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Inflammatory Bowel Diseases (G Lichtenstein, Section Editor)

Health Maintenance for Adult Patients with Inflammatory Bowel Disease

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Abstract

Purpose of review This review serves as a summary of healthcare maintenance items that should be addressed when managing patients with inflammatory bowel disease (IBD). This manuscript discusses vaccine-preventable illnesses, cancer prevention recommendations, and other screenings that are important to gastroenterologists and primary care physicians caring for patients with IBD.

Recent findings Patients with IBD often require immunomodulator agents and/or biologics to induce and maintain disease remission which can increase the risk of developing several infections. Also, subsets of patients with IBD are at an increased risk for a number of malignancies including colon, cervical, and skin cancers.

Summary Staying up-to-date with health care maintenance of patients with IBD is critical, especially given their increased risk for vaccine-preventable infections as well as comorbidities such as cancers, bone health, and mood disorders. Gastroenterologists and primary care physicians should familiarize themselves with the required screenings and vaccines that are recommended for adult patients with IBD, particularly those who are immunosuppressed.

Introduction

Health maintenance is crucial for patients with inflammatory bowel diseases (IBD), especially those who are receiving immunosuppressive therapy or those with plans to be started on such drugs. IBD is a chronic condition that can affect patients of all ages. It does not only involve the gastrointestinal tract but may impact the entire body. Up to 40% of patients with IBD have associated extra-intestinal manifestations which may involve the eyes, skin, joints, and liver [1]. The importance of healthcare maintenance does not only include vaccinations, but also involves screening and surveillance for certain cancers, depression, osteoporosis, and smoking, among other conditions. Many patients with IBD are on immunosuppressive medications such as corticosteroids, thiopurines, methotrexate, small molecules, and/or biologic agents making them not only at an increased risk for the development of opportunistic infections and malignancies, but for developing a more severe and complicated course [2].

Patients with IBD often consider their treating gastroenterologist as their primary care provider. Previous studies have shown that rates of preventative care for patients with IBD are lower than that of the general population [2, 3]. This is likely due to several reasons. Primary care providers may be less comfortable making recommendations about immunizations particularly in the setting of immunosuppression due to a lack of knowledge regarding required vaccinations and screenings for patients with IBD. Gastroenterologists, being more focused on the gastrointestinal tract and not addressing healthcare maintenance issues due to time constraints, and/or their inability to provide vaccinations in their office due to extra cost and storage issues, may defer this responsibility to primary care physicians [4, 5]. For this reason, it is imperative that gastroenterologists work closely with primary care clinicians as one team in order to make sure that their patients with IBD are receiving appropriate and up-to-date healthcare maintenance [6, 7]. Treating gastroenterologists should make recommendations about vaccines, communicate these recommendations to primary physicians, and define who is responsible for vaccine administration, health maintenance, and screenings [8••].It is also of paramount importance for gastroenterologists to be able to recognize the other primary, secondary, and tertiary prevention tasks required for every patient with IBD [9]. Several checklists have been created to facilitate healthcare maintenance for patients with IBD [10•, 11•].

In this manuscript, we will discuss the different healthcare maintenance aspects that need to be addressed by clinicians caring for patients with IBD. This paper will address vaccine-preventable illnesses, screening for malignancy, osteoporosis, and mental health.

Vaccine-preventable illnesses

Vaccines are important for the prevention of a number of infectious illnesses [12••].There has been no association between vaccination causing flares of underlying IBD [13, 14]. Among patients with IBD, it is very important to make sure that patients have received their age-appropriate vaccines ideally prior to initiation of immunosuppressive medications for optimal immune response [15]. Equally as important, family members of patients with IBD should also be up-to-date with their immunizations.

