Chapter 7
Healthcare Maintenance in the Patient with Inflammatory Bowel Disease: High-Yield Interventions

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Introduction

Inflammatory bowel disease (IBD) and the immune suppressive medications used to treat moderate to severe disease are associated with treatment-related complications including increased risks of infection and malignancy. Ensuring appropriate vaccinations and healthcare screenings can help to minimize the complications associated with this disease.

Healthcare providers managing IBD patients must familiarize themselves with the complexities of healthcare maintenance (HCM) in this population. Most IBD patients receive care from a gastrointestinal specialist, but primary care providers or general gastroenterologists may solely care for these patients as well [1]. In Bilal et al.'s analysis comparing implementation of IBD health maintenance quality measures among IBD specialists (those whose practice is at an IBD center) vs. non-IBD gastroenterologists, IBD specialists were more likely to deliver these indices (Fig. 7.1) [2]. Merging both specialty IBD care and preventive care can bridge the healthcare maintenance delivery gaps in IBD management.

Immunizations

Medications such as corticosteroids, immunomodulators, and biologics used in the management of IBD can increase susceptibility to infection. Despite this increased risk and the clear value of mitigating this risk through the use of vaccinations, the vaccination rates in the IBD population is lower than the general population [3]. It

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Quality measures	IBD physicians n=216	Non-IBD physicians n=109	P-value
Corticosteriod-sparing therapies	43.9%	20.3%	0.001
Type, anatomic location and activity assesed	100%	100%	-
Bone loss assessment	65.7%	35.5%	0.001
Influenza immunization	61.4%	45.9%	0.008
Pneumococcal immunization	57.7%	34.3%	0.001
Testing for latent tuberculosis before initiating anti-TNF therapy	72.1%	100%	0.004
Assessment of hepatitis B virus before initiating anti-TNF therapy	79.1%	95.7%	0.06
Tobacco screening/cessation counseling	96.8%	89.0%	0.15
Adherence (percentage of core measures completed)	71.8%	58.8%	0.001
Average score out of 100 (Based on AGA BTE 100 point score)	73.9	66.3	0.001

AGA, American Gastroenterology Association; BTE, bridges to excellence; IBD, inflammatory bowel disease; TNF, tumor necrosis factor

Fig. 7.1 Compliance with bridges to excellence quality indicators among IBD and non-IBD gastroenterologist

is uncertain as to whether this is due to concerns about safety, efficacy, or just a lack of knowledge. The Crohn's and Colitis Foundation and Cornerstone Health have created a checklist to address this hesitancy and promote immunizations [4]. This checklist can be a practical reference and is easily accessible on the CCF web site. The importance of vaccinating IBD patients against influenza, pneumococcal pneumonia, hepatitis A and B; varicella, herpes zoster, human papillomavirus, tetanus, diphtheria, and pertussis; measles, mumps, and rubella; and meningococcal meningitis will be discussed in this chapter.

Education around this topic requires a longitudinal discussion because newly approved IBD medications may pose unique infection risks; the new vaccines may become available. Staying up to date on immunization guidelines for the general population and the immunocompromised population is advised, as providers are currently the most trusted advisors when it comes to vaccines. Keeping an open dialogue with patients and counseling them on the utility of vaccine implementation is a known predictor for vaccine acceptance [5]. The earlier this conversation occurs with the patient, the more time there will be available for the patient to make informed decisions, especially given the current climate of vaccine hesitancy [6].

Several strategies exist to optimize vaccine rates. Vaccination reviews and using checklists or the electronic health record can be done routinely by both the gastroenterologist and the primary care provider (PCP) [7]. Communication between gastroenterologist and PCP is advised via note sharing and/or direct communication to increase awareness of required vaccines. Educating and involving additional clinical staff, such as nurses, pharmacists, and advanced care providers, can promote IBD health maintenance beyond solely the doctor's encounters.

Timing of vaccine administration is critical. Vaccines should be administered prior to planned immunosuppressive treatments, although necessary IBD treatment should never be delayed in order to immunize. Waiting at least 2 weeks after administration of an inactivated vaccine to start immunosuppression may optimize immunogenicity of the vaccine [8]. According to the Infectious Diseases Society of

America, the ideal window to administer a live vaccine is at least 4–6 weeks prior to starting any immunosuppression in order to ensure safety [8].

Studies have shown that IBD patients on immunosuppressive treatments, especially anti-TNF agents, have reduced humoral response to the trivalent Influenza vaccine, the polysaccharide pneumococcal vaccine, and the hepatitis B vaccine [9]. Monitoring vaccine titers 4–8 weeks after immunization of hepatitis A and B to confirm seroconversion may be beneficial; however there is no universal consensus on result interpretation and management [10].

Live vaccines should be avoided in patients on immunosuppressive therapy due to the risk of disseminated infection; however a case by case decision may be considered when necessary [3]. According to the Crohn's and Colitis Foundation Professional Education Sub-Committee, systemic immunosuppression is defined as prednisone >20 mg/day for more than 14 days, azathioprine >2.5 mg/kg/day, mercaptopurine >1.5 mg/kg/day, methotrexate >0.4 mg/kg/week), cyclosporine, tacrolimus, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, or tofacitinib [11]. Live adult vaccines include the intranasal flu vaccine (FluMist); the measles, mumps, and rubella (MMR); oral polio; chicken pox (varicella, Varivax), herpes zoster (Zostavax), or the yellow fever vaccine [12].

Immunizations: Influenza

Influenza is one of the most common vaccine-preventable illnesses in adults. Inflammatory bowel disease patients have a higher risk of influenza as well as its sequelae, including pneumonia and hospitalization, when compared to control populations [13]. More than 5% of IBD patients who develop symptoms from influenza infection require hospitalization (Fig. 7.2) [13]. Corticosteroids are an independent risk factor for acquiring influenza in the IBD population [13].

The influenza vaccine decreases hospitalization rates as well as morbidity and mortality associated with the flu [14]. Therefore, it is recommended annually for all IBD patients. The two available forms of the influenza vaccine are the live attenuated vaccine administered intranasally and the inactivated vaccine administered via injection. Although no studies have proven the risk of live vaccine transmission in the IBD population, it is advised that IBD patients on immunosuppressive therapies *and their household contacts* should receive the inactivated flu vaccine [15]. This vaccine is well tolerated among IBD patients and generally induces the appropriate immune response [15]. Given the ubiquitous availability of the influenza vaccine in pharmacies, clinics, and workplaces, modifiable barriers to patients receiving the vaccine are common misconceptions and fears. Providing vaccine counseling and Vaccine Information Sheets (VIS) to patients may help dispel these myths. Several studies have demonstrated that the provider role is vital in achieving successful influenza vaccine rates, and many patients attribute their physicians as the reason for getting vaccinated [16].

