonitis. A chest x-ray, complete blood count (CBC), and liver enzyme tests are recommended prior to initiation of treatment (21). Risk factors for hepatotoxicity include obesity, diabetes, chronic alcohol use, abnormal liver chemistries, and a cumulative dose exceeding 1.5 g of methotrexate (23).

<SH> **Anti-tumor necrosis factor agents**

Three tumor necrosis factor antagonist (anti-TNF) therapies (infliximab, adalimumab, and certolizumab pegol) are FDA approved for moderate to severe CD. Anti-TNF therapy may be considered in patients with moderate to severe active CD not responsive to corticosteroids or immunosuppressive therapy or in patients in whom corticosteroids are contraindicated or not desired. Relative or absolute contraindications to anti-TNF therapy include sepsis, tuberculosis, optic neuritis, infusion reaction, or cancer. A negative Purified Protein Derivative (PPD) and a chest x-ray prior to treatment with anti-TNF are important as this therapy is associated with reactivation of tuberculosis (24). Anti-TNF therapy has been shown to be effective at induction and maintenance of remission in patients with moderate to severe CD (21, 25, 26).

<LH>**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 an abscess. These patients require emergent

hospitalization for further treatment with specialty consultation (8). Evaluation often includes abdominal imaging and laboratory tests: CBC, complete metabolic panel, blood cultures, urinalysis, urine culture, stool for culture and *C. difficile* antigen. CT or MRI 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 provided, using elemental feeding or parenteral hyperalimentation (27). Use of anti-TNF agents is controversial in the treatment of severe CD. Failure to respond or worsening symptoms may require surgical intervention.

<LH>**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 (28). A placebo-controlled trial suggested benefits with infliximab in the closure of cutaneous CD fistulae that had not responded to prior therapy with antibiotics, corticosteroids, or immunomodulators (29). There are no controlled trial treatment data for internal fistulae closure (entero-enteric, entero-colic, entero-vesicular and entero-vaginal) with alternative immunomodulatory agents; surgery may be considered.

<LH> **Maintenance therapy**

AZA is effective for maintenance of remission [OR 2.1 (95% CI, 1.4-3.5, NNT 7)] (30). In a randomized controlled trial with 24 weeks of follow-up, 65% of patients maintained remission with methotrexate (31). Anti-tuberculous therapy may be effective at maintaining remission in patients with CD when remission has been induced with corticosteroids combined with antituberculous therapy [OR 3.37 (95% CI 1.38-8.24), NNT=3] (32). There is increasing evidence that “top-down” therapy beginning with infliximab and azathioprine may offer steroid-

sparing benefits for steroid-naïve patients (33). Evidence demonstrates that low-dose conventional steroids and 5-ASA preparations are ineffective for maintaining remissions in CD, and high dose corticosteroids have not been evaluated as maintenance therapy (34, 35). There are no published studies evaluating antibiotics in the maintenance of remission. Budesonide is no more effective than placebo for maintenance of remission in CD patients at 12 months (RR 1.13; 95% CI 0.94 to 1.35; *P* = 0.19) (36).

<LH> **Surgical therapy**

The most common indications for surgery include refractory disease, intractable hemorrhage, perforation, obstruction, abscess, dysplasia, cancer, and unresponsive fulminant disease. Patients who have active luminal CD and who fail to improve within 7-10 days of intensive inpatient medical management should be considered for surgery. The most common surgical procedures performed in CD include surgical resection, stricturoplasty, and drainage of abscess. In a recent review of 6 population studies involving 25,870 patients with an average follow-up of 11.1 years, surgery was required in one third of patients after steroids were initiated, and the risk of postoperative recurrence over 10 years was 44-55% (37). In this study, half of all patients required surgery within 10 years of the diagnosis of CD, and only 10% of patients had a prolonged clinical remission (37).

Limited segmental resection is superior to subtotal colectomy with fewer symptoms (*P* = 0.039), fewer loose stools (*P* = 0.002), and better anorectal function (*P* = 0.027) (38). Postoperative infections are not associated with AZA, 6-MP, or infliximab but are associated with corticosteroids (39). 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.