Non-live (inactive/killed) vaccines can be administered to all patients, regardless of their immunosuppression status per the Centers for Disease Control (CDC) recommendation, Advisory Committee on Immunization Practices (ACIP), and the Infectious Disease Society of America (IDSA) [16–19]. These vaccines include the inactivated influenza vaccine, pneumococcal vaccine (PCV13 and PPSV23), tetanus, diphtheria, and pertussis (Tdap), meningococcal vaccine, hepatitis A and B vaccines, human papillomavirus (HPV), and the inactivated recombinant herpes zoster vaccine [8••].Live

vaccines, on the contrary, are contraindicated in immunosuppressed patients. Per the CDC, patients with IBD are considered severely immunocompromised if on (1) prednisone ≥ 20 mg daily for at least 2 weeks, (2) thiopurines (≥ 1.5 mg/kg of 6-mercaptopurine or ≥ 3 mg/kg of azathioprine), or (3) methotrexate (≥ 0.4mg/kg weekly) [20]. Additionally, patients on biologic agents are considered immunosuppressed. Novel messenger RNA (mRNA) and adenovirus COVID-19 vaccines are approved and are recommended in all patients with IBD. Given the high likelihood of needing immunosuppressive medication during their illness, required vaccinations should be given to all patients with IBD whenever possible. It is very important for gastroenterologists to vaccinate their patients with IBD early on prior to initiation of immunosuppression to achieve a maximum immune response [21]. Table 1 summarizes the immunization schedule of adult patients with IBD.

This review will not address vaccinations of patients with IBD planning international travel. The reader is referred to the CDC website as well as the ACG preventive care clinical guideline [8••, 20, 22].

Influenza vaccine

Patients with IBD have been shown to have a higher risk for contracting influenza compared to individuals with no IBD. Steroid use was found to be the only medication to independently be associated with this risk [23]. Additionally, patients with IBD were found to have a higher likelihood for hospitalization. Studies have demonstrated that patients with IBD receiving immunosuppressive therapies are at an increased risk for developing influenza and if infected, they were found to have worse outcomes defined as higher rates of hospitalization and superimposed pneumonia compared to individuals without IBD [24]. Consequently, all patients with IBD should receive the inactivated non-live influenza vaccine annually, regardless of their immunosuppression status. Additionally, household members of patients with IBD should receive the annual influenza vaccine also. Timing of influenza vaccine administration should not be delayed based on the timing of biologic agent dose administration. Despite the blunted immune response noted among immunosuppressed patients with IBD, the vaccine still provides some protection [25–28]. In one study, up to 80% of patients with IBD on infliximab who received the influenza vaccine mounted a serologic response [29].

Currently, the most commonly administered influenza vaccines are the standard dose and the high dose preparations of the inactivated influenza vaccines. It has been shown that the high-dose inactivated influenza vaccine may lead to higher antibodies in patients with IBD who are receiving anti-tumor necrosis factor (anti-TNF) monotherapy when compared to the standard dose administration therefore this is what has been recommended in a recent expert review [30, 31]. The live attenuated influenza vaccine is contraindicated among patients with IBD who are receiving immunosuppressive medications.