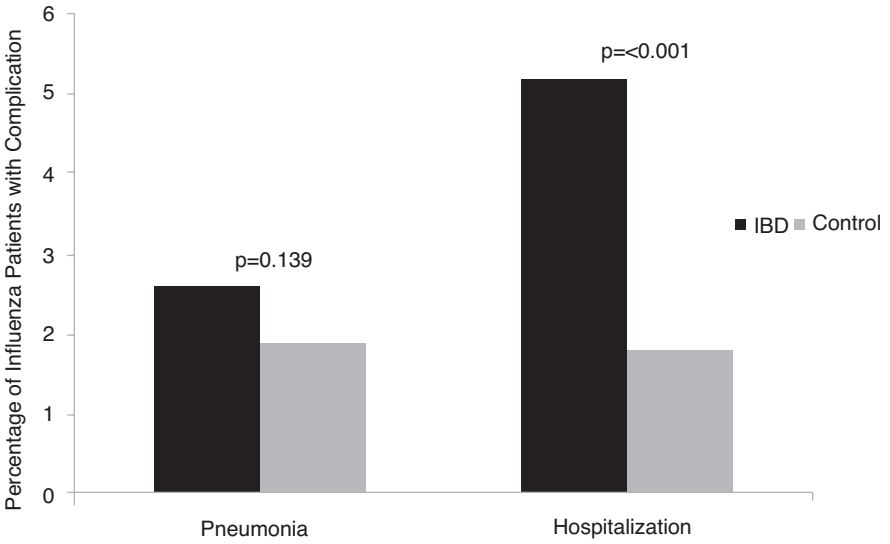

Fig. 7.2 Complications within 30 days of influenza diagnosis

Immunizations: Pneumococcal Pneumonia

Patients with IBD, particularly those treated with immunosuppressive medication, are at a higher risk for pneumococcal pneumonia [17]. According to CDC guidelines, immunization against pneumococcal pneumonia is advised for adults above age 65 and those younger with immunocompromising conditions including iatrogenic immunosuppression, which includes all biologic and immunomodulator therapies [18]. All adult IBD patients above the age of 19 planning to receive or are currently on immunosuppression should receive the pneumococcal vaccine [19]. This is different to the conventional recommendations for those age 65 and older and may contribute to vaccine hesitancy as potential insurance coverage may not be universal. This generally requires contacting the insurance company to verify coverage.

There are two pneumococcal vaccines: Prevnar 13 (PCV 13) and Pneumovax 23 (PPSV 23). For adult IBD patients, administration of *both* vaccines is recommended in order to provide immunity to all 24 serotypes of pneumonia [20]. Up until 2019, both vaccines were advised for the general population aged 65 and older; however, due to lower incidence of PCV 13 due to universal pediatric immunization for PCV 13, currently only PPSV 23 is recommended [21]. For IBD patients on immunosuppressive therapy however, PCV 13 is still advised, in order to improve overall immune response [19]. The order in which these vaccines are given is important: PCV 13 first, then PPSV 23 at least 8 weeks later, as this enhances immune response to the vaccines [19]. Subsequently, a PPSV 23 booster is advised every 5 years. If PPSV is given first, PCV13 should be administered 1 year later [22]. For IBD

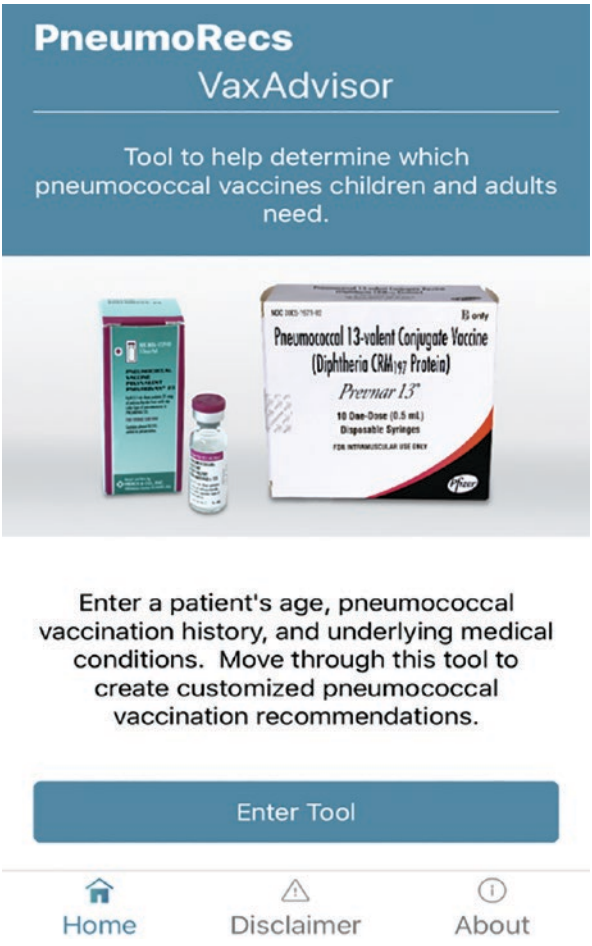

Fig. 7.3 CDC PneumoRecs VaxAdvisor App

patients under age 65 not on immunosuppressive therapy but with other risk factors, like smoking or asthma, PPSV 23 only is advised due to indirect effects of pediatric immunization of PCV 13 [21]. A helpful tool that can aid in identifying which pneumococcal vaccine is indicated is the PneumoRecs VaxAdvisor app (Fig. 7.3) [23]. This application factors in age, risk profile, and prior vaccination history and can be a practical guide for providers.

Immunizations: Varicella and Herpes Zoster

Herpes zoster (HZ) reactivation, also known as shingles, can be an agonizing condition that causes blistering of the skin and pain along involved dermatomes. Complications from herpes zoster include postherpetic neuralgia, bacterial skin

infection, ocular injury (if V1 involvement of the trigeminal nerve), and meningitis [24]. According to Long et al.'s study comparing the prevalence of HZ in an IBD cohort with non-IBD individuals, IBD patients are at a higher risk of herpes zoster, especially those on combination anti-TNF and thiopurine therapy, with an odds ratio of 3.29 [24]. Tofacitinib (Xeljanz) was released for the treatment of ulcerative colitis in 2018. Higher rates of herpes zoster have been detected in patients treated with tofacitinib, greatly emphasizing the need for immunization. The risk of HZ infection is observed to be a dose-related effect, with IR of 3.45 and 4.25 per 100 py at 5 mg and 10 mg twice daily dosing, respectively [25]. When appropriate, considering a decreased dose can mitigate this infection risk [26].

