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Vaccinations for Patients with Inflammatory Bowel Disease: An Updated Review

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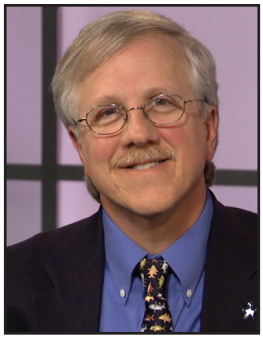

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Patients with Inflammatory Bowel Disease (IBD) are at an increased risk for infectious complications due to the immune disturbance inherent with disease pathophysiology and immunosuppressive therapies. Some of these infections are vaccine preventable, making immunizations of critical importance for the preventative care of patients with IBD. Physicians caring for these patients should familiarize themselves with vaccination schedules to ensure that not only are patients up to date with their vaccines, but that patients receive them at the appropriate time, ideally before initiating immunosuppressant therapy. This review highlights vaccinations for patients with IBD, suggestions for increasing vaccination rates in your practice and new changes in practice guidelines.

INTRODUCTION

Patients with Inflammatory Bowel Disease (IBD) are a patient population where a focus on increasing preventative health care measures is needed.[1] The pathophysiology of IBD involves the activation of a systemic inflammatory process with release of cytokines and other inflammatory mediators.[2] As a result, patients with IBD are at an increased risk of infections due to their altered immune system; further complicating this is the fact that many patients with IBD are treated medically with immunosuppressive therapies, increasing risk of infection.[3] For instance, a retrospective cohort study demonstrated patients with IBD are at increased risk for pneumonia, a risk further increased with steroids and opioids.[4] Immunosuppressive therapies for IBD includes agents such as 6-mercaptopurine (6-MP), azathioprine, methotrexate and tofacitinib. In addition, biologic agents including infliximab, adalimumab, certolizumab, golimumab, vedolizumab and ustekinumab are being used more frequently, while corticosteroids continue to be used in acute flare management.[5] Infectious complications are an important cause for hospitalization in IBD patients.[6] With these heightened risks, it is important to understand the best practices in vaccinating patients with IBD, both before and after therapy is initiated. This article will discuss current guidelines for vaccination recommendations in patients with IBD and review how to implement a vaccination process in your practice.

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Vaccination and Disease Activity

A growing body of literature has served as the basis of current expert recommendations on how and when to vaccinate patients with IBD, and has concluded that vaccinating IBD patients is not associated with a flare in disease activity.[7,8]

Defining Immunosuppression in Patients with IBD

Patients with IBD on immunosuppressive agents are considered to have either low or high levels of immunosuppression depending on their medications. High levels of immunosuppression include those on treatment of daily steroid therapy with doses equivalent or greater than 20 mg of prednisone for 14 days or more, treatment with anti-TNF agents, ustekinumab, tofacitinib as well as patients with severe protein calorie malnutrition. Patients receiving 20 mg of prednisone or less for less than 14 days, those receiving methotrexate less than or equal to 0.4 mg/kg per week, and those on azathioprine less than or equal to 3 mg/kg per day or 6-mercaptopurine less than or equal to 1.5 mg/kg per day are considered to have low levels of immunosuppression.[9,10]

Vaccination Recommendations

Live Vaccines

Varicella

In general, IBD patients should be immunized with live attenuated vaccines at a minimum of 6 weeks before starting immunosuppressant therapy.[1] Before initiating immunosuppressive therapy for IBD, the Advisory Committee on Immunization Practices (ACIP)[11] recommends confirming immunity for varicella. If a history of vaccination cannot be confirmed or if they are not shown to be immune serologically, the 2013 Infectious Diseases Society of America (IDSA guidelines) recommend administration of the live varicella vaccine prior to immunosuppression.[9]

Measles, Mumps and Rubella

Vaccinating for measles, mumps and rubella (MMR) is typically accomplished in early childhood so a majority of patients with IBD are already immune. If patients have not been vaccinated or have negative serologies, MMR should be administered prior to initiating immunosuppressant therapies.[12] ACIP guidelines give attention to growing outbreaks of these preventable illnesses in the United States, including mumps.[13] Patients determined to be at increased risk are recommended to receive an additional, third dose through the MMR vaccination.[11]

