Vaccinating Patients With Inflammatory Bowel Disease

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Abstract: Patients with inflammatory bowel disease (IBD) are not vaccinated at the same rate as general medical patients. IBD places patients at increased risk for developing vaccine-preventable illnesses, and this risk is further exacerbated by immunosuppressive therapy. Therefore, gastroenterologists should familiarize themselves with health maintenance measures pertaining to patients with IBD. This article highlights the vaccinations required for patients with IBD, especially those who are immunosuppressed: influenza; pneumococcal pneumonia; hepatitis A and B viruses; human papilloma virus; meningococcal disease; tetanus, diphtheria, and pertussis; measles, mumps, and rubella; varicella zoster; and herpes zoster. This article also discusses issues regarding patients with IBD who travel outside of the United States, as well as highlights and provides suggestions for areas of quality improvement that are needed in the field.

Patients with inflammatory bowel disease (IBD) are at an increased risk for developing vaccine-preventable illnesses such as influenza, pneumococcal pneumonia, and hepatitis B virus.[1] This risk is further exacerbated by immunosuppressant medications used to treat IBD. In fact, fatal cases of hepatitis B infection and pneumococcal pneumonia have been reported in patients treated with biologic therapy.[2,3] In addition, patients with IBD do not receive routine preventive care at the same rate as general medical patients.[4] Therefore, providers who care for IBD patients should recognize the importance of providing this patient population with appropriate vaccinations prior to initiation of immunosuppressive therapy. This article details key issues regarding vaccinating patients with IBD, with particular attention paid to patients on immunosuppressive therapy.

Immune Response to Vaccination

IBD is a disorder in which dysregulation of the immune system predisposes patients to an impaired response to infectious diseases. Immune dysregulation occurs both in patients who are immunosuppressant-naive and those who have been exposed to immunosuppressive medications.[5]

In general, when a healthy patient is vaccinated, the immune system responds by developing protective antibodies to combat future exposure to the infectious agent. Studies have shown that patients with IBD on immunosuppressive therapy have a diminished immune response to vaccinations.[6-8] The level of immune response typically correlates with the degree of immunosuppression; for instance, a patient on biologic agents may have a greater diminished response to a vaccination compared with a patient taking a thiopurine.[9]

Vaccination Rates in Patients With Inflammatory Bowel Disease

In a busy office practice, it can be difficult to focus on health maintenance issues (eg, vaccinating IBD patients), especially if patients are presenting with urgent issues, such as abdominal pain, bloody diarrhea, or other symptoms. Gastroenterologists should recognize the importance of vaccinating patients early in the course of the disease. Providers may be uncertain as to whose role it is to vaccinate IBD patients; a survey revealed that the majority of gastroenterologists felt that it is the role of the primary care physician to administer vaccines.[10] Additionally, almost one-third of gastroenterologists reported that they would incorrectly recommend a live vaccine to an IBD patient on a biologic therapy.[10]

A lack of knowledge exists regarding vaccinating IBD patients, and it is reflected in the low vaccination rates among patients with IBD.[11] This patient population is known to have decreased vaccine uptake compared with the general population, with rates ranging from 10% to 60% for influenza and pneumococcal pneumonia vaccinations, respectively.[11] Low vaccination rates may be explained by numerous barriers, including general public apathy, fears and concerns about the side effects of vaccination, and costs associated with storage and administration of vaccines.[11,12]

In our practice, a vaccination history is taken during the patient's first office visit. Unfortunately, many patients are often unsure of their vaccination history or are unable to provide records from other medical providers. Therefore, it is appropriate to obtain titers for hepatitis A and hepatitis B viruses to confirm a previous vaccination and to determine a possible need for a booster dose. A checklist developed by Cornerstones Health facilitates documentation of routine preventive health for patients with IBD.[13]

Degree of Immunosuppression in Inflammatory Bowel Disease

As mentioned above, the degree of immunosuppression in IBD is positively correlated with the type of immunosuppressive medication used. The Infectious Diseases Society of America categorizes immunosuppression into both high and low levels based upon the strength of the immunosuppressive medication (Table 1).[14,15] Sands and colleagues add that patients with significant protein-calorie malnutrition are classified as immunosuppressed.[16]

Table 1. Levels of Immunosuppression Based Upon Strength of Immunosuppressive Medication

