Routine Health Maintenance and Disease Prevention in Patients with Inflammatory Bowel Disease

Disease prevention and health maintenance is crucial, however patients with inflammatory bowel disease (IBD) do not receive the same rate of preventative interventions as the general population. Vaccine preventable illnesses affect patients with IBD at a higher rate secondary to chronic illness and immunosuppression, yet many patients with IBD go unvaccinated. A lack of awareness regarding the significance of vaccinations, poor insight about the safety, and ambiguity about the gastroenterologists’ role in providing vaccinations may be contributing factors to the lower vaccination rates. Since patients with IBD often identify their gastroenterologist as their primary care provider, gastroenterologists need to specifically define and help coordinate the unique needs of these patients with other healthcare providers. This article highlights recommendations regarding health maintenance issues in patients with IBD including vaccinations, screening for colorectal, skin and cervical cancers, screening for osteoporosis and guidance on smoking cessation.

INTRODUCTION

Inflammatory bowel disease is a chronic gastrointestinal disease that includes both ulcerative colitis (UC) and Crohn’s disease (CD). The course of these diseases is characterized by intermittent relapses. Agents used to manage more aggressive disease include corticosteroids, immunomodulators and biologic agents. It is now recognized that patients with IBD are at an increased risk for a number of different health issues that include infections, osteoporosis, depression, skin and colorectal cancers. The importance of health maintenance and prevention has emerged as a crucial objective in the overall delivery of care. Patients with IBD frequently have a strong relationship with their gastroenterologist and often turn to them for primary care needs and questions. However, data has shown that patients with IBD get less preventative and health maintenance care than non-IBD patients of the same age. This may be due to the fact that the gastroenterologists do not feel it is their job as the specialist, and the primary care physicians often feel uncomfortable managing these issues in patients who are often immunocompromised. It is therefore important for both the gastroenterologist and primary care physician to work closely together to ensure these preventive interventions are carried out properly.
Routine Health Maintenance and Disease Prevention in Patients with Inflammatory Bowel Disease

**Vaccinations**

Though patients with IBD are at risk for infectious complications secondary to the disease and immunosuppression from medical therapy, they tend to be under vaccinated. The reasons for these low vaccination rates are likely multifactorial. Gastroenterologists have reported a lack of knowledge about the importance of vaccinations in this group of patients. Furthermore, gastroenterologist often do not have the vaccines available at their medical practice and feel it is the job of the primary care physician to administer vaccinations. Another barrier to vaccination often raised by patients is the concern of vaccines causing or exacerbating a flare. Fortunately, vaccines have not been shown to lead to flares in patients with underlying rheumatologic diseases or IBD. Patients with IBD who were given the influenza vaccine were not found to have an increased risk for disease flare within four weeks of its administration. Similarly, another study that included 43 patients with IBD on thiopurines did not observe any increase in disease severity attributable to vaccinations. Therefore, inactivated vaccinations should not be withheld from patients for the fear of causing a disease flare.

National guidelines for age appropriate vaccinations should be implemented for patients with IBD, with special considerations given to those who are on, or planning to initiate, immunosuppressive therapy. Luckily, most patients in the United States will have received routine childhood vaccinations. For patients who need to begin treatment with immunosuppressive therapy, delaying live vaccines in order to timely start treatment will be necessary.

All patients with IBD, regardless of immunosuppression, should receive inactivated vaccines (Table 1). The level of immunosuppression will dictate which patients should receive live vaccines. Typically, the level of immunosuppression has been broken down into “low” and “high.” Patients on low-level immunosuppression can safely receive live vaccines while those on high-level should avoid live vaccines. “Low-level” immunosuppression is defined as patients receiving a daily dose of systemic corticosteroids for ≥14 (20mg/day equivalent and within three months of stopping), methotrexate ≤0.4 mg/kg/week and within three months of stopping, azathioprine ≤3.0 mg/kg/day, and 6-mercaptopurine ≤1.5mg/kg/day and within three months of stopping. Patients on the typical IBD doses of methotrexate and thiopurines fall into this category. The Infectious Disease Society of America guidelines consider all patients on anti-tumor necrosis factors (anti-TNF) to have high level immunosuppression and should not receive live vaccines. These guidelines were written prior to the availability of vedolizumab and ustekinumab, but avoidance of live vaccines should likely still apply to ustekinumab. And, given the gut selectivity of vedolizumab, oral live vaccines should probably be avoided.

