

Inflammatory Bowel Disease: Epidemiology, Evaluation, Treatment, and Health Maintenance

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The incidence and prevalence of inflammatory bowel disease are rising. Crohn's disease and ulcerative colitis each have distinct features. Treatments are changing rapidly, and there are many new drugs in the pipeline. Health maintenance also plays a key role in the care of this patient population.

A former medical instructor at Duke often declared, "A happy rectum is a happy patient." Spending a few minutes chatting with a patient who has active inflammatory bowel disease (IBD) with proctitis will drive home this point. Indeed, this idea is not new. Even in the 17th century, efforts to calm the rectum were emphasized; one historical treatment was rectal fumigation in which "smoke enema... was blown by the surgeon through the broken stem of a pipe." Eventually, the innovation of a machine fumigator "eliminated the need for a surgeon to blow the smoke" [1]. Fortunately, alternative therapies are now available, yet the desperation of such a patient is unchanged!

The broad category IBD includes both ulcerative colitis (UC), first described in the mid-1800s, and Crohn's disease (CD), first described in the early 1900s. Both conditions are marked by episodes of relapse and remission [2]. The exact cause of these conditions is unknown, but it is theorized that CD and UC occur in response to an environmental factor or exposure and/or an alteration in the gut microbiome in a genetically susceptible patient [3].

The incidence and prevalence of IBD have been increasing worldwide in the past few decades in both the adult and pediatric populations [4]. The incidence of UC is highest in Northern Europe, at 24 cases per 100,000 person-years; for CD it is highest in Australia, at 29 cases per 100,000 person-years [4]. IBD has a lower prevalence in developing nations; however, as a nation develops, UC will emerge first, followed by the eventual onset and growth of CD. Both diseases are likely to occur between the 2nd and 4th decades of life [4]. A bimodal peak of onset was described in the past, but this has not been seen in more recent studies. The disease incidence is now relatively equal between males and females [5].

UC involves the colon alone, while CD can involve the bowel anywhere from the mouth to the anus (although typically it involves the ileum and/or colon). Both conditions can be associated with extraintestinal manifestations including arthritis, dermatologic symptoms, kidney stones, osteo-

penia or osteoporosis, vitamin deficiencies, and liver diseases such as primary sclerosing cholangitis [6].

In terms of symptoms, UC presents with bloody diarrhea, lower abdominal pain, and tenesmus, as the rectum is always initially involved. It is typically the rectal involvement that is most troublesome to UC patients. The rectum is intended to store stool until it is socially acceptable to defecate; however, with active inflammation, this ability is markedly reduced, leading to increased stool frequency, difficulty emptying the rectum, and ultimately fecal accidents. The inflammation in UC is continuous and is confined to the lining of the bowel wall.

The clinical presentation of CD can be variable. In some patients, the symptoms of CD are more subtle than in UC, with abdominal pain and typically nonbloody diarrhea; at other times, CD is more severe, as it can penetrate through the bowel wall and lead to fistula formation, strictures, and abscesses. CD involves the bowel in a patchy fashion, with "skip" lesions, and it can affect the rectum as well. Some more severely affected patients have enterocutaneous fistulas or even rectovaginal fistulas.

To diagnose IBD, clinicians must consider other possible causes such as infectious causes (*Clostridium difficile* infection, yersinia, or other fecal pathogens), vascular causes, and medication-related causes (use of nonsteroidal anti-inflammatory drugs [NSAIDs]). In addition, it is important to perform an endoscopy and collect biopsies, which should be reviewed by a gastroenterology pathologist. Imaging with computed tomography or magnetic resonance enterography also plays a role in diagnosis, as they are helpful in defining the extent and severity of inflammation in both UC and CD. In CD, such imaging is also helpful for identification of strictures and fistulae. Magnetic resonance enterography is preferred over computed tomography to avoid radiation exposure. Prior to treatment, much time is spent reviewing imaging and biopsy results to ensure that masqueraders of IBD—such as endometriosis, ischemia, NSAID enteropathy, and infection—are identified and dealt with appropriately.