When prescribing tofacitinib, prior varicella exposure and immunity should be verified through history taking and serologic titers if the history is unknown. If the patient has no history of varicella exposure, the live varicella vaccine should be considered prior to starting therapy. If positive varicella titers are detected, with no record of previous dose of varicella vaccine, the recombinant HZ vaccine, Shingrix, should be given [8]. It is important to note that standard immunoassays are not as reliable in detecting prior varicella vaccination because the vaccine leads to lower antigen-antibody concentrations compared to active immunity from past infection [22]. Therefore, obtaining vaccine records and a patient's history can help identify those previously vaccinated [22].

Two HZ vaccines are currently FDA approved in the United States: live zoster vaccine (Zostavax) and the non-live recombinant zoster vaccine (Shingrix). The latter is recommended for use in the IBD population because of higher immunogenicity and better overall safety data in this population [25]. The Shingrix vaccine is currently recommended for patients aged 50 and older, but any adult with acquired immunity from past varicella infection is advised to obtain the HZ vaccine regardless of age prior to initiation of tofacitinib [25]. This may create an insurance hurdle given the strict reimbursement coverage for the vaccine. The cost for patients paying out of pocket can range from $101–$190 per injection, which may be an alternative option [25, 27]. To determine coverage and out of pocket expenses, the prescription can be sent to the patient's pharmacy for benefit and cost analysis [25].

The HZ series includes two injections with the second following 2–6 months after the first. Patients should be counseled on the adverse reaction of pain at the injection site with Shingrix, which occurred in up to 78% of patients in clinical trials [28]. IBD patients experience a similar rate of a local adverse reaction (74.6%) and a low risk of flares (1.5%) after immunization [25]. Despite this unpleasant though short-lived experience, Shingrix should be recommended due to its high efficacy rates. Among non-immunosuppressed populations, Shingrix is greater than 90% effective in preventing shingles, a significant improvement from the earlier live zoster vaccine, Zostavax, which is at most 51% effective [25]. For those patients who have previously received Zostavax, Shingrix should still be considered based on the improved efficacy rates [24]. Immunogenicity trials in IBD are lacking, but four phase 3 studies have demonstrated that the recombinant zoster vaccine produces persistent humoral response for at least 12 months after vaccination in immunocompromised adults [25].

Immunizations: Hepatitis A, B, and C

Screening for viral hepatitis prior to initiation of immunosuppressive therapy is one of the most important healthcare maintenance indices. Although hepatitis A is often short-lived and self-limiting, hepatitis B and C can be reactivated by common IBD treatments that alter immunity. Hepatitis B can reactivate in up to 50% of patients receiving immunosuppressive therapy, but reactivation of HCV is quite uncommon and has been only rarely reported in the IBD literature [29]. Reactivation of viral hepatitis can result in hepatic decompensation, a fate best avoided by identifying all patients at risk.

The hepatitis A virus (HAV) is a GI illness that is transmitted through the fecal-oral route. The HAV vaccine is routinely advised for all children aged 1–2 and to anyone older who has not been previously vaccinated [30]. All IBD patients are advised to receive the HAV vaccine, in alignment with CDC recommendations for the general population, especially if there is no previous history of vaccination or there are undetectable titers. Serologic testing prior to hepatitis A vaccination is not necessary but can be cost-effective by detecting patients who are already immune. Vaccination should not be postponed if titers or records cannot be obtained as there is no harm associated with re-vaccination [31]. Post-vaccination antibody confirmation 4–8 weeks after immunization can be considered to ensure seroconversion, given the lower rates in immunosuppressed patients [10]. Higher-risk individuals who should be monitored for vaccination completion include those traveling to endemic areas, males who have sex with males, people with HIV, or anyone with chronic liver disease [31]. The hepatitis A vaccine can be given as two injections over 6 months or in combination with the hepatitis B vaccine, in a three-part series over the same time span. Although two doses are recommended over a span of 6 months, if a delay in the second dose is unavoidable, the series does not need to be restarted [31]. The immunogenicity of a single dose of hepatitis A can last up to 10 years, with a second dose lasting up to 20 years in immunocompetent patients [30].

Hepatitis B is an infectious disease transmitted through body fluids with a prevalence of 2–8% in the global population [10]. All IBD patients should be screened for a prior history and immunization for hepatitis B virus (HBV), particularly those anticipating biologic, steroid, or immunomodulator therapy given the potential risk of reactivation. Therefore checking hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) *at the time of IBD diagnosis* is advised. If there is evidence of chronic hepatitis B (positive HBsAg and anti-HBc IgG) with or without detectable HBV DNA, antiviral prophylaxis should be started at least 7 days prior to initiation of immunomodulator and continued throughout and after treatment to reduce the risk of reactivation [10]. If HBsAg is negative, with positive anti-HBc IgG and undetectable HBV DNA, prophylactic antiviral treatment is not supported in those on monotherapy biologics, but close monitoring of ALT and HBV DNA is advised. Reactivation of hepatitis B can occur in up to 40% of immunocompromised patients [10]. Collaboration with a

hepatologist to co-manage these patients is strongly advised in order to adhere to the best practices of management.

Screening for hepatitis C virus (HCV) is advised for all IBD patients given the rising prevalence of hepatitis C in the aging population, as well as the unique challenges treating both HCV and IBD simultaneously can introduce. Timing and monitoring of biologic and hepatitis C antiviral therapy are important strategies during treatment. Although there is theoretical risk for biologics decreasing the efficacy of antiviral hepatitis C therapy, there are encouraging studies that dual IBD and hepatitis C therapy is safe and effective [32]. Given the possibility of cure for most patients, HCV should be treated prior to initiation of immunosuppressive treatment if possible. Withholding necessary IBD treatment is never advised. Therefore if immunosuppressive treatment is started prior to antivirals, close monitoring of concomitant therapy with serial liver function tests is advised, even though the risk of HCV reactivation is infrequent [29]. Collaborating with a hepatologist is essential in preventing progression of liver disease in those IBD patients with hepatitis C.

Immunizations: MMR, HPV, Meningococcal, and Tdap

Children aged 12 months to 12 years old are routinely advised to receive the measles, mumps, and rubella (MMR) vaccine. If there is no previous evidence of MMR immunity, vaccination is recommended for teens and adults, given as two doses 28 days apart [33]. MMR should be avoided in patients on immunosuppressive treatment because this is a live vaccine, but household contacts can be safely given the vaccine [22].

The human papillomavirus (HPV) vaccine, Gardasil 9, is recommended for all males and females aged 9–26. For those inadequately vaccinated, the HPV vaccine can be considered up until the age of 45 for IBD patients as a “catch-up” vaccine [34]. Studies indicate complete immunogenicity from Gardasil 9 in IBD patients even on immunosuppressive treatments with no increased adverse events when compared to healthy controls [35].