Herpes Zoster

The incidence of herpes zoster virus reactivation is roughly 3 to 13/1000 person years and increases in patients who are receiving combination therapy, including anti-tumor necrosis factor alpha (TNF-α) with azathioprine and/or steroids.[14,15] Two retrospective studies demonstrated that patients on thiopurines or a combination of thiopurines and TNF antagonists had an increased risk of developing herpes zoster.[16] Previous ACIP guidelines recommended all immunocompetent patients receive the live-attenuated vaccine Zostavax at age 60. IBD patients aged 60 or older should receive this vaccine before initiating immunosuppressant therapies given the risks of administering live vaccines to immunosuppressed patients.[11] However, patients with IBD considered to have a low level of immunosuppression fit a safety profile that still allow for vaccination.[8]

Recent data suggests that vaccinating patients with Zostavax while on anti-TNF therapy is relatively safe, as the use of these medications alone was not associated with increased incidence of vaccine related infection.[18] Additionally, administration of the live zoster vaccine was associated with a significant reduction in the risk of developing shingles.[17] Therefore, expert opinion recommends shared decision making with patients on anti-TNF agents, as well as an individual case review before offering the live vaccine.[8] Potential barriers to vaccinating IBD patients against herpes zoster have recently been reduced with the new inactivated vaccine for herpes zoster, Shingrix (reviewed below). The recent Food and Drug Administration (FDA) approval of Shingrix has allowed for a review of vaccination guidelines.[19]

Inactivated Vaccines

Herpes Zoster

Shingrix, a two-dose, inactivated vaccine against herpes zoster, was approved by the FDA in 2017 for adults aged 50 years or older (Table 2). Phase

I and Phase II trials of Shingrix suggested that the effectiveness of the vaccines would wane a full 19 years after administration.[17] The ACIP and CDC now recommend this vaccine to all immunocompetent adults aged 50 years or older instead of the live Zostavax vaccine, and also approving it for immunocompetent adults irrespective of prior Zostavax administration.[18] With the prospect of a safe inactivated vaccine for healthy individuals against herpes zoster, additional studies are needed in immunosuppressed patients, including those with IBD. Studies demonstrating the efficacy and safety of Shingrix in hematologic malignancies and renal transplant patients offer the impetus to complete studies in immunocompromised patients with IBD.[20]

Hepatitis A Virus

Patients in developed nations, including the United States, are at a lower risk of contracting hepatitis A virus (HAV) infection, but patients with IBD should still be vaccinated with the HAV vaccine if they are not immune.

Patients on anti-TNFs have a statistically significant decreased response to HAV vaccine compared to those not treated (p=0.001); however, the rate of seroconversion was still notably high in the anti-TNF group with a rate of 92.4% (85/92) compared to 99.1% (324/327) in the non-treatment group.[21]

Patients diagnosed with IBD should be tested for HAV immunity and should receive the routine two-dose series administered at 0 and 6 months if they are not immune.[5] The 2018 ACIP guidelines does not address immunosuppressed patients in its HAV guidelines, although prior ACIP recommendations noted this inactivated vaccine is safe to administer such populations.[1]

Hepatitis B Virus

The prevalence of hepatitis B virus (HBV) is similar in patients with IBD and the general population.[22] The ACIP recommends that patients with IBD who are not immune to HBV receive the vaccination series, even after initiating immunosuppressant therapy. The most commonly administered vaccine for HBV is a recombinant formulation that consists of the HBV surface antigen (HBsAg) administered in three doses. A newer vaccine, Heplisav-B, a single-antigen HepB vaccine with a immunostimulatory adjuvant, was approved by the FDA in 2018 for use in adults ≥18 years old.[23] This vaccine generates a strong serologic response in adults (95%), although long-term implications on safety have yet to be studied.[24] The ability to generate antibodies depends on a robust T-cell response and for B cells to proliferate and differentiate into anti-HBs-secreting plasma cells.[25] While these immune system components are fully functional in healthy individuals, patients with IBD have immune alterations and further suppression when on therapy. A lower antibody titer response may be seen in older age adults and the use of anti-TNF treatments.[26,27] When vaccinating patients on anti-TNF therapy, we ideally recommend vaccinating prior to initiation of therapy.[28]

Influenza

The ACIP recommends patients receive the inactivated or recombinant influenza vaccination (available in trivalent or quadrivalent forms) annually to target the evolving viral strain.[29] Patients with IBD have a lower serologic response to this inactivated vaccine and this response is worse in those on immunosuppressant therapy.[30,31] There are no recommendations for an additional booster.[32] Current ACIP guidelines allow for vaccinating IBD patients already on immunosuppressant therapies. There is improved serologic response to a higher-dose trivalent or quadrivalent dose, a reliable option for the elderly.[11]

Pneumococcal Pneumonia

Two vaccines are available for pneumococcal pneumonia (Table 3), the 23-valent polysaccharide (Pneumovax; PPSV23) and the 13-valent conjugate vaccine (Prevnar; PCV13). The ACIP recommends immunosuppressed patients receive a two-dose vaccination series.