**Inactivated Vaccinations**

**Influenza Vaccination**

Influenza infection may result in serious life threatening illness and therefore it is recommended that all immunosuppressed patients receive the vaccine. Patients with IBD are felt to be at an increased risk for infection regardless of immunosuppressive treatment. Currently it is recommended that the injectable forms of the influenza vaccines be given, not the live attenuated nasal spray. Yearly vaccination is required secondary to antigenic drift of the virus in order to best provide protection. It is of value to discuss the importance of receiving the influenza vaccination with all patients with IBD because even a partial, blunted response may provide some degree of protection.

**Pneumococcal Vaccination**

Pneumococcal pneumonia is more prevalent in patients with IBD compared to age-matched controls and patients with IBD who are hospitalized secondary to pneumonia tend to have worse outcomes. Certain risk factors such as proton pump inhibitors, anti-TNFs, narcotics, and steroids appear to increase this risk. Recent guidelines recommend that all immunosuppressed patients with IBD receive immunization against pneumococcus, ideally prior to starting immunosuppression. The typical vaccination schedule is to receive a single dose of PCV13 (pneumococcal conjugate vaccine), followed by the PPSV23 (pneumococcal polysaccharide vaccine) 2-12 months later. If the patient has already received the PPSV23 vaccine, then the PCV13 vaccine should be given after one year. A booster PPSV23 should be given five years
Routine Health Maintenance and Disease Prevention in Patients with Inflammatory Bowel Disease

Hepatitis A Vaccination

The incidence of hepatitis A infection (HAV) in the United States has decreased by 95% since the vaccination became available in 1995.¹⁹ Currently, the HAV vaccine is part of the recommended series of childhood vaccines. However, there still remain many unvaccinated adults. Gastroenterologists should inquire about prior vaccination to HAV. If patients are unable to recall, they can be given the vaccine again as there are no known harms of receiving a second dose series of the vaccine. The vaccine is given in a two-part regimen at zero months followed by a second dose at six months. It is not recommended to perform post-vaccination testing as there is a high rate of vaccine response and not all testing methods are reliable for detecting low, but protective anti-HAV concentrations.²⁰

(continued on page 18)
Hepatitis B Vaccination
Hepatitis B virus (HBV) infection can cause both acute and chronic liver disease and have long-term health implications. Patients with IBD are at an increased risk for HBV infection secondary to immunosuppressive therapy, surgery and blood transfusions. Understanding the HBV immunologic status for patients with IBD is of particular importance given the implications and serious repercussions immunosuppressive therapy can have on HBV reactivation.\textsuperscript{21} Testing for HBV infection or prior exposure [hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb)] in all patients with IBD is encouraged, and certainly for those who will need treatment with biologic therapy.

If not already immune, vaccination for HBV is recommended ideally at the time of IBD diagnosis, during disease remission or before starting immunosuppressive therapy.\textsuperscript{22} There are currently two single antigen HBV vaccines (Engerix and Recombivax) and one combined vaccine (Twinrix, HBV and HAV) that are indicated for the adult population.\textsuperscript{23} The typical schedule in which the vaccination should be administered is a dose at 0, 1, and 6 months with the goal to achieve Hepatitis B surface ab >10IU/L. Accelerated vaccination protocols have been established for patients traveling to endemic areas who are at high risk for HBV exposure; these schedules can be applied to patients with IBD who are not immune to HBV prior to starting immunosuppressive therapy if needed. The protocol schedule gives the vaccine at day 0, 7, 21-30, and a booster at 12 months.\textsuperscript{24} Regardless of the regimen used, serologic titers should be checked one to two months after completion of the vaccination series. If no vaccine response is seen (Hepatitis B surface ab >10IU/L), then patients should receive an additional series of either double dose HBV vaccine or the combined HAV/HBV vaccine at 0, 1, and 6 months.