REFERENCES

1. Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007 Dec;5(12):1424-9.
2. Sandler RS, Loftus EV. Epidemiology of inflammatory bowel disease. In: Sartor RB, Sandborn WJ (editors). Inflammatory Bowel Diseases. Saunders, 2004:245-262.
3. Yu AP, Cabanilla LA, Wu EQ, Mulani PM, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. Curr Med Res Opin. 2008 Feb;24(2):319-28.
4. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009 Nov 19;361(21):2066-78.
5. Cosnes J, Carbonnel F, Carrat F, Beaugerie L, Gendre JP. Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. Gut. 1999 Aug;45(2):218-22.
6. Yamamoto T, Keighley MR. Smoking and disease recurrence after operation for Crohn's disease. Br J Surg. 2000 Apr;87(4):398-404.
7. Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006 Feb;4(2):196-202.
8. Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. Gut. 2006 Mar;55 Suppl 1:i1-15.
9. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. Ann Med. 2010 Mar;42(2):97-114.
10. Zholudev A, Zurakowski D, Young W, Leichtner A, Bousvaros A. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. Am J Gastroenterol. 2004 Nov;99(11):2235-41.
11. Kallel L, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol. 2010 Mar;22(3):340-5.
12. Sidhu R, Wilson P, Wright A, Yau CW, D'Cruz FA, Foye L, et al. Faecal lactoferrin - a novel test to differentiate between the irritable and inflamed bowel? Aliment Pharmacol Ther. 2010 Mar 20.
13. Solem CA, Loftus EV, Jr., Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointest Endosc. 2008 Aug;68(2):255-66.
14. Cross RK, Wilson KT, Binion DG. Narcotic use in patients with Crohn's disease. Am J Gastroenterol. 2005 Oct;100(10):2225-9.
15. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2007(1):CD000542.
16. Colombel JF, Lemann M, Cassagnou M, Bouhnik Y, Duclos B, Dupas JL, et al. A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active

Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). Am J Gastroenterol. 1999 Mar;94(3):674-8.
17. Steinhart AH, Feagan BG, Wong CJ, Vandervoort M, Mikolainis S, Croitoru K, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. Gastroenterology. 2002 Jul;123(1):33-40.
18. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008(3):CD000296.
19. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008(2):CD006792.
20. Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev. 2000(2):CD000545.
21. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006 Mar;130(3):935-9.
22. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev. 2005(1):CD003459.
23. Vandeputte L, D'Haens G, Baert F, Rutgeerts P. Methotrexate in refractory Crohn's disease. Inflamm Bowel Dis. 1999 Feb;5(1):11-5.
24. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104.
25. Osterman MT, Lichtenstein GR. Current and Future Anti-TNF Therapy for Inflammatory Bowel Disease. Curr Treat Options Gastroenterol. 2007 Jun;10(3):195-207.
26. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007 Sep;56(9):1232-9.
27. Kornbluth A, Marion JF, Salomon P, Janowitz HD. How effective is current medical therapy for severe ulcerative and Crohn's colitis? An analytic review of selected trials. J Clin Gastroenterol. 1995 Jun;20(4):280-4.
28. Jakobovits J, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. Am J Gastroenterol. 1984 Jul;79(7):533-40.
29. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999 May 6;340(18):1398-405.
30. Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev. 2000(2):CD000067.
31. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med. 2000 Jun 1;342(22):1627-32.

32. Borgaonkar MR, MacIntosh DG, Fardy JM. A meta-analysis of antimycobacterial therapy for Crohn's disease. Am J Gastroenterol. 2000 Mar;95(3):725-9.
33. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
34. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2003(4):CD000301.
35. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Cochrane Database Syst Rev. 2005(1):CD003715.
36. Benchimol EI, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009(1):CD002913.
37. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010 Feb;105(2):289-97.
38. Andersson P, Olaison G, Hallbook O, Sjodahl R. Segmental resection or subtotal colectomy in Crohn's colitis? Dis Colon Rectum. 2002 Jan;45(1):47-53.
39. Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology. 2003 Aug;125(2):320-7.
40. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. Radiology. 2008 Apr;247(1):64-79.
41. Cummings JR, Keshav S, Travis SP. Medical management of Crohn's disease. BMJ. 2008 May 10;336(7652):1062-6.

Key recommendations for practice.