The inactivated meningococcal vaccine is advised in standard guidelines for children and young adults living in college dormitories. As patients with IBD are not at higher risk for meningitis, vaccination using routine recommendations is advised [36].

Tetanus and diphtheria (Td), although uncommon in developed countries, is still routinely advised for the general population [22]. All IBD patients should be given the Td vaccine every 10 years, with at least one series containing pertussis (Tdap) [22]. Pregnant women are advised to receive the Tdap vaccine in the third trimester regardless of previous vaccination [22].

Screenings

Patients with Inflammatory bowel disease should undergo heightened cancer surveillance due to the higher risks of skin, colon, and cervical cancer in this population. Some increases in risk are related to underlying disease and others due to the treatment strategies employed. Bone and eye health should be monitored as well, given the high frequency of related issues encountered in this patient group. Screening for mental health disorders and tobacco use is advised given its associations to worsening disease severity. Although not addressed in routine IBD guidelines, our practice screens for fatigue after noticing a high prevalence of this complaint in our patients [37].

Screenings: Bone Health

Metabolic bone disease (MBD) is one of the most common invisible systemic complications of IBD, ranging anywhere in prevalence from 10 to 60% [38]. Low bone density can lead to osteopenia or osteoporosis, putting patients at higher risk for bone fractures. For IBD patients, the biggest cause of MBD is corticosteroid use, but chronic inflammation causing impaired intestinal absorption of calcium and vitamin D; malabsorption due to extensive small bowel surgery; recurrent flares leading to low appetite or food avoidance, low BMI, and poor nutritional state; diminished overall energy and physical activity; and dairy avoidance in those who are sensitive or intolerant can all contribute to MBD [39] [40]. In order to manage bone health, a baseline axial bone density scan via dual energy x-ray absorptiometry (DXA) is advised for patients with at least one of the above risk factors. A DXA will provide an in depth understanding of the presence of osteopenia (T score between −1 and – 2.5 SD) or osteoporosis (T score of −2.5 or lower), which is associated with increased risk of bone fracture [40, 41]. If the DXA scan is normal, the Crohn's and Colitis Foundation recommends a repeat scan in 5 years. However more conventional guidelines recommend repeating only if the patient develops new risk factors including recurrent corticosteroid exposure for greater than 3 months [11]. If osteopenia is detected, bone density scans can be repeated at least every 2 years while also undergoing appropriate treatment [11].

Therapeutic management of osteopenia includes weight-bearing exercises, tobacco cessation, avoiding excessive alcohol intake, and increased dietary and supplemental calcium and vitamin D [42]. Adequate dosages of elemental calcium for those between the ages of 19 and 50 are 1000 mg/day and 1200 mg/day for women 51–70 years of age [43]. Many multivitamin formulations do not contain calcium citrate, the recommended form of supplemental calcium, as it can affect absorption of iron, zinc, and magnesium [44]. As a result, additional calcium supplementation with or without vitamin D can be purchased when indicated.

Vitamin D, most commonly vitamin D3 or cholecalciferol, 400 to 800 IU/day is advised for patients with osteopenia [42]. If deficiencies exist, higher doses with close monitoring of levels may be required (see Sect. 7.3) [42]. Once osteoporosis is detected, treatment by an endocrinologist and primary care provider is recommended. Avoiding high-dose corticosteroids in patients with MBD is preferred. For patients on steroid therapy, supplementation with 1 g calcium and 400 IU of vitamin D has shown to slow, but not prevent, bone loss [45].

Screenings: Eye Health

About 2–3% of IBD patients develop an eye manifestation of their inflammatory bowel disease [46]. Having regular, annual eye exams are advised for all IBD patients regardless of treatment modality to assess and monitor any irregular findings.

The two most common eye manifestations seen in IBD patients are scleritis and episcleritis [47]. These conditions can be unpredictable; therefore any sudden complaint of eye redness, pain, or visual changes requires prompt ophthalmologic evaluation. A more uncommon manifestation in IBD is uveitis, which does not reflect IBD activity and can sometimes precede IBD diagnosis [47]. Uveitis often presents in patients with other known EIMs such as joint or skin manifestations. Distinguishing between uveitis and other eye ailments requires ophthalmologic evaluation with slit lamp testing [47]. More subtle changes from corticosteroid use, like cataracts or glaucoma, are best identified by routine scheduled evaluations [39, 48].

Screenings: Colon Cancer

Colon cancer tends to occur 2–6 times more in patients with Inflammatory bowel disease compared to the general population [49]. A chronic inflammatory state, as well as genetic and environmental risk factors, likely leads to this increase [49]. Independent risk factors include inflammation involving more than one-third of the colon, increased severity of inflammation (as assessed by endoscopic and histologic scoring using 0–5 grading) and disease duration of at least 8 years (cumulative risk increases as duration increases) [50]. Colonoscopy is the gold standard for colon cancer detection; therefore IBD patients with colonic disease beyond proctosigmoiditis for 8 years or more should undergo surveillance colonoscopies [49]. American society recommendations differ, ranging between 1 and 3 years for colon cancer surveillance, although annual and biennial surveillance are most adopted [51]. For IBD patients with primary sclerosing cholangitis (PSC), annual screening starts at diagnosis given the higher rates of colon cancer among patients with PSC [52]. For patients with PSC and ulcerative colitis (UC), the odds ratio of developing CRC is 4.8, compared to IBD patients without PSC [53]. The higher cumulative risk

of developing colorectal cancer in PSC patients with IBD has been postulated at 2% in 5 years, 7–9% at 10 years, and 15% at 15 years, developing at an average age of 49.5 years old [52].

Managing colonic inflammation may help lower the risk of colon cancer, although there is no therapy that is proven to have specific chemopreventive effects on lowering cancer risk [49]. Epidemiologic studies have identified a lower incidence of colon cancer in the IBD population that has been attributed to better control of inflammation with the use of biologics [50]. Additional modifiable risk factors include avoiding tobacco, eating a high-fiber diet of fruits and vegetables, and limiting intake of processed foods and red meat [49]. In our practice, patients with excellent colon preparations, adherence to therapy and in endoscopic remission without a personal history of dysplasia, are offered less intensive biennial screening. Surveillance intervals should always be determined and discussed on a case by case basis based on history and risks.

Screenings: Skin Cancer

IBD patients have an increased risk of skin cancer, particularly nonmelanoma skin cancer (NMSC). In Long et al.'s review looking at NMSC incidence in IBD, the overall annual incidence rate of NMSC was 733 per 100,000 in the IBD sample, compared to 447 for controls [54]. This is likely due to the use of immunosuppressive medications, although the underlying immune dysfunction that occurs as part of the disease itself may also contribute through the decreased ability to repair damaged DNA [55]. The use of immunosuppressive treatments in IBD, like cyclosporine, mercaptopurine, azathioprine, and anti-TNF therapies, is the key driver of a higher cancer risk. As a result, screening for skin cancer with routine dermatologic exams is essential in this group. At a minimum, annual full body skin examinations are recommended to identify early abnormal skin changes [56]. In order to reduce skin cancer risk, patients should be counseled to wear SPF 30 or higher in the sun and minimize UV light exposure by avoiding tanning beds and excessive sunbathing (which varies depending on skin type, geographic location, and UV index) [54].