Table 1 Immunization schedule for adult patients with inflammatory bowel disease

Infectious pathogen	Vaccine		Dosing schedule	Special considerations
Influenza	Inactive influenza vaccines	Inactivated standard dose (SD) quadrivalent influenza vaccine (multiple formulations)	Annually	
		Inactivated high dose (HD) influenza vaccine (Fluzone)	Annually	Preferred for patients ≥ 65 years or 18–64 years who are on anti-TNF monotherapy
	Live attenuated influenza vaccine	Live attenuated intranasal influenza vaccine (FluMist)	Contraindicated in immunosuppressed patients	
Streptococcus pneumonia	Inactivated pneumococcal vaccines	Pneumococcal conjugate 13 valent (PCV13 Prevnar) Polysaccharide 23 valent (PPSV23 Pneumovax)	All ages ≥18 years; PCV13 followed by PPSV23 8 weeks later if immunosuppressed or 1 year later if immunocompetent; repeat PPSV23 5 years after the initial dose and then the third dose at age 65 years	
Herpes zoster virus	Inactivated/recombinant	Recombinant zoster vaccine (Shingrix)	Two doses (2–6 months apart) for all ≥18 years who are or will be at increased risk due to immunodeficiency or immunosuppression caused by disease or therapy*	
Human papillomavirus (HPV)	Inactivated HPV vaccine	9 valent human papilloma virus (Gardasil, Cervarix)	Three doses: 0-, 2-, and 6-month schedule for all ages between 9 and 26 years; individualize for patients 27–45 years*	
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Messenger RNA vaccines	Pfizer BioNTech	Two doses 21 days apart, third dose 6 months after second dose for select populations[£]	Patients ≥ 12 years
		Moderna	Two doses 28 days apart	Patients ≥ 16 years
	Viral vector vaccine	Johnson and Johnson	Single dose	Patients ≥ 18 years

Table 1 (continued)

Infectious pathogen	Vaccine		Dosing schedule	Special considerations
Corynebacterium diphtheria, Clostridium tetani, Bordetella pertussis	Inactivated Tetanus, diphtheria, pertussis (Tdap or Td) vaccine	Tdap or Td (Daptacel, Infanrix)	A single dose of Tdap between 11–64 years then Td or Tdap every 10 years	1 Tdap during the third trimester of each pregnancy
Hepatitis A virus	Inactivated vaccine	Hepatitis A (Havrix, Vaqta)	Two dose series 6–12 months apart	
		Hepatitis A/Hepatitis B (Twinrix)	Three dose series at 0, 1, 6 months or 4 doses accelerated dosing schedule 0, 7, 21–30 days, and 12 months	Accelerated dosing for patients who start the vaccination series but are unable to complete the 3 dose schedule due to high-risk travel
Hepatitis B virus[¥]	Inactivated vaccine	Hepatitis B virus (Engerix-B, Recombivax)	Three dose series on 0, 1, 6 months	Check antibody to the surface antigen (antiHBs) 4–8 weeks after completing series
		Hepatitis A/hepatitis B (Twinrix)	Three dose series at 0, 1, 6 months or 4 doses accelerated dosing schedule 0, 7, 21–30 days, and 12 months	Accelerated dosing for patients who start the vaccination series but are unable to complete the 3 dose schedule due to high-risk travel
		Heplisav	2 dose series (HepB-CpG) at 0 and 1 months	Check antibody to the surface antigen (antiHBs) 4–8 weeks after completing series
Measles, mumps, and rubella	Live attenuated vaccine	MMR (M-M-R II)	2-doses at least 4 weeks apart if not previously vaccinated or 1 dose if previously received 1 dose MMR	Contraindicated in patients on immunosuppressive therapy
Varicella	Live attenuated vaccine	Varicella vaccine (Varivax)	2 doses 4–8 weeks apart if not previously vaccinated or if did not develop varicella or herpes zoster infection previously	Contraindicated in patients on immunosuppressive therapy

Table 1 (continued)

Infectious pathogen	Vaccine		Dosing schedule	Special considerations
Neisseria meningitidis	Inactivated vaccine	Meningococcal A, C, W, Y (MenACWY) (multiple formulations)	One or two doses depending on indication	Recommended only for adults with certain risk factors Please see ACIP recommendations for more details[38]
		Meningococcal B (MenB) (multiple formulations)	A two- or three-dose series depending on vaccine and indication	

The above recommendations do not apply to pregnant women with IBD

*See text

[¥]For patients with a previous history of hepatitis B immunization, a single dose of hepatitis B vaccine is given followed by a hepatitis B surface antibody titer check 3–4 weeks later. If the quantitative hepatitis B surface antibody titer is < 10, then the complete hepatitis B vaccination immunization series is given