PPSV23 is a polysaccharide vaccine that depends on B-cell immune response. This humoral immune response creates specific antibodies (IgM and IgG) that target 23 pneumococcal bacterial strains. IgM memory cells are primarily responsible for targeting the bacteria.[34]

Since IBD patients have lower circulating levels of IgM B cells due to their altered immune

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Table 1. Vaccination Recommendations for Patients with Inflammatory Bowel Disease

Vaccination	Timing	Schedule
MMR (Measles, Mumps, Rubella)	All ages with negative titers prior to starting immunosuppressant therapy All patients with increased risk from new outbreaks Contraindicated if immunocompromised*	Two doses Additional third dose
Varicella	All ages if no history of vaccination or negative titers prior to starting immunosuppressant therapy Contraindicated if immunocompromised*	Two doses
Hepatitis A	All ages with negative serology	Two doses 6 months apart
Hepatitis B	All ages with negative serology	Three doses at 0,1,and 6 months respectively
HPV (Human papillomavirus)	Ages 9-15 Ages 16-45	Two doses 6 months apart Three doses at 0, 1-2, and 6 months respectively
Tdap (Tetanus, Diptheria, Pertussis)	Ages>11	One dose followed by booster every 10 years
Meningococcal	Ages 16-23	Two doses 1-6 months apart
Influenza	All ages	One dose annually
Pneumococcal Pneumonia	Ages>19	One dose PCV13 followed by one dose PPSV23, 2-12 months later depending on immune status Second dose PPSV23 5 years after first dose and again after age 65
Zostavax (Herpes Zoster)	Age >60 before starting immunosuppressant therapy Contraindicated if severely immunocompromised *	One dose
Shingrix (Herpes Zoster)	Ages >50	Two doses 2-6 months apart

* High levels of immunosuppression include those on treatment of daily steroid therapy with doses equivalent or greater than 20mg of prednisone for 14 days or more, treatment with anti-TNF agents tofacitinib.

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function, and deficient spleen function, their response to the vaccine may be suboptimal.[35]

Patients with IBD had lower circulating antibodies after receiving PPSV23, with patients on combination therapy having a decreased immune response.[36] Per the 2018 ACIP guidelines, adults aged ≥19 years with anatomical or functional asplenia, cerebrospinal fluid leak, or cochlear implant or who are immunocompromised should receive PCV13 and then PPSV23 at least 8 weeks after.[11] We recommend that patients with IBD receive these vaccines at initial diagnosis of IBD.[37] They should then receive an additional PPSV23 booster at least five years after their first dose as long as they received their initial PPSV23 before they turn 65 years of age. If a patient has already received PPSV23, PCV13 should be administered 1 year later.

Tetanus and Diphtheria

The tetanus and diphtheria vaccine (Tdap) should be administered to all patients with IBD every 10 years, as per ACIP recommendations.[1] A meta-analysis assessing IBD patient response to this vaccine has revealed no conclusive results on immune response and seroconversion.[38] Patients receiving combination therapies or single biologics were found to have significantly decreased response, and, should therefore ideally receive Tdap before starting immunomodulators, particularly when used in combination with anti-tumor necrosis factor alpha agents.[39,40]

Meningococcal

Neisseria meningitides infection poses a risk of meningitis; young adults are especially vulnerable due to their proximity to other individuals in colleges and the military. The 2018 ACIP guidelines recommends young adults aged 16-23 should be vaccinated. Given the vaccine is inactivated, patients with IBD in this age group are also recommended to receive the vaccine even if they are on immunosuppressive therapies. This however remains a conditional recommendation, as there have been few evidence-based studies to support this action.[8,39] There are multiple vaccine options against Neisseria, which cover different serotypes. The conjugate Menactra, Menveo and polysaccharide Menomune act against serogroups A, C, W, and Y, while Bexero and Trumenba only cover serogroup B (MenB) with a two-dose or three-dose series, respectively.[8] As MenB is the prevalent serogroup observed in meningitis cases in the United States, the vaccine series targeting it is recommended for adolescents.[40]

HPV

The *human papillomavirus* (HPV) is the strongest risk factor for cervical cancer, which is the second most common cause of cancer in women worldwide.[42] Additionally, it is also associated with penile, vulvar, vaginal, anal and oropharnygeal cancers. Specific HPV genotypes are associated with both low and high-grade cervical dysplasia on cytology.[43] There are two vaccines available that protect against HPV types 6, 11, 16 and 18—the former two genotypes are associated with low grade dysplasia and the latter two are associated with cervical cancer.[44] The bivalent vaccination protects against types 16 and 18 while the quadrivalent targets all four types.