Screenings: Cervical Cancer

Screening for cervical cancer in immunocompromised IBD patients is advised annually due to the higher rates of cervical cancer and high-grade cervical dysplasia when compared to the general population [57]. The HPV vaccine is the best way to minimize this risk, and it is recommended for all IBD patients. Males and females can receive the vaccine as early as 9 years of age and up until age 45. In addition to the vaccine, yearly cervical exams with a pap smear are advised for all women with IBD. Female IBD patients should be encouraged to establish care and follow regularly with a gynecologist.

Screenings: Depression

Depression and anxiety rates are higher in IBD patients when compared to the general population. It is not clear which comes first, i.e., if IBD or depression and anxiety precede the other. Both mental states are situational to active disease, but baseline levels are also increased in patients with IBD [58].

Depression is linked to a lower quality of life, poor medication adherence, and worsened disease activity [58]. Routine mental health screenings should be implemented in this population to detect depression or anxiety. Objective screening tests, most often the Patient Health Questionnaire-2 and 9 (PHQ-2 and PHQ-9) or the Generalized Anxiety Disorder-7 (GAD-7), are brief, highly sensitive questionnaires that can be used [59]. Specific screening intervals have not been established; however screening at diagnosis, and when clinical or medication status changes, is reasonable [60]. If either depression or anxiety is detected, facilitating a referral for appropriate treatment, such as psychological counseling, is advised. In our practice, we have incorporated cognitive behavioral therapy (CBT) delivered by a licensed medical social worker (LMSW), because CBT has shown to improve quality of life and decrease anxiety and depression in IBD patients [61, 62]. Unfortunately, not all patients will have access to psychotherapy due to insurance coverage, so Support groups, through organizations like the Crohn's and Colitis Foundation or community health centers, should be offered, as a supplementary strategy.

Screenings: Fatigue

Fatigue is one of the most common complaints among IBD patients, affecting more than half of the IBD population [63]. Considered another extraintestinal manifestation of IBD, fatigue is observed in patients during both active and quiescent states of the disease. Although screening for fatigue is not part of standard healthcare maintenance recommendations, addressing fatigue may improve quality of life. The etiology of fatigue is multifactorial, stemming from the disease itself or the complications, medications, mood, and sleep disorders associated with it. Given the complex nature of fatigue, we focus on getting the disease into a deep remission. If the fatigue persists, we evaluate for non-IBD-related etiologies. We developed an algorithmic approach to screening for non-IBD etiologies of fatigue with attention to correcting anemia, nutritional deficiencies, mood disorders, and sleep disorders and identifying culprit medications. Often, these investigations occur in parallel. Our algorithm is presented in Fig. 7.4 [63].

Screenings: Tobacco

Tobacco cessation is strongly advised in Crohn's disease patients given the associations with worsened disease severity, flare-ups requiring hospitalization, and higher incidence of surgical complications [64]. The cessation of tobacco is associated

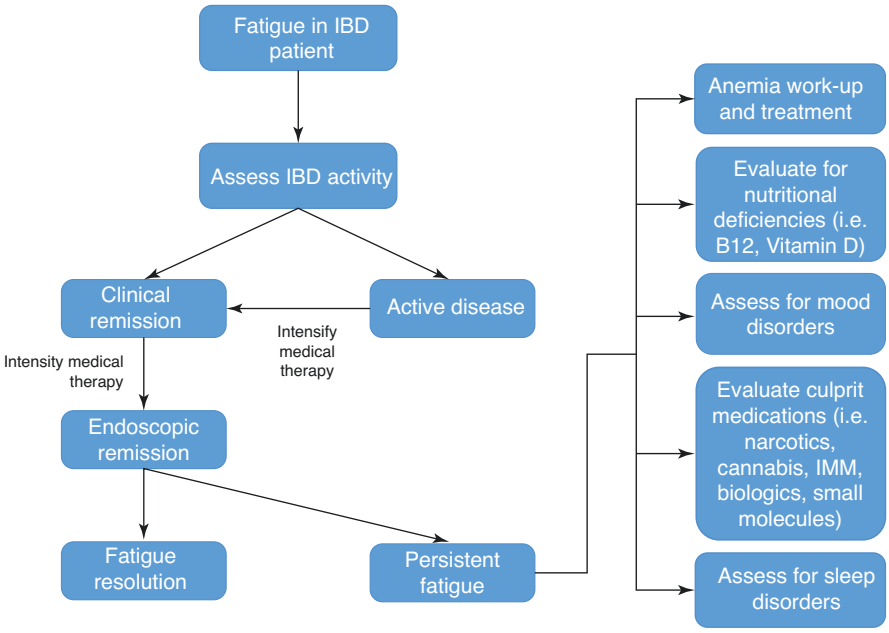

Fig. 7.4 Fatigue algorithm

with significant benefits that should be emphasized to patients including decreasing extraintestinal manifestations and lowering risk of surgical recurrence [65]. Patients' motivation to quit should be assessed at each visit [66]. Higher rates of depression and anxiety in Crohn's disease may contribute to a lower motivation to quit [64]. An interdisciplinary approach to tobacco cessation, including smoking cessation programs, pharmacotherapy, and psychological counseling, has been shown to be effective in the general population [64].

Several pharmaceutical options for tobacco cessation exist, including nicotine replacement (NRT), bupropion (Zyban), and varenicline (Chantix) [67]. Nicotine replacement is available in several forms including patch, gum, lozenge, nasal spray, and inhaler. NRT is available over the counter and is relatively inexpensive [67]. Bupropion (Zyban) and varenicline (Chantix) require a prescription and must be monitored carefully.

Bupropion is an attractive option to some patients as it can prevent weight gain and relapses [67]. It may also be combined with nicotine replacement for higher efficacy [66]. Treatment should begin 1–2 weeks before quit date, and dosing starts at 150 mg (sustained release) each morning for 3 days, then 150 mg twice daily for 3–6 months [68]. Some notable side effects include insomnia, dry mouth, and increased suicidal ideation in patients with a history of depression [68]. Contraindications to therapy include use of monoamine oxidase inhibitors within 14 days, history of eating disorder, and seizures [68].