Key Clinical Recommendation	Evidence Rating	References
Colonoscopy with ileoscopy and biopsy is a valuable initial test in the diagnosis of ileocolonic CD.	C	(8)
Ultrasound, computed axial tomography scan, scintigraphy, and magnetic resonance imaging are helpful to exclude extramural complications.	C	(8, 40)
Esophagogastroduodenoscopy is only recommended in patients with upper gastrointestinal symptoms.	C	(8)
There is no difference between elemental and non-elemental diets in inducing remission in patients with Crohn's disease.	A	(15)
Budesonide is effective at inducing remission but not at maintaining remission in patients with CD.	B	(18, 36)
Azathioprine and 6-mercaptopurine are effective in inducing remission in active CD	A	(20)

Corticosteroids are more effective than placebo and 5-ASA products for induction of remission in patients with CD.	A	(19)
Methotrexate is effective for induction and maintenance of remission.	B	(22, 31)

Table 1. Location of Crohn's disease and associated symptoms

Location	Symptoms	Comments	Frequency (%)	Common diagnostic testing
Ileo-colonic	Diarrhea, cramping, abdominal pain, and weight loss	Most common form of Crohn's disease	35	CI, CTE
Colon only	Diarrhea, rectal bleeding, perirectal abscess, fistula, perirectal ulcer	Skin lesions and arthralgias more common	32	
Small bowel only	Diarrhea, cramping, abdominal pain, and weight loss	Complications may include fistula or abscess formation	28	CI, CTE, CE, SBFT, enteroscopy
Gastroduodenal	Anorexia, weight loss, and nausea and vomiting	Rarely occurs and may cause bowel obstruction	5	EGD,SBFT, enteroscopy

CE: Capsule endoscopy, CTE: CT enterography, CI: Colonoscopy with ileoscopy, EGD: esophagogastroduodenoscopy, SBFT: Small bowel follow-through

Original, Print

Table 2. Comparison of Crohn's disease and ulcerative colitis

	Crohn's Disease	**Ulcerative Colitis**
Location	Any part 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	Pseudopolyps, continuous areas of inflammation
Anemia	+	++
Abdominal pain	++	+
Blood per rectum	+	++
Colon cancer risk	++	++++

Original, Print

Table 3. Differential diagnosis of Crohn's disease

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

Source: (41)

Original, Print

Table 4. The prevalence of extraintestinal manifestations of Crohn's disease

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

Source: (9)

Original, Print

Table 5. Laboratory tests to assess disease activity and complications in Crohn's disease

Category	Test	Initial testing	Subsequent testing	Comments
General	White blood cell count	X	X	Elevated due to inflammation, infection, or secondary to glucocorticoid use
				Decreased due to treatment with 6-mercaptopurine and azathioprine use
	Hemoglobin and Hematocrit	X	X	Anemia
Acute Phase Reactants	Platelet	X	X	Increased with inflammation or decreased with treatment, e.g. azathioprine
	C-reactive protein and sedimentation rate	X	X	If elevated may correlate with disease activity
Stool studies	Stool for culture, ova and parasites, and *Clostridium difficile* toxin	X	X	Rule out infectious cause of diarrhea
Nutritional status	Iron, ferritin, TIBC, vitamin B12, and folate levels		X	Decreased absorption or increased iron loss leading to anemia
	Albumin and Prealbumin		X	Decreased with poor nutritional status and with protein losing enteropathy
	Vitamin D		X	Decreased secondary to malabsorption, small bowel resection or steroid impairment of Vitamin D metabolism, measure when initiating steroid therapy
Complications	Liver Function Tests	X	X	Performed to rule out sclerosing cholangitis
	BUN, creatinine	X	X	Monitor renal function

Diagnosis	Lactoferrin and fecal calprotectin		X	Surrogate marker for bowel inflammation, may distinguish between flare of Crohn's disease and symptoms of irritable bowel syndrome
	Escherichia coli outer membrane porin (Anti-OmpC), antibodies to *Saccharomyces cerevisiae* (ASCA), and perinuclear antineutrophil cytoplasmic antibody		X	Distinguish between Crohn's disease and ulcerative colitis

Sources: (8, 11, 12)

Original, Print

Figure 1. Colonoscopic images showing erythematous and friable mucosa with numerous pseudopolyps.

Figure 2. Gross anatomical specimen and histological sections of a patient with Crohn's disease.

A. Gross anatomical photo of patient with ileocolonic Crohn disease. Note the sharp demarcation between the cobblestone mucosa of the involved segment and the grossly normal ileal and colonic mucosae.

B. Transmural inflammatory distribution in Crohn disease. The majority of mucosa in the photo is mildly inflamed with minimal crypt distortion. On the right there is a sharp demarcation between the intact mucosa and an ulcer with muscular inflammation. There is transmural inflammation, involving muscularis propria (arrows) and the junction of muscularis propria and subserosa (arrowheads). These lymphoid aggregates with germinal centers have a string of beads appearance.