High-Level Immunosuppression
Treatment with glucocorticoids (prednisone >20 mg/day for ≥2 weeks and within 3 months of stopping therapy)
Treatment with effective doses of 6-mercaptopurine, azathioprine, or methotrexate compared with those with low-level immunosuppression (described below) or discontinuation within 3 months
Treatment with adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, or vedolizumab, or recent discontinuation within 3 months
Low-Level Immunosuppression
Treatment with lower total daily doses of corticosteroids compared with those with high-level immunosuppression for more than 14 days
Patients receiving methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or mercaptopurine (<1.5 mg/kg/day)

Although recent guidelines for the management of IBD do not define the use of newer biologic agents, such as golimumab (Simponi, Janssen) and vedolizumab (Entyvio, Takeda), patients on these agents should be classified as immunosuppressed.

Inactivated Vaccines

Inactivated vaccines consist of viral or bacterial proteins and carbohydrates that are grown in culture and denatured using heat or chemical methods. Because the organism of interest is inactivated, these vaccines typically produce a weaker immune response upon administration compared with live vaccines and, therefore, often require future booster administration of vaccine.[17] Inactivated vaccines can be safely administered to patients with IBD who are on immunosuppressive therapy. Table 2 presents a summary of inactivated vaccines for patients with IBD.

Influenza

Patients with IBD are at increased risk for developing influenza.[1] The influenza vaccine is available in 2 forms:

Table 2. Inactivated Vaccines for Patients With IBD

Influenza: All patients with IBD should be vaccinated seasonally with the intramuscular/intradermal inactivated influenza vaccine prior to starting immunosuppressive therapy.
Pneumococcal pneumonia: All patients with IBD should be vaccinated once with the PCV13 followed by the PPSV23 (first dose after 8 weeks if immunocompromised, or after ≥1 year if immunocompetent; second dose after 5 years; and third dose after 65 years of age). If previously vaccinated with the PPSV23, then the PCV13 should be administered at least 1 year after the PPSV23 in both immunocompromised and immunocompetent adults.
Hepatitis A: Check hepatitis A immune status at the patient's initial visit. If nonimmune to hepatitis A, vaccinate the patient with a 2-dose series (0 months and 6-12 months).
Hepatitis B: Check hepatitis B immune status at the patient's initial visit. If nonimmune to hepatitis B, vaccinate the patient with a 3-dose series (0 months, and 1 and 6 months after first dose) and recheck titers 1 to 2 months after last vaccination. If the patient remains nonimmune, offer booster with a double dose of hepatitis B vaccine or offer combined hepatitis A/B vaccination.
Human papilloma virus: All male and female IBD patients between the ages of 11 and 26 years should be vaccinated with the human papilloma virus vaccine.
Meningococcal disease: Patients with IBD should be vaccinated with the meningococcal vaccine according to standard ACIP recommendations for the general population.
Tetanus, diphtheria, and pertussis: All patients with IBD should be vaccinated with Td every 10 years. TDap should be substituted once for the Td vaccine to provide additional coverage for pertussis.

ACIP, Advisory Committee on Immunization Practices; IBD, inflammatory bowel disease; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria; TDap, tetanus, diphtheria, and acellular pertussis.

an inactivated intramuscular and intradermal form, as well as a live intranasal form. A recent study examining serologic response to the inactivated influenza vaccine in patients receiving infliximab (Remicade, Janssen) infusions found that patients mounted an immune response to the influenza vaccine 45% to 80% of the time.[7] Interestingly, vaccine administration at the time of infusion, or between infusions, did not impact serologic response.[7] While the inactivated influenza vaccine is safe to administer to patients on immunomodulators or biologic therapy, the ideal time to vaccinate patients is prior to starting immunosuppressive therapy. The live intranasal vaccination should be avoided in immunosuppressed patients.