Varenicline (Chantix) should also be started 1 week prior to quit date and continued for a total of 12 weeks. Dosing can be gradually increased from 0.5 mg per day on days 1 to 3, 0.5 mg twice daily on days 4 to 7, and then 1 mg daily after that [68]. If smoking cessation is not achieved, another 12 weeks can be added. Unlike bupropion, varenicline should not be given with nicotine replacement therapies [68]. Some common side effects like abnormal dreams, headache, and nausea are usually tolerable; however more severe adverse side effects that usually require cessation of treatment include behavior changes, aggression, and suicidal thoughts and actions [68].

Given the potential for serious adverse events from smoking cessation drugs, partnering with a primary care provider is advised for close monitoring [15]. Proposed complementary therapies include hypnotherapy, exercise, and acupuncture, although more studies need to be conducted to prove efficacy [64].

Nutrition

Comprehensive nutritional counseling is universally sought after by IBD patients and providers. Given the risk for nutritional deficiencies and malnutrition in the IBD population, close monitoring of lab values, weight, and appetite should be implemented routinely. Guidance from a dietician can be beneficial as supplemental nutrition and diet plans are highly individualized. Despite heavy interest in nutritional research within the IBD community, a "one-size-fits-all" diet has yet to be established.

Nutrition: Diet Counseling

Diet is perceived as a vital aspect of disease management for a majority of IBD patients. In a questionnaire sent to almost 300 Dutch IBD patients, more than half of participants reported diet as either more or equally as important as their medication for the treatment and outcomes of their disease [69]. In that same survey, 81% of patients stated their main source of nutritional knowledge was from their own experience. Providing accurate information to patients seeking dietary counseling is an integral part of healthcare maintenance. Dietary guidance can serve as a useful tool to promote healthy habits and prevent nutrient deficiencies. The addition of a dietician to discuss personalized diet plans with patients may provide extra insight and motivation. Diet is not a replacement for conventional therapy, especially in those with moderate to severe disease activity.

Exclusive enteral nutrition (EEN) has been studied and proven to induce clinical remission and even endoscopic remission in pediatric Crohn's patients [70], 2017. The same success has yet to be replicated in adult patients [71]. EEN has limitations

such as unpalatability, high cost, and difficulty with administration since some children require nasogastric tube placement [72]. Dietary studies in IBD are relatively inconclusive, and therefore there is no definitive diet that can be recommended for IBD patients [73]. There are limited animal studies that suggest eating food emulsifiers as well as red meat may induce a flare [73]. Recommending a diet rich in fruits and vegetables (may not be possible in those with symptomatic small bowel strictures) and low in red meat and processed foods may be advised [73]. A Mediterranean diet has shown some overall health benefits and seems to be in line with these recommendations [73]. The only randomized trial of diet compared Mediterranean diet with specific carbohydrate diet in Crohn's disease, DINE-CD, and we eagerly await the analysis of those results [74]. Monitoring for response with clinical and objective markers, evaluating for vitamin deficiencies, and ensuring adequate caloric intake should be part of routine dietary assessments.

Nutrition: Vitamin B12

Folate and vitamin B12 deficiencies are more prevalent in IBD patients as a result of malabsorption, history of ileal resections, and medication side effects [75]. Ileal involvement with Crohn's disease is an independent risk factor for folate deficiency, and ileal resection is an independent risk factor for vitamin B12 deficiency [76]. Medications, including sulfasalazine and methotrexate, additionally put patients at risk for folate malabsorption. Patients taking either medication should be supplementing with 1 mg folic acid daily. Particular attention should be given to IBD patients who follow a vegetarian diet as B12 is derived primarily from animal products.

Vitamin B12 and folate should be monitored frequently in Inflammatory bowel disease especially when deficiencies are detected [79]. Recognizing and treating abnormal values are vital given the debilitating outcomes that can occur. Clinical features of B12 and folate micronutrient deficiencies are often subtle, such as fatigue, paresthesia, and mouth ulcers; however more severe manifestations can involve neuropsychiatric complications [77].

Vitamin B12 deficiency is diagnosed when B12 levels are less than 150 pg per mL. Vitamin B12 can be supplemented either intramuscularly by mouth or via nasal spray. Given the controversy over efficacy of oral and nasal solutions, intramuscular cyanocobalamin is the standard recommended treatment [77]. Dose replacement can vary, as limitations to self-injection can prevent patients from obtaining appropriate dosing. The *American Family Physician* guidelines recommend B12 injections of 1 mg three times per week for 2 weeks, in those without neurologic complications [78]. In our practice, patients who are not willing to self-inject come in for weekly office injections for 4 weeks. These injections are often ongoing; therefore transitioning to oral replacement can bridge injection treatments. Some nutritional sources of vitamin B12 include shellfish, fatty seafood, and fortified cereals [79].

Nutrition: Iron

Iron deficiency anemia (IDA) is a common manifestation in inflammatory bowel disease due to chronic blood loss and malabsorption. Common symptoms of IDA include fatigue, pallor, and tachycardia, but this condition can often go unnoticed leading to delayed diagnosis. Since IDA leads to an overall lower quality of life in the IBD patient, prompt detection and treatment are important [80].

An iron panel, which includes ferritin, transferrin, transferrin saturation, and hemoglobin, should be checked every 3 months in patients with active disease and every 6–12 months in patients in remission [80]. When assessing for response during supplementation, monitoring levels 4 weeks after initiation of treatment is advised [81]. The type of repletion, oral or IV, depends on the severity of anemia, tolerance to the chosen medication formulation, and current disease activity. In patients with hemoglobin above 10 g/dL and quiescent disease, with no prior intolerance to oral formulations, oral iron may be initiated. Oral iron should be avoided during an active flare because of the risk of worsening IBD activity, which has been seen in animal studies from the rise in pro-inflammatory effects of oxidative stress [82]. Side effects to oral iron may be mitigated by using slow release iron formulations and daily doses less than 100 mg of elemental iron [81]. If intolerable side effects such as abdominal pain, constipation, or nausea develop or there is a known history of intolerance, then IV iron should be initiated [80]. The role of the gastroenterologist in treating IDA depends on availability of resources and comfort with infusion replacement protocols.

New formulations of IV iron are well tolerated and safe in the IBD population. Previous formulations of high molecular weight iron dextran, no longer in use, caused serious infusion reactions, causing many of the current misconceptions surrounding IV iron [82]. Anaphylactic risk was evaluated between four common forms of IV iron in a study by Wang et al. [83]. Between iron dextran, ferumoxytol (FXT), gluconate, and sucrose, iron sucrose had the least risk, while iron dextran had the highest risk [83]. In our practice, our preferred IV iron formulation is ferric carboxymaltose (FCM) because it has the most clinical evidence and is also well tolerated. Dosing for FCM is 1000 mg or 20 mg/kg once weekly, infused over 15 minutes. Iron levels should be re-evaluated 4 weeks after treatment. Referral to a hematologist should be considered to manage anemia, especially when deficiencies persist despite standard treatment approaches. It is crucial to note that treatment of the underlying disease should be the first aim in treating patients with IBD, as the most common cause of IDA in this population is blood loss through active disease state [82].