[£]United States Food and Drug Administration amended the emergency use authorization to allow for use of a single third dose for individuals 18 through 64 years of age who are at high risk of severe COVID-19 (to include immunocompromised patients with IBD), individuals 65 years and older, and individuals whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19

Pneumococcal vaccines

Patients with IBD are at an increased risk for developing pneumococcal pneumonia compared to the general population [32]. Although there are some studies showing an increased risk for pneumococcal pneumonia in patients receiving immunosuppression, a nationwide Danish cohort study showed that immunosuppressive medications, namely steroids and anti-TNF agents, did not increase the risk of invasive pneumococcal disease among patients with IBD [32, 33]. Currently, there are 2 pneumococcal vaccines: the pneumococcal conjugate vaccine PCV-13 (Prevnar 13®) and the pneumococcal polysaccharide PPSV23 vaccine (Pneumovax®23, and both can be given to patients with IBD regardless of immunosuppression status.

For immunocompromised patients, PCV-13 is given first followed by PPSV23, 8 weeks later. In immunocompetent patients, PPSV23 should be given 1 year after PCV-13. Additional PPSV23 vaccine doses should be given 5 years after the initial PPSV23 dose and then dose 3 at the age of 65 years. In the event that an immunocompromised patient is given PPSV23 first, it is recommended that patients receive PCV-13 1 year later. As with all vaccines, patients should be vaccinated early on after diagnosis of IBD and preferably before initiation of immunosuppression as to not have a blunted immune vaccine response. However, in patients already on biologic agents, vaccination should not be delayed based on the timing of biologic treatment [34].

Herpes zoster vaccine

Patients with IBD are at increased risk for the development of herpes zoster compared to the general population,32]. and those receiving immunosuppression, especially tofacitinib, are at a further increased risk [35]. A recombinant zoster vaccine (Shingrix) was approved in 2017 as an alternative to the live zoster vaccine (Zostavax) which is no longer available in the USA. All individuals over the age of 50 years should receive the recombinant zoster vaccine. Experts have proposed that a subgroup of patients with IBD who are at high risk of developing herpes zoster should receive the vaccine earlier than 50 years and these include (1) 40 years and older with a history of herpes zoster, (2) repeated courses of steroids, (3) combination therapy and receiving steroids, (4) tofacitinib use with one of the following: oral corticosteroids at baseline, Asian race, history of diabetes mellitus, prior anti-TNF failure, or chronic tofacitinib use of 10 mg twice a day [30, 35, 36]. In July 2021, the FDA approved Shingrix for the prevention of herpes zoster in adults 18 years of age and older who are, or will be, at an increased risk of shingles because of immunodeficiency or immunosuppression.

HPV vaccine

Patients with IBD who are receiving immunosuppression are at a 30% increased risk for cervical neoplasia compared to the general population [37]. Persistent HPV infection and an immunocompromised system predispose to cervical cancer. The Food and Drug Association (FDA) approved the recombinant HPV 9-valent vaccine (GARDASIL 9) for all boys, men, girls, and women between the ages of 9 and 45 years (https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9). Even though most women have been exposed to HPV by the recommended vaccination age of 9 to 26, societies still endorse this recommendation [12••].In older patients between 27 and 45 years, the ACIP recommends individualizing these scenarios and encourages shared clinical decision-making between the patient and the provider based on their risk for acquisition of HPV [38••, 39]. COVID-19 vaccine

Currently, there are several COVID-19 vaccines that have been used in patients with IBD including mRNA vaccines, viral vector vaccines, and inactivated vaccines. In the USA, the mRNA vaccines, Pfizer BioNTech and Moderna, and the viral vector vaccine from Johnson and Johnson have been approved and can be administered to all patients with IBD. Currently, all patients with IBD should be vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the earliest opportunity to do so and regardless of which vaccine they are offered [12••, 40].

