

# Osteopathic Primary Care of Patients With Inflammatory Bowel Disease: A Review

Jack D. Bragg, DO

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Address correspondence to  
Jack D. Bragg, DO,  
Division of Gastroenterology  
& Hepatology,  
School of Medicine,  
University of Missouri  
Health System,  
1 Hospital Dr, DC043.00,  
Columbia, MO 65201-5276.

E-mail:  
braggj@health.missouri.edu

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**Ulcerative colitis and Crohn disease are relatively common inflammatory diseases of the gastrointestinal tract that have unknown causes. A combination of abnormalities in genetics, the immune system, and the microbiome of the gut may cause inflammatory bowel disease (IBD). The majority of patients with IBD are in their late teens or early twenties. Most present to their primary care physician for a diagnosis. Although gastroenterologists and surgeons do most of the endoscopy and management of IBD, these patients require a great deal of health maintenance that many never receive. Osteopathic primary care physicians can play a pivotal role in the care of patients with IBD by understanding what areas of the body are affected by the disease and what screening and monitoring are needed to keep patients healthy with the highest quality of life possible.**

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Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn disease (CD) and affects a large portion of the US population. The majority of patients with IBD have either UC or CD, are in their late teens or early twenties, and have a family history of IBD. The incidence and prevalence of UC are 2.2 to 19.2 per 100,000 person-years and 238 per 100,000 population, respectively, and of CD are 3.1 to 20.2 per 100,000 person-years and 201 per 100,000 population, respectively.<sup>1(p1941)</sup> Idiopathic IBD comprises conditions characterized by chronic or relapsing immune activation and inflammation within the gastrointestinal tract.

The cause of UC and CD is unknown, but current evidence<sup>2</sup> indicates that there are probably abnormalities in 3 body systems involved in the pathogenesis of IBD: genetics, immune system, and the microbial milieu of the colon. First, there are now more than 100 genes linked to CD, UC, or both.<sup>2</sup> Second, perturbations of both the innate and adaptive immune system help to induce a continuous inflammatory process in the gut that causes most of the intestinal damage seen in patients with IBD. Most of the current medications used to treat patients with IBD are aimed at halting the abnormal immune function in the gut. Third, the microbiome in the gut of the individual affected with IBD plays an important role in the pathogenesis of IBD. By providing antigens that cross the epithelial barrier in the gut and initiate the inflammatory process in an individual with the genetic and immune abnormalities already mentioned, the bacterial population in the colon plays a major role in the etiologic process of IBD.

For the most part, UC affects only the mucosal layer of the colon, but CD is transmural and can be found anywhere from the mouth to the anus. This characteristic explains why

patients with CD may develop fistulas and abscesses and patients with UC do not.<sup>1(pp1948-1949)</sup>

A 2008 study<sup>3</sup> reported that patients with IBD receive less primary care, fewer screening tests, and less maintenance care than patients without IBD. According to a survey-based study by Sinclair et al,<sup>4</sup> gastroenterologists and family physicians believed that vaccines in patients with IBD were the responsibility of the other physician and not themselves. A similar survey by Kane<sup>5</sup> indicated the same attitude in regards to osteoporosis. Gastroenterologists and surgeons do most of the endoscopic diagnosis and management of IBD, but osteopathic primary care physicians can play a major role in the care of patients with IBD by monitoring several areas of their patients' well-being in addition to their bowel function. Areas of concern include anemia, cancer screening, vaccinations, bone health, smoking cessation, and depression.

In the present article, I review the health care issues that osteopathic primary care physicians need to be aware of and address how they can offer the highest quality of care to their patients with IBD.

## Anemia

Up to a third of all patients with IBD have iron deficiency anemia, anemia of chronic disease, or both.<sup>5</sup> Symptoms of anemia can include fatigue, headache, dyspnea, and poor physical endurance. According to Reinisch et al,<sup>6</sup> gastroenterologists consider anemia a "low priority" in the care of patients with IBD. However, a 2004 review article<sup>7</sup> indicated that management of anemia in patients with IBD can significantly improve the quality of life of many patients and therefore warrants the attention of physicians.