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Treatment

The goals of IBD treatment are to minimize corticosteroid use and surgery and to induce clinical and endoscopic remission rapidly with minimal side effects. Currently, several classes of drugs are available for treatment of CD and UC (see Table 1).

Steroids have little role in the modern treatment of IBD, and their use should be limited to induction of remission at the time of diagnosis or, rarely, to treatment of an exacerbation. The use of budesonide preparations minimizes the side effects of steroids, but this should still be a short-term bridge to safer long-term treatment options.

Remission is the goal of therapy in the treatment of IBD, and those patients who achieve endoscopic and/or histological (“deep”) remission are more likely to remain in remission. The growing use of biologic agents has led to the concept of using drug levels and antibodies (when available) to optimize drug dosing before considering an agent or class of medication to be a treatment failure. An ongoing study will help to determine whether aggressive treatment of CD and achievement of deep remission improves quality of life, reduces hospital admissions, reduces complications, and/or leads to increased side effects of medications [7].

The backbone of treatment for UC remains 5-aminosalicylic acid (5-ASA) compounds, which are delivered in various forms. Once or twice daily dosing of 5-ASA is just as effective as more frequent dosing and improves compliance [8]. Use of 5-ASA in topical form should be considered in conjunction with oral therapy for ongoing activity or as monotherapy for more distal disease. This therapy, in the form of suppositories or enemas, will often bring symptoms under control by calming the rectum. For patients who fail to achieve remission with topical and oral 5-ASA and steroids, who fail a steroid taper, or who require intermittent use of steroids, the use of azathioprine is effective and allows steroids to be avoided in 30% of patients. An ongoing trial

funded by the National Institutes of Health is looking at the use of subcutaneous methotrexate in UC, and interim data analysis looks promising [9].

The anti-tumor necrosis factor (anti-TNF) agents—including infliximab, adalimumab, and golimumab—are effective for the treatment of steroid- and azathioprine-refractory UC and have supplanted cyclosporine for treatment of severe steroid-refractory UC prior to consideration of colectomy. The newest biologic agent, vedolizumab, an $\alpha 4\beta 7$ integrin inhibitor, prevents transmigration of activated T-cells through capillaries into surrounding tissue. This medication is gut-specific and does not appear to lead to progressive multifocal leukoencephalopathy, a lethal brain disease that has been associated with its sister drug natalizumab in patients exposed to John Cunningham virus (JCV). Vedolizumab appears most effective in UC patients with left-sided disease who have not been treated with anti-TNF agents; greater than 50% symptom improvement has been demonstrated in this group [10]. Approximately 15% of patients with UC will present with fulminant or subfulminant colitis. Aggressive dosing of infliximab may avert the need for colectomy in the majority of these patients.

Treatment of CD is dictated by the severity of inflammation, the presence of perianal disease, and/or the presence of stricturing and fistulization. Unlike in UC, 5-ASA has little to no role in the treatment of CD [11]. Steroids may be used short-term in CD to improve symptoms or as a bridge to medications with a better safety profile. Azathioprine and methotrexate are associated with a 30% likelihood of induction and maintenance of steroid-free remission. The availability of biologic agents—infliximab, adalimumab, certolizumab, and vedolizumab—have revolutionized treatment of moderate to severe CD, and the addition of an immunomodulator (such as azathioprine or methotrexate) appears to improve the efficacy and durability of these agents [12]. If possible, use of azathioprine should be avoided in men under the age of 30 years due to the risk of a very rare hepa-