As an inactivated vaccine, the quadrivalent form (Gardasil) is given in three doses at 0, 2 and 6 months, respectively for males and females aged 16-26.[11] Additional recommendations from 2018[11]

Table 2. October, 2017 Advisory Committee on Immunization Practices (ACIP) Recommendations on Zoster Vaccination

Recombinant zoster vaccine (RZV) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥ 50 years
RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL).
RZV is preferred over ZVL for the prevention of herpes zoster and related complications

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Table 3. Pneumococcal Pneumonia Vaccination Schedule

Patient Group	PCV13	PPSV23	PPSV23	PCV13	PPSV23	PPSV23
IBD Patients (both prior to and already on immunosuppressant therapy)	Ages 19-64	Ages 19-64 2-12 months after PCV 13 depending on immune status	Ages 19-64 at least 5 years after first PPSV23	Age 65 or older if no prior PCV13 If already received PPSV23, should receive PCV13 at least 1 year after PPSV23	Age 65 or older at least 8 weeks after PCV13	Age 65 or older at least 5 years after first PPSV23 if that dose received before 65

guidelines now also include children aged 9-15, who can instead receive two doses 6 months apart. On October 5, 2018 the FDA approved Gardasil for adults aged 27 through 45. We await updated recommendations from the ACIP.[45] In measuring serologic response to this vaccine, 94% of IBD patients who received three doses, seroconverted to all four types of the virus, which was a similar response to rates previously documented in healthy individuals.[46]

Implementation

It is important to note that despite vaccination schedule guidelines, there is no current consensus on who is responsible for coordinating and administering vaccinations. Surveys of gastroenterologists and family practitioners revealed that the majority of physicians believe the responsibility to ensure vaccine completion lies with the patient [41.7%] and the family physician [32.3%]. Furthermore, this survey revealed that significant predictors of vaccine completion were annual vaccination review by family physician (odds ratio [OR] = 1.82) or gastroenterologist [OR = 1.72], current steroid use [OR = 1.28], and current or prior treatment with biologics [OR = 1.42].[47] An understanding of how to implement a vaccination program is therefore necessary. New innovative approaches to aid clinicians and patients alike have been developed and introduced to improve vaccination rates amongst IBD patients. One example is the utilization of electronic medical records to create smart phrases, which can be auto-populated in notes or letters to patients to include completed and overdue vaccinations;[1] these templates can be used whenever a patient is seen in the office so that it is always updated. The Crohn's and Colitis Foundation and Cornerstones have developed useful checklists for office use. If offices carry vaccines, it is efficient to use this template and administer the vaccine before a patient leaves the appointment. Utilizing nurses has also been demonstrated to increase vaccination rates.[48] For practices that do not stock vaccines, or have limited resources to administer vaccinations, an alternative approach is to prescribe vaccines for patients to receive at a local pharmacy. Pharmacy resources can prevent delays to vaccination and have the added benefit of offering more flexible hours and vaccine availability.[48] Finally, the success of implementing a vaccination program rests on shared decision-making with patients. Office visits should include educational components to emphasize the importance of vaccines and patients should be kept up to date on recommended scheduling. If patients are not seen regularly, then patient portals can be utilized with routine automated messages to remind patients of preventative health care tasks.[1]

CONCLUSION

This review highlights current guidelines for vaccinating patients with IBD, including implications of the recent FDA approval of the new herpes zoster vaccine, the two-dose hepatitis B vaccine and new recommendations for the HPV vaccine. Vaccinating IBD patients is an important focus within the broader preventative care sphere, especially prior to initiating immune-modulating therapies. The optimal time to review vaccination schedules are when patients with IBD are seen for their initial gastroenterology visits. While live vaccines should generally be administered on these early visits if not already given, recommendations vary for inactivated vaccines and primarily differ on age; supporting data included here generally favor administration at any time, with minimal risk to patients on immunosuppressant therapy. The vaccinations discussed in this review article are imperative given the elevated risk patients with IBD are at for contracting infectious diseases. Further work to improve vaccinations rates in this population includes clarifying whether the gastroenterologist or primary care physician is primarily responsible for this task. Educating physicians in both fields will help spread knowledge on current guidelines and is an area for improvement in preventative care of IBD patients. ■

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