Tetanus, Diphtheria, and Pertussis Vaccination
There is a five part childhood vaccination series DTaP that provides protection against diphtheria, pertussis and tetanus and a Td booster is recommended every ten years thereafter.\textsuperscript{25} Recently there has been a rise in pertussis epidemics and it is now recommended that patients between the ages of 11-64 receive one Td booster substituted by Tdap. The timing of the Tdap vaccine in patients with IBD seems to be important. In a prospective study looking at post vaccination Tdap antibody titers, patients with IBD on immunomodulator monotherapy or combination immunomodulator/anti-tumor necrosis factor (TNF) alpha therapy had decreased response rates.\textsuperscript{26} Based on this observation, the ideal time to administer the Tdap booster in patients with IBD would be prior to the initiation of immunosuppressive therapy.

Meningococcal Vaccination
Meningococcal disease can lead to serious complications such as sepsis, limb ischemia, meningitis, and rarely death. There are two serogroup B meningococcal (MenB) inactivated vaccines currently available in the United States, MenB-FHbp and MenB-4C.\textsuperscript{27} All adolescents and young adults between the ages of 16-23 should receive the vaccination. As there is no current evidence that patients with IBD are at increased risk for meningococcal infection, patients should receive the vaccination according to the Advisory Committee on Immunization Practices (ACIP) guidelines.\textsuperscript{27} The MenB-FHP is currently approved for both a two-dose series (0 and 6 months) and a three-dose series (0, 1-2, 6 months) while the MenB-4c is given in a two-dose series (0 and 6 months). Persons considered being at highest risk should be given the three dose series as it likely provides better immunogenicity. Importantly, the same vaccine must be used for all doses and are not interchangeable.

Human Papilloma Virus Vaccination
Human papilloma virus (HPV) has been clearly linked to the development of cervical cancer. Female patients with IBD have been found to have an increased risk of abnormal Papanicolaou (Pap) smears linked to HPV 16 or 18 serotypes, which has been associated with immunosuppressive therapy.\textsuperscript{28} There are currently two licensed vaccines available in the United States against HPV that include protection against serotypes 16 and 18. Gardasil comes in a quadrivalent and 9-valent form. The 9-valent vaccination covers five additional serotypes that account for 15% of cervical cancers
as well as HPV serotypes 6 and 11 that cause most anogenital warts. The additional coverage of the 9-valent vaccine is felt to mostly provide beneficial protection to women over men. Since patients with IBD are considered to be immunocompromised, the three-dose regimen of either vaccine should be administered at 0, 1-2 and 6 months to patients aged 9-26.

**Live Vaccinations**

**Measles, Mumps, Rubella Vaccination**

Since the adoption of universal vaccination protocols, the incidence of measles, mumps and rubella (MMR) has drastically decreased in incidence. The vaccination is a live vaccine and is given to children around the age of one in a two-part series. If a patient with IBD is not immune to MMR, then the vaccination can be safely administered to the patient as long as there is no plan to start high-level immunosuppressive therapy within 6 weeks or high-level therapy has been discontinued for at least three months.10

**Varicella Zoster**

Varicella Zoster virus (VZV) is a highly contagious infection that can lead to severe disseminated disease in immunocompromised patients. Corticosteroid use in combination with immunosuppressive agents appears to be a significant risk factor for infection. The majority of adults have immunity to VZV either through acquisition during childhood infection or vaccination. The VZV vaccine is a live attenuated vaccine. Given the high risk for complications, all patients with IBD should have their immunity to VZV assessed (documentation of two-dose regimen, history or varicella infection, or laboratory evidence of immunity). If the patient is not immune, a two-dose vaccination series should be initiated if there is no plan to start high-level immunosuppressive therapy within six weeks or high-level therapy has been discontinued for at least three months. For patients with IBD without immunity who are on high-level immunosuppressive therapy (and who cannot stop it without risk of flare) but are at increased risk for exposure to varicella, such as health-care workers or teachers, the risk of infection needs to be weighed against receiving the vaccination.32 There is some evidence available in small case series that administration of the VZV vaccine was safe in pediatric patients who were on either thiopurines or infliximab.