Nutrition: Vitamin D

The association between low vitamin D and inflammatory bowel disease is unclear, but some studies indicate that vitamin D plays a vital role in keeping inflammation at bay through regulation of inflammatory cytokines and inhibition

of proinflammatory cell proliferation [84]. Vitamin D deficiency has not yet been established as a cause or an outcome of IBD. Patients who are at a higher risk of vitamin D deficiency are those with impaired nutritional absorption, food restriction, or who avoid the sun (through skin coverings due to cultural reasons or to avoid sun damage) [85].

The cutoff values for treating vitamin D deficiency vary across several societies, ranging between 20 and 30 ng/mL of 25(OH)D [85]. The optimal vitamin D concentration in IBD patients has yet to be determined, although 30–50 ng/mL is considered a safe and potentially beneficial target [86]. Preferred treatment includes supplementation with vitamin D3, as this is the most potent form of vitamin D and should be used over alternative formulations, such as vitamin D and D2. Society guidelines vary in suggestions for what is adequate dosing. IBD patients may even require higher dosing than what is recommended for the general population [86]. The recommended range of dosing for IBD patients is between 1800 and 10,000 IU of cholecalciferol [86]. Although sun exposure increases vitamin D synthesis, there is no harmless threshold to recommend to patients that will not increase the risk of skin cancer. Dietary sources of vitamin D include egg yolks, oily fish, liver, and fortified foods such as some brands of yogurt, plant milks, and orange juice [85].

Special Considerations

Special Considerations: Healthcare Maintenance in the Older Adult

Older IBD patients, aged 65 and older, are a vulnerable group that requires special attention, because they received even less patient-directed preventive services. Only 50% of older adults receive the recommended vaccines and cancer screenings despite the higher risk of infection and malignancy [87]. Establishing routine healthcare maintenance visits with the older patient is imperative in order to prevent disease, monitor comorbidities, and manage polypharmacy.

Infection risks are higher in the older patient, and many of these risk factors, such as malnutrition, surgery, vaccination, hospital readmission, and immunosuppressive therapy, are modifiable [88]. Special care regarding monitoring disease response should be taken to avoid relapse and hospital admission. The older IBD population engages in higher healthcare utilization and costs with longer lengths of stays, higher hospitalization rates, and hospital mortality rates [89].

Age-specific vaccinations are advised for the older IBD patient. The high-dose influenza vaccine and the pneumococcal vaccine (PPSV 23) are recommended at the age of 65. Ensuring patients have received their shingles vaccine, as well as all other routine vaccinations, is recommended.

Nutritional screening and correction for at risk vitamin deficiencies including thiamine, riboflavin, vitamin D, calcium, magnesium, selenium, and zinc are important.

Treating anemia may prevent cognitive impairment, falls, fractures, and mortality [90]. Dietician counseling can be offered in order to maximize nutritional intake. For patients with comorbidities like diabetes and chronic kidney disease, improved insurance coverage may be obtained, and there is dual benefit to dietary counseling.

Screening for depression, which can often be accelerated in aging, should be performed routinely. If any signs of depression or mood changes are detected, resources for community services and mental health counseling should be offered. For patients with any cognitive decline, medication adherence may be a challenge. Creating a collaborative healthcare team, with the primary care provider, pharmacist, nurse, and family member can help keep older patients on track.

Special Considerations: Medication Adherence

Pharmacotherapy for IBD management is the backbone of therapeutic intervention. Medication adherence is associated with better disease outcomes and decreased hospitalization burden. Despite this, medication adherence rates in the IBD population are poor [91]. Nonadherence rates greatly vary in the IBD population, ranging anywhere from 2 to 93% [91]. Nonadherence, which can be defined as taking medications less than 80–95% as prescribed, can lead to disease relapse, loss of response to biologic therapy, worse quality of life, and increased morbidity and mortality [91]. Monitoring adherence and identifying risk factors for nonadherence should be at the forefront of HCM encounters. Providing supportive modalities to promote treatment adherence can be implemented in order to optimize patient outcomes. Providers should address patient's medication concerns before beginning treatment and periodically throughout maintenance therapy.

Monitoring for adherence can be performed using objective and subjective measurements. Serum drug levels for biologic and immunomodulator treatment can be obtained. Low drug levels may indicate missed doses, and undetectable levels may suggest self-discontinuation of treatment [91]. Patient confirmation should verify any speculation as other issues may be driving behavior. We have seen drug affordability result in pill splitting. Self-reporting with diary entries, interviews, and questionnaires can provide useful insights into adherence rates and reasons for avoidance [91]. Asking open-ended questions that are nonjudgmental can prevent biased responses and provide clinical insight [91].

Provider interventions to promote medication adherence should consist of patient engagement and encouragement. Direct observation of patients undergoing infusion or injection therapy may endorse compliance. Maintenance therapy in the form of subcutaneous injections can be offered to be administered in the provider's office if nonadherence is predicted. Office injections may be especially beneficial to those patients with a history of nonadherence or needle phobia. If patients plan to self-inject at home, virtual visits can be offered as an additional means of ensuring good technique, while also monitoring compliance.

Visual and auditory reminders, such as alarms and pill boxes, can aid in medication adherence. Cognitive behavioral therapy can be offered to patients who are not

motivated or have negative thoughts associated with treatment [91]. Medication counseling from an IBD pharmacist has been shown to decrease nonadherence rates in the IBD population [92]. Combination of several patient-centered methods to help motivate medication adherence may lead to improved patient outcomes.

Special Considerations: Complementary Medicine

Complementary medicine includes a variety of treatment options that are used in conjunction with conventional therapies. IBD patients are known to have high levels of fatigue, anxiety, and depression, all complex conditions that require a multidisciplinary, integrative approach [93, 94]. Some studies have shown that complementary medicine can help with symptom and pain control, improve quality of life, and improve overall mood and attitude toward health and well-being. There are a variety of emerging complementary medicine options in the literature including medical cannabis, various diets, acupuncture, vitamin and minerals supplements, probiotics, and mind-body therapies. Patients are increasingly turning to alternative and complementary options, and it is estimated that up to half of IBD patients use these at some point [95]. However, appropriate evidence is often lacking**.** In fact, patients are willing to spend large amounts of money for complementary and alternative therapies. A recent national health survey estimated that 38% of adults in the United States use alternative therapies and spend over $30 billion dollars [96]. There is a perceived favorable side effect profile for alternative therapies because traditional medicine is associated with complications including, but not limited to, infection, myelosuppression, and malignancy [97]. It is important to note that this is a dynamic and evolving field and more rigorous testing is needed to understand the risks and benefits of complementary medicine in IBD. Although these therapies can have positive benefits, complementary medicine should not replace conventional therapies. Considering the popularity of these therapies among IBD patients, it is important for both patients and practitioners to be informed about the safety and efficacy of these treatments to allow for evidence-based practices. While a review of all complementary interventions is beyond the scope of this chapter, we have included a section on cannabis since this product will become increasingly available, and adopting a strategy to discuss this in a nonjudgmental and transparent manner will be useful to both the practitioner and the patient. We have incorporated this topic into our healthcare maintenance visits, which is less disease and drug focused, since patients are sometimes curious and have questions that lead to a more detailed discussion.