Live vaccines

Administration of live vaccines is not recommended for patients on immunosuppressive therapies. Certain immunosuppressed patients who are not severely immunosuppressed may safely receive selected live vaccines; however, this option needs to be considered on a case-by-case basis until more prospective data is available [41]. The common live vaccines include the varicella vaccine, the measles, mumps, and rubella (MMR) vaccine, and the live influenza vaccine. Several travel vaccines are live vaccines, and these include the cholera vaccine, yellow fever vaccine, and one of the available typhoid vaccines.

Considerations for patients on immunosuppression or planned to start immunosuppression

The IDSA advises that live vaccines should be given at least 4 weeks prior to initiation of immunosuppression and definitely not within 2 weeks. They also advise inactivated vaccines to be given at least 2 weeks prior to initiation of immunosuppression [18]. As for patients who are already receiving immunosuppression, current recommendations are that they should avoid receiving live vaccines. If live vaccines are needed, then patients should be categorized into those with severe immunosuppression and those without significant immunologic compromise. Patients without significant

immunologic compromise can consider receipt of essential live vaccines on a case-by-case basis after discussion with infectious disease experts. Patients who are considered highly or severely immunosuppressed include those on high dose steroids ≥ 20 mg per day of oral prednisone for ≥ 14 days, immunomodulator use (azathioprine ≥ 3mg/kg/day, 6-mercaptopurine ≥ 1.5mg/kg/day, or ≥ 0.4mg/kg/week), use of anti-TNF agents, ustekinumab, or transplant-related immunosuppressive medications (cyclosporine, tacrolimus, mycophenolate) [20, 35

Bone health

Prevalence of osteoporosis in patients with IBD is reported to be as high as 42%, with higher rates among CD patients when compared to UC patients [42–44]. Even in newly diagnosed patients with IBD, and before any medications are started, osteoporosis prevalence is as high as 5% [45]. The reasons behind low bone mass are related to the inflammatory disease itself, medications that are used particularly corticosteroids, malabsorption especially of vitamin D, as well as dietary restrictions. In a conditional recommendation with very low-level evidence, the 2017 American College of Gastroenterology made a statement that all patients with IBD with conventional risk factors for abnormal bone mineral density should undergo screening for osteoporosis with bone mineral density testing at the time of diagnosis and periodically thereafter [8••].This recommendation includes patients with a pre-existing fragility fracture, women 65 years and older, men 70 years and older, and those with risk factors for low bone mass including those who have received steroid treatments, who suffered from systemic chronic inflammation, and malnutrition [45, 46]. Previously, it was thought that having IBD alone is an independent predictor for developing the bone disease, but newer data failed to support this theory. Based on the Crohn's and Colitis Foundation checklist, a DXA scan of the hip and spine should be performed for all high-risk patients with IBD to screen for osteoporosis [11•]. These high-risk patients include patients with a low body mass index (BMI), those with a cumulative steroid exposure longer than 3 months, smokers, post-menopausal women, and those with hypogonadism [11•]. In case the DXA scan is normal, it is recommended to repeat the scan after 5 years [11• Other experts (Cornerstones Health) recommend serial monitoring of vitamin D levels, and if deficient, appropriate replacement is needed [10•]. As for assessment for osteoporosis, a DXA scan is recommended for any patient with IBD who also has one of the following risk factors: chronic steroid use greater than 3 months, maternal history of osteoporosis, malnourished or very thin (i.e., low BMI), amenorrheic, or if post-menopausal [10•]. Additionally, it is recommended that with any course of steroids, patients also get a prescription of calcium and vitamin D [10•].

Malignancy

Cervical cancer screening

There has been the consensus among the European Crohn's and Colitis Organization, the American College of Obstetrics and Gynecology along with the CDC, and the most recent ACG Preventive guidelines that all women with IBD who are receiving systemic immunosuppressive therapy should have an annual cervical cancer screening examination/PAP smear [8••, 47, 48], (https://www.cdc.gov/std/tg2015/specialpops.htm.)] Up to 70% of cervical cancer is caused by HPV 16 or 18 infection [37]. Vaccination recommendations are detailed above.