Pneumococcal Pneumonia

Patients with IBD are at increased risk for developing pneumococcal pneumonia, and this risk is further exacerbated by use of corticosteroids, thiopurines, and biologic therapy.[18] The Advisory Committee on Immunization Practices (ACIP) recently implemented new guidelines for pneumococcal pneumonia vaccination. Because of the increased risk for this disease, patients with IBD should receive the 13-valent pneumococcal conjugate vaccine (PCV13) in addition to the 23-valent pneumococcal polysaccharide vaccine (PPSV23). The PCV13 should be administered once to all patients with IBD followed by a dose of the PPSV23 after 8 weeks in immunosuppressed patients or after a minimum of 12 months in immunocompetent patients. A second dose of the PPSV23 should be administered 5 years after the first dose and then again after the age of 65 years. If the patient has previously been vaccinated with the PPSV23, then the PCV13 should be administered at least 12 months after the PPSV23 in both immunocompromised and immunocompetent adults.[19] A recent study found that pediatric patients with IBD could mount an appropriate serologic response to the PCV13.[6] In this study, patients on biologic therapy had a slightly diminished response compared with nonimmunosuppressed patients; however, compared with healthy controls, immune response was not diminished.[20] Patients with IBD on anti–tumor necrosis factor (TNF) therapy have a diminished immune response to the PPSV23.[21] However, it is still encouraged to give the inactivated vaccine to patients already on immunosuppression, as the vaccine can continue to offer a benefit.[21]

Hepatitis A Virus

Hepatitis A virus is the most common cause of viral liver disease worldwide.[22] Patients at increased risk include men who have sex with men, injection drug users, patients with chronic liver disease, and those traveling to endemic regions. Hepatitis A titers should be checked in all patients with IBD. If patients are nonimmune, a 2-dose schedule of the hepatitis A vaccine should be administered at 0 months and at 6 to 12 months.[23] Park and colleagues assessed the efficacy of the hepatitis A vaccine in IBD patients on immunosuppressive therapy.[24] Overall, seroconversion rates were greater than 90%, but were slightly diminished in patients on anti-TNF therapy and/or immunosuppressive therapy compared with controls.[25]

Hepatitis B Virus

Patients with IBD have an increased risk of developing hepatitis B.[26] Risk factors include traveling to regions in which hepatitis B virus is endemic, intravenous drug use,

and unprotected sex with multiple partners. Hepatitis B immune status is of particular importance in patients with IBD, as there are reports of reactivation of hepatitis B infection in patients starting anti-TNF therapy.[2,27] Belle and colleagues tested the efficacy of the hepatitis B vaccine in patients with IBD and in healthy controls.[27] Patients with IBD had significantly lower hepatitis B surface antibodies compared with the healthy controls.[27] Immunomodulator and anti-TNF use did not have an impact on vaccine response.[28] Although the response rate of the hepatitis B vaccine in patients with IBD is lower compared with the general population, it can be improved by administering a booster vaccination.[28] Patients who are nonimmune to the hepatitis B virus should be vaccinated during their initial visit with a 3-dose series of the hepatitis B vaccine (0 months, 1 month after the first dose, and 6 months after the first dose). Titers should then be checked 1 to 2 months after the last dose to confirm seroprotection. Titers less than 10 mIU/mL are considered inadequate, and patients should undergo a double dose of the hepatitis B series. Alternatively, patients can be vaccinated with the combined hepatitis A/B vaccination (Twinrix, GlaxoSmithKline). Patients with IBD should also be vaccinated for hepatitis A virus.

Human Papilloma Virus

The human papilloma virus is a known risk factor for the development of cervical dysplasia. Female patients with IBD on immunosuppression have been found to have an increased risk of developing cervical dysplasia.[29] Compared with ulcerative colitis, the risk is slightly elevated with Crohn's disease and in patients taking immunosuppressive therapy.[30] Human papilloma virus vaccination is recommended for all male and female patients between the ages of 11 and 26 years.[31]

Meningococcal Disease

There is no evidence to suggest that patients with IBD are at increased risk for developing meningococcal meningitis. Therefore, patients with IBD should receive the meningococcal vaccine according to standard ACIP recommendations, which include vaccinating patients living in college dormitories, military recruits, patients traveling to endemic areas, patients with complement deficiencies, and asplenic individuals.[32]

Tetanus, Diphtheria, and Pertussis

Data regarding IBD patients' response to the tetanus vaccine are inconclusive.[33,34] The tetanus and diphtheria vaccine should be administered to all patients with IBD every 10 years, as per ACIP recommendations. This vaccine should be replaced with a 1-time dose of the tetanus, diphtheria, and acellular pertussis vaccine.[35]

Table 3. Live Vaccinations for Patients With IBD

MMR: Vaccinate all nonimmune patients with the MMR vaccine as long as they have not been on immunosuppressive therapy within the previous 3 months and there are no plans to start immunosuppressive therapy within the next 6 weeks.
Varicella zoster: Vaccinate all nonimmune patients with the varicella zoster vaccine as long as they have not been on immunosuppressive therapy within the previous 3 months and there are no plans to start immunosuppressive therapy within the next 6 weeks.
Herpes zoster: Vaccinate all patients over the age of 60 years with the herpes zoster vaccine. Vaccination is safe in patients on low-dose immunosuppression but contraindicated in patients on biologic therapy or on corticosteroids. Do not vaccinate patients on high-dose immunosuppressive therapy within the past 3 months or who plan to start high-dose immunosuppressive therapy within the next 6 weeks.