Cannabis

Cannabis sativa, best known as marijuana, has earned significant interest from patients and investigators for its perceived benefit to manage bowel-related symptoms. In fact up to a third of IBD patients have reported trying marijuana [98].

Although cannabis has gained its popularity for its psychogenic effects, there are endogenous cannabinoid receptors in the enteric nervous system, which have an influence on gut motility [99]. Cannabinoids are involved with activating the endocannabinoid system, which helps to regulate gastrointestinal functions including pain, motility, and inflammation. Activating the endocannabinoid system can help in IBD [100]. The two most studied and active chemicals in the *C. sativa* plant are tetrahydrocannabinol (THC) and cannabidiol (CBD). While THC is responsible for psychoactive effects, both THC and CBD have roles in modulating pain, motility, and inflammation in the gut [101].

Cannabis seems to have a therapeutic role for IBD patients, but research is still in nascent stages and is still evolving. Furthermore, the variability of available cannabis preparations and modes of consumption make studying cannabis in a randomized, controlled trial setting extremely challenging. In the United States, cannabis is considered a Schedule I substance at the federal level and is considered illegal for recreational use and medicinal use and cannot be given for research purposes [102]. However as of 2020, at the individual state level, marijuana is legal for recreational use in 15 states and Washington DC and decriminalized in 16 others, and medical marijuana is legal in 35 states and Washington DC.

Initial interest came from studies in mice showing possible anti-inflammatory effects which prompted studies in humans [103]. Although less robust in humans, early trials showed improvement in clinical symptoms for patients with Crohn's disease [104, 105]. While there are several observational studies showing improvement in pain, diarrhea, and mood symptoms with patients using cannabis, at the moment, there are only three small randomized placebo-controlled trials investigating cannabis in active Crohn's disease. The early randomized trials were comparing smoked cannabis cigarettes to placebo, and over 90% of the cannabis group reported positive response. In a placebo-controlled trial, patients were given 230 mg THC in the form of cigarettes for 8 weeks, and the treatment group had a statistically significant improvement in CDAI scores, but the benefit was lost within 2 weeks after stopping the drug suggesting the absence of a more definitive interruption of inflammation [104]. In a follow-up study, patients with active Crohn's disease, many of whom had failed immunomodulators and biologics, were given 10 mg CBD oil twice a day for 8 weeks vs. placebo. The treatment group reported improved symptoms, but there was no difference in CDAI reduction between the groups [106]. In a similar study presented at UEG week, Naftali et al. recruited 46 patients with moderately severe Crohn's disease and randomized them to 8 weeks of cannabis oil containing 15% cannabidiol and 4% tetrahydrocannabinol versus placebo. Patients report significant improvement in symptom severity and quality of life but no statistically significant difference in endoscopic scores or inflammatory markers [107]. It is interesting to postulate whether cannabis temporarily relieves symptoms but has no effect on the biological activity of the underlying disease. These later studies used a different administration method of cannabis than previous studies, oral cannabis compared to the previous smoked cannabis. This oral mode of administration method allowed the ability for proper blinding, which was challenging with smoked preparations since smoked cannabis can give a sense of euphoria. In light of these

findings, it is essential to emphasize to patients the importance of staying on their conventional therapies and that cannabis has a supplementary role in treating patients with IBD. Interestingly there is some data showing statistically significant improvement in Mayo scores in UC patients using THC cannabis cigarettes. Unfortunately objective disease activity markers including C-reactive protein (CRP) and fecal calprotectin (FC) and endoscopic disease activity did not show any statistical differences [98].

Aside from a lack of data showing that cannabis decreases inflammation in IBD, there are legal and psychosocial ramifications with cannabis use, particularly in the young and adolescent population. Access remains restricted in certain states with concerns about the link between marijuana and dependency and addiction. Additionally, there is no standardization in the quality and dose of cannabis product that patients are getting. Cannabis and, in particular, higher cannabis doses, chronic marijuana use, and synthetic marijuana preparations are associated with cognitive impairments including amotivational syndrome, psychosis, learning deficits, as well as nausea, vomiting, cyclic vomiting syndrome, motor vehicle accidents, and fertility issues [95, 108, 109]. Chronic cannabis use in CD patients was also a strong predictor for needing surgery [110]. Patients should also be counseled about the risk of e-cigarette, or vaping, product use-associated lung injury (EVALI). Vitamin E acetate is an additive in THC-containing e-cigarettes and is now known to be strongly linked to EVALI, a severe pulmonary illness [111]. At our clinic, we advise our patients to avoid vaping and use alternative methods for ingestion.

Questions surrounding the safety profile and side effects of cannabis, particularly regarding the dosing and mode of administration, highlight the need for additional research. The European Crohn's and Colitis Organization has recently published a review with recommendations for complementary medicine and psychotherapy in IBD. They do not recommend cannabis and suggest there is limited evidence to suggest any positive effect on disease course [112]. The Crohn's and Colitis Foundation similarly notes that more research is needed regarding cannabis and IBD and that currently there is not enough evidence to suggest that medical cannabis reduces IBD inflammation or improves disease activity [113]. Prior to cannabis being recommended as an adjunct to address specific symptoms, more trials establishing safety and efficacy of cannabis are needed, and patients should be counseled about potential adverse effects.

Conclusion

IBD specialists must have a comprehensive understanding of the unique needs of IBD patients and take a proactive role in the assessment and screening of healthcare needs in order to improve the quality and rates of preventive care administered to IBD patients. Many of these patients are on immunosuppressive agents, so the benefit of interventions to mitigate treatment-related adverse effects is especially critical. To effectively co-manage these patients, IBD teams must advise primary care

physicians regarding the wide range of issues that IBD patients need assessed including vaccinations, osteoporosis screening, cancer and dysplasia surveillance (colorectal cancer, skin cancer, cervical cancer screening), depression and anxiety, and smoking. We have found that a multidisciplinary approach with the gastroenterologist "quarterbacking" the team is the most effective strategy to guide the IBD patient through a complex care pathway.

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