The World Health Organization defines anemia as hemoglobin concentration of less than 12 g/dL in non-pregnant women and less than 13 g/dL in men.<sup>8</sup> Physicians must distinguish between iron deficiency anemia and anemia of chronic disease because treatment differs

for each. The evaluation of anemia should begin with iron studies to include serum iron, ferritin, reticulocyte count, transferrin saturation, and a marker of inflammation such as C-reactive protein or the erythrocyte sedimentation rate.

Patients may have iron deficiency without anemia. Iron stores have to be depleted before the hemoglobin level begins to fall. Body iron stores can best be determined by serum ferritin level in the absence of inflammation and transferrin saturation in the presence of inflammation. Patients with iron deficiency anemia and no inflammation will have a ferritin level below 30 ng/mL, which defines iron deficiency anemia. Patients with iron deficiency anemia and inflammation will have a transferrin saturation lower than 20%.

In the case of iron deficiency without anemia, the hemoglobin level is normal. The only symptom may be chronic fatigue because iron is required for the enzymes involved in oxidative metabolism. In the case of iron deficiency anemia, the whole blood cell count would show a low normal mean corpuscular hemoglobin level of less than 27 pg/cell. In the case of anemia due to chronic disease, inflammation must be present as reflected in an elevated C-reactive protein or erythrocyte sedimentation rate, the hemoglobin will be decreased, and transferrin saturation will be below 20%. Ferritin will be normal or increased at less than 100 ng/mL. When iron deficiency anemia and anemia of chronic disease coexist, there must be inflammation, low hemoglobin level, low transferrin saturation, and an intermediate or low ferritin level (20-100 ng/mL) (*Table*).

To distinguish between the 2 types of anemia in cases where the numbers are not clear, Reinisch et al<sup>6</sup> suggest performing the reticulocyte hemoglobin content test and measuring zinc protoporphyrin. Oustamanolakis et al<sup>9</sup> provide a more in-depth discussion of current and future laboratory tests to evaluate anemia.

Management of mild to moderate iron deficiency anemia (hemoglobin >10 g/dL) should begin with oral iron replacement. Most oral iron is an inorganic ferrous

salt and is oxidized in the lumen or mucosa of the small bowel. Many patients have poor tolerability of oral iron and may experience gastrointestinal upset from it. If tolerated well, it may still take 2 to 3 weeks for the patient's hemoglobin level to increase and up to 2 months to reach normal values. Replenishment of iron stores can take 6 months.<sup>7</sup>

Intravenous iron preparations are used in patients with IBD who do not tolerate or do not respond to oral iron, in patients with hemoglobin levels less than 10 g/dL, or in patients also being treated with erythropoietin for anemia of chronic disease. There are different preparations of intravenous iron, and their use in patients with IBD has been well studied and appears to be safe, effective, and faster than oral iron.<sup>7</sup>

Once iron stores have been replenished and there remains a substantial component of anemia that is caused by anemia of chronic disease, erythropoietin therapy is indicated. Anemia of chronic disease is secondary to chronic activation of cell-mediated immunity, and it is essential to bring the IBD into remission.<sup>5</sup>

## Cancer Screening

### Cervical Cancer

Screening women for cervical cancer using the Papanicolaou (Pap) test has reportedly reduced the incidence of that malignancy by 70%.<sup>10</sup> Human papillomavirus (HPV) is the most important risk factor for cervical cancer. Various host factors such as age, nutritional status, immune function, and smoking are thought to enhance the incorporation of the DNA from the virus into the host genome.<sup>11</sup> There is a higher prevalence of abnormal Pap test results among women with IBD, which is associated with treatment with immunomodulators.<sup>4</sup> Kane et al<sup>12</sup> reported in a study of 40 patients with IBD that the incidence of an abnormal Pap test result was 42.5% compared with 7% among age-, race-, and parity-matched controls. Immunomodulators were a significant risk factor in this group of female patients.