TABLE 1.
Pharmacologic Options for Treatment of Inflammatory Bowel Disease

	Crohn's disease	Ulcerative colitis	Disease severity	Induction of remission	Maintenance of remission	Monitoring
5-ASA (mesalamine)	No	Yes	Mild to moderate	Yes	Yes	Creatinine
Steroids (prednisone, budesonide, methylprednisolone)	Yes	Yes	Mild, moderate, or severe	Yes	No	Infections, bone health, glaucoma, diabetes, avascular necrosis, mood disorders/psychosis
Immunomodulators (AZA, 6MP, MTX)	Yes	Yes	Moderate or severe	Yes ^a	Yes ^a	Complete blood count, complete metabolic panel, infections, pancreatitis (AZA, 6MP), pregnancy prevention (MTX), NMSC, cervical dysplasia
Anti-TNF (IFX, ADA, CTZ, golimumab)	Yes	Yes	Moderate or severe	Yes	Yes	Infections including TB, complete metabolic panel, signs/symptoms of infusion reaction, drug and antibody levels (IFX and ADA only)
Anti-integrin (vedolizumab)	Yes	Yes	Moderate or severe	Yes	Yes	Infections including TB, signs/symptoms of infusion reaction

^aUsually used in combination with a biologic agent.

Note. 5-ASA, 5-aminosalicylate; 6MP, 6-mercaptopurine; ADA, adalimumab; AZA, azathioprine; CTZ, certolizumab; IFX, infliximab; MTX, methotrexate; NMSC, non-melanoma skin cancers; TB, tuberculosis; TNF, tumor necrosis factor.

tosplenic T-cell lymphoma. Methotrexate is contraindicated in women of childbearing potential due to marked congenital abnormalities and abortifacient effects. Vedolizumab is probably less effective for CD than for UC, but it is still effective in some patients. In CD patients who are anti-TNF naïve, vedolizumab is associated with a 50% likelihood of inducing clinical remission. In CD patients who have received prior anti-TNF therapy, vedolizumab induces clinical remission in about 15% of patients [13]. Vedolizumab is also slower to produce results than other biologic agents; therefore, patients treated with vedolizumab may demonstrate an improved response after 12 weeks of therapy.

Ustekinumab, an interleukin 12/23 inhibitor that is not yet approved by the US Food and Drug Administration for treatment of IBD, leads to improvement of symptoms in 40%–50% of patients with CD who fail to respond to other biologic agents [14]. Knowledge of the association between perturbations in the immune response and development of IBD is growing and leading to promising new treatments.

Health Maintenance

Attention to health maintenance is a crucial part of caring for IBD patients; this includes preventing complications from the disease itself, preventing infections resulting from the disease or from treatment, and minimizing adverse effects from IBD medications. Links to IBD health maintenance checklists for providers are listed in Table 2.

Serious infection is one of the most feared complications of the immunosuppressing IBD treatments, occurring in 3%–6% of patients on anti-TNF and immunomodulator therapy per year [12, 15]. As these therapies are the most effective treatments available for the management of CD and moderate to severe UC, the risks are outweighed by the benefits in most patients. However, attention to infection surveillance, prevention, and prompt treatment are vital. Additionally, it is important to note that some IBD patients seem to be at increased risk of infections independent of immunosuppressive medications, likely due to dysregulation of the immune system, systemic inflammation, and/or malnutrition [16, 17].

Infection prevention begins at the time of IBD diagnosis. Regular age-appropriate vaccinations should be reviewed and brought up to date at the time of IBD diagnosis, even if an immunosuppressive regimen is not immediately planned (see Table 3). Particular attention should be paid to live vaccines—such as the measles, mumps, and rubella vaccine and the varicella zoster virus vaccine—as these vaccinations cannot be administered once immunosuppression is initiated or within 4 weeks prior to initiation of immunosuppression. Annual inactive influenza vaccination is recommended for all IBD patients.

Vaccination for pneumonia is also recommended, but this vaccine is less effective when the patient is immunosuppressed, so ideally it should be administered at the time of IBD diagnosis. Vaccination for pneumonia is still possible after initiation of immunosuppression, but it requires

TABLE 2.
IBD Health Maintenance Checklists for Providers

- Cornerstones IBD Checklist for Monitoring & Prevention: <http://cornerstoneshealth.org/checklist/checklist-for-ibd.pdf>
- ECCO Inflammatory Bowel Disease checklist: www.ecco-ibd.eu/images/6_Publication/6_3_ECCO%20Guidelines/MASTER_OI_Consensus_UpdateCheckList_OI_guidelines_2014.pdf

Note. ECCO, European Crohn's and Colitis Organisation; IBD, inflammatory bowel disease.