C. Early fissure invading the submucosa consisting of a cleft in the tissue with lining inflammation (arrow).

D. Intramucosal granuloma. Note the multinucleated giant cells (arrowhead).

Figure 3. CT images showing inflamed ileum.

Figures 1 and 2a Original, Print
Figures 2b, 2c, 2d, and 3 Original, Online only

Table 6. Accuracy of common diagnostic tests for active small bowel Crohn's disease †

Test	Sensitivity (%)	Specificity (%)	Positive likelihood ratio ‡ *	Negative likelihood ratio ‡ *	Positive predictive value (%) *	Negative predictive value (%) *
Individual test						
CE	83	53	0.38	0.07	27.9	93.4
CTE	82	89	1.6	0.04	62.0	95.7
CI	74	100	∞	0.06	100	94.6
SBFT	65	94	2.4	0.08	70.4	92.4
Pairs of tests						
CE + CTE	92	53	0.43	0.03	30.0	96.8
CE+ CI	100	57	0.51	0.0000	33.8	100
CE+ SBFT	92	53	0.43	0.03	30	96.8
SBFT + CI	78	100	∞	0.05	100	95.4
CTE + CI	84	94	3.0	0.03	75.4	96.4
CTE + SBFT	85	94	3.1	0.04	75.6	96.6

CE: Capsule endoscopy, CTE: CT enterography, CI: Colonoscopy with ileoscopy, SBFT: Small bowel follow-through

† Involves 28% of all patients with Crohn's disease

‡ Weighted for prevalence

* Calculated from sensitivity and specificity

Assume prevalence of 0.18% or approximately 1 and 556

Source: (13)

Original, Print

Table 7. Comparison of various diagnostic tests for Crohn's disease

Test	Comment
Capsule Endoscopy	Better yield for non-stricturing small bowel CD 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
CT enterography	Permits visualization of the bowel wall and lumen; ionizing radiation
CT scan	Reveals intraintestinal inflammation and extraintestinal manifestations; ionizing radiation
MR enterography	Permits visualization of the bowel and lumen. Expensive. No ionizing radiation.
MRI	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)
Ultrasound	Detects increase in vacular flow, abscess, sinus tracts, and lymphadenopathy

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Table 8. Accuracy of common radiological 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 scan	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
Ultrasound	89.7	95.6	4.4	0.02	81.6	97.5

† Includes both Crohn's disease and ulcerative colitis

‡ Weighted for prevalence

* Calculated from sensitivity and specificity

Assume prevalence of 0.18% or approximately 1 and 556

Source: (40)

Original, Print

Table 9. Preventative measures in patients with Crohn's disease

Treatment modality	**Preventive measure**
All therapies	Stop smoking
	Avoid NSAIDs and oral contraceptives as these medications are associated with exacerbation of symptoms
	Stay up-to-date with routine immunizations, e.g. influenza and Pneumovax
	Obtain pregnancy test in women of child-bearing age
Anti-tumor necrosis factor therapy	Obtain PPD and chest x-ray prior to initiating therapy. Update immunizations including for hepatitis B.
Corticosteroids	Baseline bone density DEXA scan, calcium and vitamin D supplementation, and consider bisphosphonate therapy
Sulfasalazine and methotrexate	Folic acid supplementation

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Table 10. Mesalamine products commonly used for Crohn's disease

Name	Generic name	Location of action	Dose	Cost per year †
Apriso	Mesalamine	Colon	0.375 g ER, 1.5 g by mouth every morning	$ 2831.76
Asacol Asacol HD (Delayed release)	Mesalamine	Colon and terminal ileum	400 mg and 800 mg tabs 800 mg by mouth three times a day	$ 5083.20
Canasa (Suppository)	Mesalamine	Rectum	1000 mg supp 1000 mg per rectum at bedtime	N/A ‡
Colazal (5-ASA + inert carrier)	Balsalazide	Colon	750 mg tabs 2.25 g by mouth three times a day	$ 5399.52
Dipentum (2 molecules of 5-ASA)	Olsalazine	Colon	250 mg tabs 500 mg by mouth twice a day	$ 3114.60
Lialda (multi-matrix system)	Mesalamine	Colon	1.2 g tabs 2.4-4.8 g by mouth once a day	$ 7944.72
Pentasa (pH controlled)	Mesalamine	Small bowel, Ileum, Colon	250 mg and 500 mg tabs 1000 mg by mouth four times a day	$ 6967.68 $ 7878.72
Rowasa (Rectal enema)	Mesalamine	Left colon	4 g/60 mL susp 4 g per rectum at bedtime	N/A ‡
Sulfasalazine	Sulfasalazine	Colon	500 mg tabs 2 g/day by mouth four times a day	$ 727.44

None of the above products are FDA approved for Crohn’s disease.