**Table.**  
**Diagnosis of Iron Deficiency and Anemia<sup>a</sup> in Patients With Inflammatory Bowel Disease**

Measure	Iron Deficiency	Iron Deficiency + ACD	ACD
Inflammation	Y or N	Y	Y
Transferrin saturation	<20%	<20%	<20%
Mean corpuscular hemoglobin	<27 pg	NA	NA
Ferritin, ng/mL	<30	30-100	>100

<sup>a</sup> Anemia defined as hemoglobin level <12 g/dL in females and <13 g/dL in males.

**Abbreviation:** ACD, anemia of chronic disease.

Primary care physicians can play a vital role in the care of patients with IBD in this area in 2 ways. First, physicians should follow the recommendations from the American College of Obstetrics and Gynecology<sup>13</sup> and include annual screening for cervical dysplasia in women younger than 30 years. Women aged 30 years or older who have had 3 normal consecutive Pap test results should undergo a Pap test every 2 to 3 years. Women who are immunocompromised, including HIV-infected patients and those who have received an organ transplant, should undergo a Pap test twice the first year that they are immunocompromised and every year thereafter.<sup>13</sup>

Second, primary care physicians should recommend HPV vaccination to their patients. The HPV vaccine is indicated for the prevention of cervical dysplasia caused by HPV types 16 and 18 as well as 6 and 11, which are associated with genital warts. It is recommended for adolescent girls older than 9 years and women aged 26 years or younger before the beginning of sexual activity but also for those who have already engaged in intercourse.<sup>11</sup> Women with IBD who are currently on an immunomodulator should be vaccinated regardless of sexual activity and should receive annual Pap testing according to the American College of Obstetrics and Gynecology's guidelines.

### Colon Cancer

Patients with a history of CD or UC for 8 years or longer are at an increased risk of adenocarcinoma of the colon.<sup>4</sup> Jess et al<sup>14</sup> reported a decline in the incidence of adenocarcinoma of the colon in these patients and speculated that current medical treatment of patients with IBD has resulted in a lower prevalence of inflammation in colonic mucosa, resulting in the decline of the incidence of adenocarcinoma of the colon.

The American Gastroenterology Association recommends a yearly colonoscopy with at least 32 biopsies after a patient has had UC or CD for 8 years.<sup>15</sup> Once the pathologist's report is available, primary care physicians should pay particular attention to the degree of inflammation or activity and the presence or absence of dysplasia. Optimal surveillance intervals for those without substantial inflammation and no dysplasia are unknown. Gastroenterologists typically request follow-up in 1- to 3-year intervals unless there are risk factors such as accompanying primary sclerosing cholangitis, diagnosis of IBD at a young age, or strictures, especially in patients with UC or the presence of many inflammatory pseudopolyps. Individuals with proctitis, proctosigmoiditis, or CD that covers less than one-third of the colon are not recommended to have surveillance.

### Skin Cancer

Both melanoma and nonmelanoma skin cancers are more common in patients with IBD. There are several risk factors for skin cancers, such as extensive exposure to sunlight. Both its intensity, in the case of melanoma, and its cumulative effect, in the case of skin cancers, are important factors. Solid organ transplant, including recipients taking immunosuppressive medication are at higher risk for both of these cancers.<sup>16</sup>

Several studies<sup>17-19</sup> have documented skin cancers in patients with IBD, especially those taking thiopurines and an even higher rate in those treated with thiopu-

rines and anti-tumor necrosis factor biologics.<sup>4</sup> In a 2012 retrospective study, Long et al<sup>16</sup> found that there was an increased incidence of melanoma in patients with IBD treated with anti-tumor necrosis factor biologics, though the absolute risk remained low at 57 per 100,000 person-years compared with 44.1 per 100,000 in the non-IBD population.