Colon cancer screening

Patients with more than 8-year history of ulcerative colitis (excluding ulcerative proctitis) and Crohn's colitis involving more than a third of their colon are at an increased risk for colon cancer. Surveillance for colon cancer should begin within 1–2 years after an initial screening colonoscopy, and if negative, surveillance colonoscopies every 1 to 3 years are recommended [49, 50]. Patients with a concomitant history of primary sclerosing cholangitis (PSC) should undergo annual colonoscopy from the time of their PSC diagnosis due to their pronounced risk of colon cancer [51].

Skin cancer screening

Patients with IBD, regardless of immunosuppression, are at an increased risk for the development of skin cancers, both melanoma and nonmelanoma skin cancers (NMSC) [52, 53]. Thiopurines increase the risk of NMSC even further by around 6-fold and this risk persists even after discontinuation of the thiopurine [8••].Anti-TNF biologic agents, increase the risk of melanoma 2-fold [54]. For this reason, patients with IBD should be referred to dermatology for a screening exam and determination of the frequency of exams, especially if they are receiving immunosuppressive medications or have had prior use of a thiopurine. Additionally, sunscreen protection is recommended for all patients with IBD, particularly those who will be starting immunosuppressive therapy, to reduce the additional risk.

Tobacco Use

All patients with IBD, regardless of their disease subtype, should be encouraged to stop smoking due to the negative effect of tobacco smoking on their general well-being and the increased risk for many malignancies including

lung and colon cancer. Data had shown that smoking may have a favorable protective effect on the development of ulcerative colitis [55]. Crohn's disease on the other hand is negatively affected by tobacco smoking. Not only does smoking increase the risk for the development of Crohn's disease, but smokers tend to develop more complications including strictures as well as the need for repeat surgical resections. Additionally, smoking tobacco has been identified as the only modifiable risk factor for post-operative recurrence of Crohn's disease [56, 57]. Regarding extra-intestinal manifestations of IBD, there have been reports showing increased prevalence of joint and skin manifestations in those patients with tobacco use regardless of the IBD subtype [58].

Mental health screening/depression screening

Like patients with other chronic illnesses, anxiety and depression are prevalent among patients with IBD compared to the general population. It is critical to screen patients with IBD for anxiety and depression especially since depressive severity was found to be a risk factor for suicidal ideation among these patients, and aggressive and early management can prevent progression to completed suicides [59]. Screening questionnaires for anxiety and depression are readily available and easy to administer. Follow-up for patients with high depression/anxiety scores should be offered and timely referral to their primary care physician or psychiatrist is crucial in order to improve outcomes of these patients [60].

Conclusions

Staying up-to-date with health care maintenance of patients with IBD is critical, especially given the increased risk for vaccine-preventable infections as well as comorbidities such as malignancies, bone, and mood disorders. There are many checklists developed to inform clinical practice for both gastroenterologists and primary care physicians [10•, 11•], who should be working hand in hand to provide the best state of the art care for patients with IBD.

Author Contribution

J.G.H.: drafting of the manuscript; M.F.P.: critical review of the manuscript; F.A.F.: drafting and critical review of the manuscript.

Declarations

Conflict of Interest

Jana G. Hashash declares no competing interests. Michael F. Picco declares no competing interests. Dr. Farraye is a consultant for Arena, BMS, Braintree labs, GI Reviewers, GSK, Innovation Pharmaceuticals, Iterative scopes, Janssen, Pfizer and Sebela. He sits on a data safety monitoring board for Lilly and TheraVance.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This is a very useful checklist which may aid gastroenterologists when they evaluate patients with inflammatory bowel disease. The checklist covers vaccine preventable illnesses, bone health, therapy related testing, cancer prevention, amongst other assessments.

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