2 separate injections. For maximum efficacy, pneumococcal vaccination (PCV13, Prevnar) should be given first, followed 8 weeks later by the pneumococcal polysaccharide vaccine (PPSV23, Pneumovax); after the initial vaccination, a PPSV23 booster should be administered every 5 years [17].

Prior to initiation of treatment with an immunosuppressing medication, the patient's risk for opportunistic infections should be evaluated. All patients should be tested for latent tuberculosis, either with a skin test of purified protein derivative and a chest radiograph or with the QuantiFERON TB assay. Hepatitis B virus (HBV) status should be assessed by testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (HBsAb). Patients who are positive for anti-HBc, with or without HBsAg positivity, will generally require antiviral prophylaxis with entecavir or tenofovir to prevent HBV reactivation if they require treatment with prednisone at a dose of more than 10 mg daily for 4 weeks or more and/or a biologic agent with or without an immunomodulator [19]. If HBsAb is positive and HBsAg and anti-HBc are both negative, then the patient is already immune due to prior vaccination, and no further testing or treatment is required. A full discussion of the complexities of treatment for latent tuberculosis

TABLE 3.
Screening and Vaccination Recommendations From the European Crohn's and Colitis Organisation

Infection	Vaccination	Screening
Hepatitis A virus	X ^a	X ^a
Hepatitis B virus	X ^b	X
Hepatitis C virus	—	X
Influenza virus (seasonal influenza and influenza A)	X	—
Pneumococcal infection	X	—
Human papilloma virus	X	X
Varicella zoster virus	X ^b	X
Tuberculosis	—	X
Human immunodeficiency virus	—	X
Epstein-Barr virus	—	X
Measles	X	X ^a
Pertussis	X	—
Poliomyelitis	X	—
Diphtheria-tetanus	X	—
Strongyloidiasis	—	X ^a

^aAt the discretion of the treating physician.

^bFor seronegative patients.

Source: Reprinted with permission from Christensen KR, et al [18].

and/or HBV is beyond the scope of this article, but evaluation and treatment should be performed in conjunction with expert consultation as appropriate.

Health maintenance in patients with IBD involves prevention of complications from the disease process itself, as well as prevention of side effects associated with medications. Bone health should be addressed, particularly in those previously treated with steroids, although patients with CD are at risk for osteoporosis independent of steroid use [20]. Smoking is associated with increased risk for complications in CD, decreased response to anti-TNF therapy, and increased risk of most malignancies, so smoking cessation should be addressed at each visit. Use of immunomodulators is associated with a slightly increased risk of cervical dysplasia and non-melanoma skin cancer; therefore regular Pap smears should be performed in women, and human papillomavirus vaccination is recommended for males and females ages 9–26 years. Annual skin examination by a dermatologist is also recommended for immunocompromised patients.

Nutritional counseling and supplementation may be necessary in many patients with IBD, particularly those with more severe disease. Not only can annual monitoring of serum albumin, vitamin D, vitamin B12, folate, and iron guide recommendations for vitamin and mineral replacement, but deficiencies in these levels may also suggest active inflammation [21]. Other specific patient populations, such as CD patients with stricturing or fistulizing disease or patients who have had bowel resection, may benefit from referral to a nutritionist with expertise in IBD to help ensure understanding of how diet may impact symptoms.

Finally, patient education is crucial to IBD health maintenance (see Table 4). Patients who are equipped with accurate information are more likely to adhere to therapy and health maintenance measures. By providing educational materials in the patient's native language and providing resources in a variety of presentation styles, clinicians can provide them with the best chance of understanding their disease and its treatments. NCMJ

TABLE 4.
Patient Education Resources

- Crohn's & Colitis Foundation of America: www.ccf.org
- You and IBD: www.youandibd.com
- American College of Gastroenterology, inflammatory bowel disease: <http://patients.gi.org/topics/inflammatory-bowel-disease/>

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