IBD, inflammatory bowel disease; MMR, measles, mumps, and rubella.

Live Vaccines

Live vaccines are those in which an attenuated form of an infectious organism is used as the primary component of the vaccine. Live vaccines typically produce a stronger immune response compared with inactivated vaccines and are of particular importance in patients with IBD, as they are often contraindicated in this patient population given the risk of disseminated infection.[35] Table 3 summarizes the live vaccines for patients with IBD.

Measles, Mumps, and Rubella

During initial office visits with patients, measles, mumps, and rubella (MMR) titers should be considered if there is no documented history of receiving this vaccine. If titers to any of the 3 viruses are absent, patients should be vaccinated with 2 doses of MMR as long as they are not currently on any immunosuppressive therapy, or if there are no plans to begin immunosuppressive therapy within the next 6 weeks. Family members of patients with IBD on immunosuppressive therapy may be safely vaccinated with MMR.[36] Patients already on immunosuppressive therapy should stop therapy 3 months prior to administering the MMR vaccine.[37] To date, no studies have evaluated the effect of immunosuppression and IBD on MMR vaccination status. Further work is needed in this area.

Varicella Zoster

Varicella zoster, the virus known for causing chickenpox in children and herpes zoster in adults, is of particular importance to patients with IBD. A large study conducted by

Tsai and colleagues demonstrated that patients with IBD are at a significantly elevated risk of developing infection with the varicella virus.[38] This risk is further increased in immunosuppressed patients. In fact, fatal cases of varicella in IBD patients have been reported.[39] A history of varicella infection should be assessed in patients with IBD. If the patient denies a history of infection or if his or her history is unclear, varicella titers should be assessed. Patients who are nonimmune should be vaccinated with 2 doses of the varicella vaccine. If there are plans to start immunosuppressive therapy, the patient should be vaccinated 4 to 6 weeks prior to commencing immunosuppressive therapy. Practitioners should wait 3 months prior to administering the vaccination if the patient has recently been on immunosuppressive therapy. Household contacts may be safely vaccinated with varicella if they have a family member with immunosuppression; however, if the household contact develops a rash after vaccination, he or she should avoid contact with the immunosuppressed family member.[40,41]

Herpes Zoster

Herpes zoster, also known as shingles, is caused by reactivation of the varicella zoster virus. Herpes zoster typically presents in adults over the age of 60 years.[42] Numerous complications are associated with the development of herpes zoster, such as conjunctivitis, uveitis, keratitis, and postherpetic neuralgia. Patients with IBD, especially those on immunosuppressive therapy, are at increased risk for development of herpes zoster because these patients develop reactivation of the varicella zoster virus at an early age as compared to the general population.[43] The ACIP recommends herpes zoster vaccination for adults over the age of 60 years, but there is no clear consensus regarding when to begin vaccination in IBD patients. According to the Centers for Disease Control and Prevention (CDC), it is safe to vaccinate patients on low-dose immunosuppression (methotrexate, azathioprine, 6-mercaptopurine).[15] A recent study revealed that while patients on low-dose immunosuppression have a diminished antibody response to the herpes zoster vaccine, they did not experience any adverse events as compared to a group of IBD patients not on immunosuppressive therapy.[8] Ongoing studies address the safety of administering the herpes zoster vaccine in patients on anti-TNFs,[44] although this practice is not currently recommended. Some physicians recommend the herpes zoster vaccine to all patients over the age of 50 years, aware that the ACIP recommends vaccination after age 60 years. Titers do not need to be assessed prior to vaccinating patients. As with varicella, household contacts of immunosuppressed IBD patients may be safely vaccinated with the herpes zoster vaccine; if the household contact develops a rash, he or she should avoid contact with any IBD family member.