Long et al<sup>16</sup> also found the increase in the incidence of skin cancers is associated with thiopurines.<sup>16</sup> Absolute risk of skin cancers in this group is 912 per 100,000 person-years as opposed to 623 per 100,000 in the non-IBD population. The benefits of these medications far outweigh the associated risks, and the emphasis should be on prevention of sun damage. Prevention is another area in the treatment of patients with IBD where well-informed primary care physicians can make a difference. The use of sunscreen, sun avoidance, and sun-protective clothing in patients taking these medications is critical. A 2011 study<sup>20</sup> showed that sunscreen can reduce the occurrence of melanoma and thus reduce the incidence of skin cancers.

A yearly thorough skin examination by the primary care osteopathic internist or family physician in these patients may also detect abnormal lesions early.

### Vaccinations

Many patients with IBD do not receive the vaccinations they should have.<sup>3</sup> With an altered and suppressed immune system, vaccinating against preventable disease should be a priority. Patients receiving immunosuppressive therapy may not mount the antibody response other patients can, and they may need boosters from time to time. There is good evidence that vaccinations provide protection against several common diseases, especially if patients are vaccinated before beginning immunosuppressive therapy.<sup>21</sup> Vaccines are available for diseases including influenza types A and B, pneumococcal pneumonia, and hepatitis A and B and may be free at public health

centers. In addition, patients with IBD need to stay current on their diphtheria and tetanus protection.

Primary care physicians should keep in mind that patients with IBD should not receive any vaccination that is a live virus if they are receiving immunosuppressive drugs because of an impaired immune system. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommended in 2008 that patients receiving low doses of methotrexate ( $\leq 0.4$  mg/kg/wk), azathioprine ( $\leq 3$  mg/kg/d), or 6-mercaptopurine ( $\leq 1.5$  mg/kg/d) for management of IBD are not considered sufficiently immunosuppressed to create vaccine safety concerns and should not have contradictions for receiving the live virus immunizations.<sup>22</sup>

Patients taking any of the biologics such as infliximab, adalimumab, certolizumab, or corticosteroids should be considered immunosuppressed. If they need a live vaccine it should be administered before starting higher dose immunomodulators. There is no agreement on how long patients should discontinue immunosuppressive drugs before being vaccinated, but a period of 1 to 3 months has been suggested.<sup>21</sup>

According to the Centers for Disease Control and Prevention,<sup>23</sup> influenza given parenterally should be given to all patients with IBD every year. The intranasal form of influenza is a live virus vaccination and should be avoided. Tetanus and diphtheria should be administered every 10 years and pneumococcal vaccine should be given to all patients with IBD. A 1-time revaccination is recommended after 5 years in patients aged 65 years or older. The meningococcal vaccine is recommended for adults who are asplenic or have complement deficiencies, military recruits or students living in a dormitory, and individuals traveling to areas endemic for meningococcal disease. Finally, any patient with IBD in a health care–related field or who may be exposed to hepatitis A and or B should be immunized against these viruses.

## Bone Health

Patients with IBD have an increased risk of developing osteoporosis and osteopenia<sup>24</sup> because of the effect of inflammation on the bones, low serum vitamin D levels, and the use of corticosteroids.

The criterion standard for evaluating bone health is to use dual-energy x-ray absorptiometry to determine whether therapy is needed. Patients with IBD who have prolonged corticosteroid use, low-trauma fracture, or hypogonadism or who are postmenopausal should be scanned (*Figure*).<sup>24</sup>

## Smoking Cessation

All patients with IBD should be encouraged to stop smoking cigarettes. The effects of smoking are particularly bad in patients with CD and include having more difficult diseases to control, especially ileal disease, and increased need for steroid treatment and surgery. In addition, patients who use tobacco do not respond as well to medications and have quicker recurrence of disease after surgery compared with their nonsmoking counterparts.<sup>25</sup>

Discontinuing the use of tobacco allows improvement in all of the above areas. The effect of smoking is dose dependent, and a small reduction in tobacco use may help patients with CD.