† Calculated from www.drugstore.com

‡ Usually only prescribed for short duration (8 to 12 weeks)

Table 11. Immunomodulator therapy for Crohn's disease

Name	Dose	Common side effects	Black box warning	Monitoring	Cost per year †
6-mercaptopurine	50 mg by mouth daily, (Max: 1.5 mg/kg/day)	Myelosuppression, hepatic toxicity, immunosuppression, hepatic encephalopathy, pancreatitis, rash, hyperpigmentation	None	Creatinine at baseline, complete blood count with differential weekly during induction, and weekly liver enzyme tests at induction	$ 1155.88
Azathioprine	50 mg by mouth daily, (Max: 2.5 mg/kg/day)	Gastritis, nausea, and vomiting. May cause pancreatitis leukopenia anemia thrombocytopenia	Chronic immunosuppression increases risk of neoplasia.	Creatinine at baseline, complete blood count weekly for one month, then every 2 weeks for 2 months, then monthly and when dose change, and liver enzyme tests	$ 335.88 50 mg/day
Budesonide	9 mg daily every morning for up to 8 weeks (induction)	Diarrhea, nausea, arthralgias, headache, respiratory tract infection, sinusitis	None	Signs and symptoms of hypercorticism and adrenal suppression with chronic therapy	$2494.02 ‡
Methotrexate	25 mg SC/IM weekly	Alopecia, photosensitivity, rash, diarrhea, anorexia, nausea and vomiting, stomatitis. May also cause hyperuricemia, gastrointestinal hemorrhage, myelosuppression, hepatotoxicity, lung fibrosis, and renal failure	Fetal death and congenital abnormalities (not recommended for use by women of childbearing age), hepatotoxicity, fibrosis, and cirrhosis with prolonged use, malignant lymphoma may occur.	Complete blood count with differential and platelet count baseline then monthly, blood urea nitrogen, creatinine, and liver enzyme tests at baseline then every 4-8 weeks	$ 124.95
Prednisone	20-40 mg daily	Hypertension, fluid retention, hypernatremia, risk for infection, osteoporosis, depression	None	Blood pressure, electrolyte panel, blood glucose, mental status, ophthalmic exam (with prolonged therapy), bone density DEXA test	$190.68
Antitumor necrosis factor agents					
Adalimumab (Humira)	160 mg SC x1 at wk 0, then 80 mg SC x 1 at wk 2, then 40 mg SC q2wk.	Injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), Infections, TB, Malignancies (lymphoma), autoantibodies/Lupus-like syndrome.	Active tuberculosis, reactivation of latent TB, invasive fungal infections	PPD and chest x-ray at baseline; monitor for signs and symptoms of tuberculosis, monitor for signs and symptoms of active hepatitis B (in those who are carriers of HBV)	$ 20,942.28
Certolizumab Pegol (Cimzia)	400 mg SC x 1 on wk 0, 2, 4 then 400 mg SC q4wk	Injection site reactions, Upper respiratory tract infection, headache, hypertension, rash, infections.	Active tuberculosis, reactivation of latent TB, invasive fungal infections, lymphoma and other malignancies	PPD and chest x-ray at baseline; monitor for signs and symptoms of tuberculosis, monitor for signs and symptoms of active hepatitis B (in those who are carriers of HBV)	$ 21,095.76
Infliximab (Remicade)	5 mg/kg IV x 1 at 0,2 and 6 wk f/b q8wk	Infusion related reactions (dyspnea, flushing, headache, rash, chest pain, hypotension, pruritus, urticaria, anaphylaxis)	Active tuberculosis, reactivation of latent TB, invasive fungal infections, hepatosplenic T cell lymphoma	PPD and chest x-ray at baseline; monitor for signs and symptoms of tuberculosis, monitor for signs and symptoms of active hepatitis B (in those who are carriers of HBV), dermatologic exams in patients with psoriasis	$ 14,108.22 (70 kg body wt) 5 mg/kg q8wk

		Delayed reaction (serum sickness, myalgia, arthralgia), Infections, pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection, autoantibodies/Lupus-like syndrome, lymphoma.			

† Calculated from www.drugstore.com

‡ 8 week course of therapy

Invasive fungal infection: histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis

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