The Traveler With Inflammatory Bowel Disease

Vaccinating the traveling patient with IBD is a clinical situation with which gastroenterologists should be familiar. Prior to travel, it is recommended that patients schedule a visit with an infectious disease clinician or a university traveler's clinic to discuss where they will be traveling and for how long. Both the patient and the practitioner can review travelers' health information from the CDC[45] and World Health Organization[46] to assess what infections may be endemic to the region that the patient will be visiting. One infection of particular concern for traveling patients is yellow fever, a flavivirus transmitted by the *Aedes* mosquito. The virus is highly endemic in Sub-Saharan Africa and South America. The yellow fever vaccine is a live vaccine and, thus, is contraindicated in patients receiving immunosuppressive therapy. The vaccine is recommended for patients traveling to areas with a high prevalence of the disease, as some countries require proof of vaccination upon entering.[47,48] Patients should stop immunosuppressive therapy for at least 4 months prior to vaccination. If patients cannot stop their immunosuppressive therapy, they should be strongly advised against traveling to regions where yellow fever is endemic. Other live vaccines that must be considered for traveling IBD patients include MMR, typhoid fever, and poliomyelitis. Hepatitis B immune status should be checked in patients prior to travel in regions where hepatitis B virus is endemic (eg, Southeast Asia, China, Africa). If patients are immunosuppressed and their titers are below 10 mIU/mL, a hepatitis B booster should be administered.[49] Inactivated vaccines include, but are not limited to, Japanese encephalitis virus, rabies, typhoid fever, poliomyelitis, and hepatitis A virus.

Practical Strategies for Improving Vaccination Rates

As noted previously, discussing and administering vaccinations for patients who may have other active medical issues can be difficult. The ideal time to assess a patient's health maintenance needs and administer appropriate vaccinations is during the patient's initial visit to a gastroenterologist. During this initial visit, timing of vaccinations should be considered if there are plans to start immunosuppressive therapy in the near future.[50] If vaccination services are not available in the office, the primary care provider should be sent concise recommendations for vaccines to administer.

Over the last decade, there have been numerous quality interventions aimed at improving vaccination rates in patients with IBD. In a survey of both patients and

parents, a lack of benefit from vaccinations was cited as the most frequent reason for low vaccine uptake.[51] Other reasons included concern about side effects and IBD flare, needle aversion, and inconvenience.[51] In similar quality improvement studies conducted by Parker and colleagues,[52] and colleagues at our institution, Boston Medical Center,[53] significant improvements in influenza and pneumococcal pneumonia rates were seen with simple educational handouts that were administered to patients. If an IBD patient is hospitalized, clinicians should use the opportunity to review vaccination status and administer missing inactivated vaccines.[54] Educational programs directed to fellows and practicing gastroenterologists have resulted in increased uptake of health maintenance issues, including vaccinations.[55-58]

The majority of practices and hospital systems currently use electronic-based health records (EHRs). EHRs can facilitate documentation of vaccinations and can also serve as a tool for providing physicians with alerts and reminders regarding vaccine administration. Karr and colleagues used a computerized order set in EHR (EPIC, Epic Systems Corporation) to remind physicians of vaccinations due for patients with IBD.[58] Karr and colleagues also implemented alerts to warn physicians if a vaccine was contraindicated, such as giving a live vaccine to a patient who is immunosuppressed.[58] The Cornerstones Health checklist can be used by both providers and patients to keep track of vaccines in addition to other key health maintenance measures.[13] Currently, the Crohn's and Colitis Foundation of America is piloting an IBD EPIC SmartForm that, when completed, will be made available to providers using EPIC as their electronic medical record (James D. Lewis, MD, University of Pennsylvania, personal communication). More work is needed to study the implementation of these new tools.

Conclusion

Taking care of patients with IBD often involves making complex medical decisions. Gastroenterologists are typically the primary provider for patients with IBD; therefore, it is essential to have a broad understanding of the issues surrounding administering vaccinations to patients with IBD. Clinicians should recognize the increased risk of vaccine-preventable illnesses that IBD patients face and understand which vaccines can and cannot be administered to IBD patients on immunosuppressive therapy. Providers should take an active role in evaluating their office practice for assessing a patient's vaccination history and administering appropriate vaccinations. Future research should examine the impact of new technologies, such as EHRs, with regard to their ability to improve vaccine uptake.

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