## Depression Screening

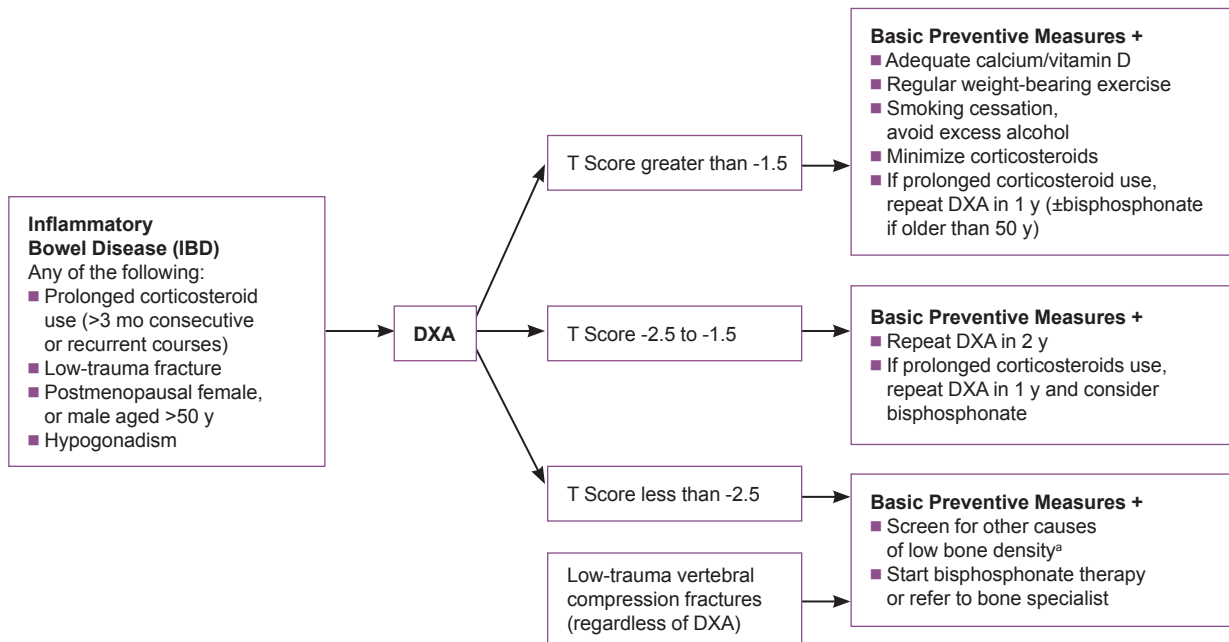
Chronic medical conditions are known to be associated with higher rates of mood disorders and substance abuse.<sup>26</sup> Depressive illness is more prevalent in patients with IBD.<sup>27</sup> Some studies show that as many as 27% of all patients with IBD have been depressed at one time or another.<sup>26</sup> Much of the disability and functional impairment in chronic disease is secondary to mood disorders.

The American College of Preventive Medicine and the US Preventive Services Task Force recommend screening patients with chronic illnesses for depression

DIAGNOSIS OF IBD

BONE HEALTH

PREVENTION AND MANAGEMENT



**Figure.**

Approach for prevention and management of osteoporosis in patients with inflammatory bowel disease (IBD).

Modified with permission from Bernstein et al.<sup>24</sup>

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<sup>a</sup> Screening tests for other causes of low bone density include complete blood cell count, serum calcium alkaline phosphatase, creatinine, 25-hydroxyvitamin D, protein electrophoresis (optional), and testosterone (in males).

*Abbreviation:* DXA, dual-energy x-ray absorptiometry.

when the expertise and ability of the practice allows. The following 2 questions can be used as an effective screening tool<sup>28</sup>:

- Over the past month, have you felt down, depressed, or hopeless?
- Over the past month, have you felt little interest or pleasure in doing things?

Primary care physicians are trained to recognize and manage depression or refer patients to psychiatric care.<sup>28</sup>

**Conclusion**

High quality care of patients with IBD involves a number of specialists. One of the most important physicians is the one who takes care of health maintenance in several different areas. These areas include diagnosis and management of anemia, cancer screening, vaccinations, management of osteoporosis, smoking cessation, and depression screening. Osteopathic primary care physicians are well trained in these areas and should work with gastroenterologists and surgeons to ensure all of their patients with IBD are receiving the best care possible.

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