**Zoster/Shingles Vaccination**

Varicella Zoster virus (VZV) persists as a latent infection in sensory nerve ganglia and can reactivate, especially in immunocompromised patients, causing Herpes zoster. About one in three people will develop zoster in the general population. The most common side effect is postherpetic neuralgia, however immunocompromised patients may suffer from disseminated infection that can be potentially fatal. In 2006, the live Zoster vaccine (Zostavax) was released and recommended by the Center for Disease Control (CDC) for patients 60 years or older. This live attenuated single-dose vaccine is at least 14 times the potency of the varicella vaccine. The CDC advises that administration of the vaccine to patients on “low-doses” of methotrexate, azathioprine or 6-mercaptopurine is safe. There is limited data to suggest the vaccine is safe for patients on anti-TNF therapy, but the CDC does not recommend its use.

Recently, an inactivated vaccine consisting of varicella zoster protein in an adjuvant system (Shingrix) was FDA approved. It has remarkable efficacy in immunocompetent individuals, reducing the risk of developing zoster by 97%. This vaccine is indicated for patients 50 years or older as a two-dose regimen, at month 0 followed by a second dose at 2-6 months. Although this vaccine has not been directly tested in patients with IBD on immunosuppression, its safety and efficacy has been demonstrated in patients post renal transplant on immunosuppression as well as patients with either
solid tumor or hematologic malignancies receiving chemotherapy.38,39

Screening and Surveillance of Cancer
Cervical Cancer Screening
Cervical dysplasia and cancer have been linked to the oncogenic properties of the HPV virus. Fortunately, the mortality rate has drastically decreased due to the implementation of mass screening with the Pap smear.40 Screening women with IBD is of particular importance as patients on immunosuppressive therapy have been shown to be at increased risk for cervical neoplasia, particularly in relationship to thiopurines.41 Unfortunately, despite these heightened risk, patients with IBD still seem to be under vaccinated for HPV42 and do not receive adequate cervical cancer screening.43 Patients with IBD who are on immunomodulator therapy should undergo yearly Pap Smears regardless if the patient has received the HPV vaccine.44 All patients with IBD who are on chronic immunosuppressive therapy should also be considered for yearly pap screening according to the American College of Obstetrics and Gynecology.45

Colorectal Cancer Screening and Dysplasia Surveillance
Patients with UC and colonic Crohn’s disease are at an increased risk of colon cancer that is two times the risk of the general population. Risk factors for development of colon cancer and dysplasia in patients with IBD include duration and extent of disease, family history of colon cancer, primary sclerosing cholangitis (PSC) and young age at disease onset.46 All patients with IBD should have a restaging (screening) colonoscopy eight years after disease onset as disease involvement may progress over time and proximal biopsies should exclude microscopic involvement in endoscopically normal appearing areas. The extent of the disease should be based either on endoscopic or microscopic involvement, whichever reveals more extensive disease.47 Patients with UC involving and proximal to the sigmoid colon and Crohn’s patients with more than a third of the colon involved should be placed in an endoscopic surveillance protocol. The presence of limited proctitis has not been proven to be a risk factor for the development of colorectal cancer.48 Ideally, surveillance should be undertaken when disease is in remission as active disease can hinder accurate interpretation of dysplasia.49

Current guidelines recommend colonoscopies every 1-3 years depending on risk factors and decided on a patient-to-patient basis. The patients at highest risk should undergo yearly surveillance colonoscopies (Table 2). For patients who are not in the high-risk group, lengthening the surveillance interval from one year can be considered if patients have endoscopically and histologically normal mucosa on two or more surveillance colonoscopies.46 The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC) guidelines recommend chromoendoscopy over white-light endoscopy with random biopsies as the preferred method of surveillance in patients with IBD. Targeted biopsies or resection (if the lesion is felt to be endoscopically resectable) should be performed if a lesion is identified with chromoendoscopy. One may also consider two biopsies from each colonic segment for histologic staging.46 If chromoendoscopy is not available or the yield is reduced by significant inflammation, poor preparation or multiple pseudopolyps, then random biopsies with targeted biopsies of any suspicious lesion should be undertaken.

Skin Cancer Screening
The awareness of the risk of skin cancer in patients with IBD has grown overtime. Non-melanoma skin cancer (NMSC) includes both squamous cell and basal cell carcinoma. The risk of acquiring NMSC is largely associated with thiopurine use (odds ratio of 4) and not IBD alone.50 There has been conflicting evidence in regards to the ongoing risk of NMSC once thiopurine use has stopped. A large French prospective cohort study demonstrated a pronounced increase in the incidence of NMSC in patients 50 or older with prior thiopurine exposure compared to controls.51 Contrary, a study on a large cohort of Veterans Affairs patients demonstrated that the incidence of NMSC reverted back to pre-exposure levels after the thiopurine was stopped regardless of the prior exposure duration.52

While NMSC appears to be strongly correlated to thiopurine use, patients with IBD have a significantly higher incidence of melanoma (continued on page 22)
(continued from page 20)

compared to the general population regardless of medical therapy.\textsuperscript{53} In addition, anti-TNF agents do appear to double the risk of melanoma.\textsuperscript{54,55} Given that there is an increased risk for melanoma in patients with IBD, routine counseling on the importance of decreased sun exposure, avoidance of tanning beds, use of protective sunscreen and clothing should be performed at office visits.

Our practices recommend referrals to dermatology for all of our IBD patients to undergo screening and in order to identify the particular risk and needs of continued surveillance according to individual risk factors based on our current understanding. Given the conflicting data of thiopurine use and risk for NMSC after cessation, it seems most reasonable to continue surveillance even after cessation in patients older that 50.

Osteoporosis and Osteopenia

Patients with IBD are at increased risk for bone mineral disorders including osteopenia and osteoporosis. The reported prevalence of osteoporosis in patients with IBD is estimated to be as high as 40% and more subtle degrees of decreased bone mineral density can be seen in 70% of patients with IBD.\textsuperscript{56} There are certain risk factors that lead to accelerated bone mineral loss. Patients with IBD who have one or more of the following risk factors should undergo screening with Dual-energy X-ray absorptiometry (DEXA): corticosteroid use more than three months or repeated use, history of low trauma-fracture, post-menopausal women, and males older than 50.\textsuperscript{57} Other risk factors to consider are chronic inflammation, active smoking, and malnutrition. If osteoporosis is found then referral to the patient’s PCP, endocrinologist or rheumatologist should be made for consideration of bisphosphonate therapy. Vitamin D levels should be checked at regular intervals and adequate calcium intake (1000mg/day) is recommended for all patients with IBD.\textsuperscript{58}

Smoking

It is important to assess for tobacco use and provide cessation counseling to all patients with IBD given the overall health implications. Despite the observation that smoking may be protective against UC, practitioners should still encourage cessation, but caution the patient about the potential for flare.

More importantly, Crohn’s patients should be advised that it is absolutely crucial to stop smoking. There is good evidence that patients with Crohn’s who smoke are at an increased risk of flare and smoking cessation lessens the risk.\textsuperscript{59} Furthermore, smoking is associated with increased steroid exposure, greater risk for surgery and increased risk of post-operative recurrence.\textsuperscript{60,61} There are a number of support systems that practitioners can refer patients to that include telephone based, mobile applications, and support group programs to help achieve cessation. Furthermore, medical therapy options that have been shown to be beneficial in smoking cessation include Nicotine replacement therapy, varenicline and bupropion.\textsuperscript{62}

CONCLUSION

Inducing and maintaining remission for patients with IBD still remains the primary goal. However, the importance of health maintenance and prevention has emerged as a crucial objective in the overall delivery of care. Providers should take an active role in maintaining the wellness of patients and preventing any future adverse events. The role of the gastroenterologist should be as the principal physician closely managing the care with other health care professionals to ensure the patients are up to date with age appropriate vaccinations, cancer screening, screening for osteoporosis, and smoking cessation.

References

Routine Health Maintenance and Disease Prevention in Patients with Inflammatory Bowel Disease


