

Seymour Katz, M.D., Series Editor

Vaccination Considerations for Patients with Inflammatory Bowel Disease



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Immunosuppressive therapies, including corticosteroids, immunomodulators and biologic agents, are commonly used for the treatment for inflammatory bowel disease (IBD). These therapies have the unintended consequence of increasing the risk of infections, some of which can be prevented with appropriate vaccinations. However, these prophylactic vaccinations are underutilized in adults with IBD. In general, standard vaccination guidelines should be followed in patients with IBD. However, live vaccines should be avoided while patients are immunosuppressed. We will review the knowledge gaps among healthcare providers and specific vaccine guidelines, with additional precautions for travel, household contacts and healthcare providers.

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated chronic intestinal disease, typically classified into Crohn's disease and ulcerative colitis. Both Crohn's disease and ulcerative colitis appear to be

associated with genetic mutations that are associated with altered immunity, thus potentially increasing the risk for an abnormal response to infections (1). In addition, in order to manage the intestinal manifestations of these diseases, patients are often prescribed immunosuppressive agents including corticosteroids, immunomodulating drugs such as azathioprine, 6-mercaptopurine, and methotrexate, and biologic agents including anti-tumor necrosis alpha (TNF-alpha) therapies. As such, patients are more susceptible to infections given their underlying disease as well as the therapies to which they are exposed. In particular, patients are at risk of opportunistic infections (2),

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potentially life-threatening pneumococcal pneumonia (3), disseminated varicella (4), and viral hepatitis causing liver failure (5). Many of these infections may be entirely preventable with prophylactic immunizations, but several studies have demonstrated that vaccine uptake among patients with IBD is inadequate (6,7,8). We present general guidelines and principles for some key vaccines and report the current recommendations including strategies for vaccination of those who are immunosuppressed. We also discuss two representative cases for consideration of vaccines:

Case 1

An 18-year-old female with Crohn's disease, controlled on adalimumab, is going to college. What vaccinations should be considered?

Case 2

A 60-year-old physician with ulcerative colitis maintained on 5-ASA products works in a community hospital. What vaccinations should be considered?

GUIDELINES AND PRINCIPLES

The purpose of a prophylactic vaccine is to expose a naïve individual to a foreign antigen to which an immunologic defense can be stimulated, in order to ensure an appropriate immune response in the case of future exposure. Patients with IBD are often treated with immunosuppressive therapy, and are exposed to circumstances of college environments, global travel, and household exposures to young children who may be receiving live virus vaccinations. Non-immunosuppressed IBD patients are thought to be able to mount the same immune response as the general population. As such, these patients can be vaccinated with the same standard recommendations as the general population (9). Those not receiving immunosuppression can safely be administered live vaccines. However, IBD patients on immunosuppressive therapy may not mount as robust an immune response to vaccination (10). Furthermore, they should not be administered live vaccines given the potential for infection, although mitigating circumstances might allow for exceptions to this guiding principal (11). Ideally, a

patient's vaccination history should be fully explored at the time of diagnosis, and appropriate vaccinations should be recommended at that time, prior to initiation of immunosuppressive therapy (6).

KNOWLEDGE GAPS AMONG HEALTHCARE PROVIDERS

Several studies have demonstrated that patients with IBD are under-vaccinated (6). Although the reasons for this are unclear, it appears that significant knowledge gaps about vaccinations exist among gastroenterologists. A survey of 169 IBD patients demonstrated that 146 were exposed to immunosuppressive therapy and thus should have been prioritized for vaccination against influenza and pneumococcal infections. However, only 41 regularly received the flu vaccine and of these patients, 49% reported the reason for their lack of immunization was due to lack of awareness of the recommendations (6). In a survey of 108 gastroenterologists in the United States, most felt that vaccinations were in the purview of primary care providers, and significant knowledge gaps among gastroenterologists were identified including that 20–30% would recommend live virus vaccines to their immunosuppressed patients (12). In a Canadian survey of 167 patients and 43 gastroenterologists, patients reported that they were most comfortable with vaccination information provided by their gastroenterologist more frequently than with information given to them by any other healthcare provider. However, only 14% of these gastroenterologists routinely obtained vaccination histories in their patients, and all thought that patients had insufficient knowledge (13). While there are risks with vaccinations, it is important to educate patients as well as physicians of the importance of vaccinating this at-risk population.

SPECIFIC VACCINE GUIDELINES

Influenza

There are two forms of the influenza vaccine: the inactivated trivalent vaccine, and the live attenuated intranasal vaccine. Recommendations published in 2010 by the Center for Disease Control advocate for

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influenza vaccination in all those over the age of 6 months, but that high-risk groups (including patients receiving immunosuppression) be specifically targeted for influenza immunization (14). In the immunocompromised host, it is best to avoid the live influenza vaccine (9). Studies have been done to evaluate if the immunosuppressed patient population is able to mount an appropriate response after receiving immunosuppressive therapy. Mamula et al compared the response to inactivated influenza vaccination among children with IBD and healthy controls. They found that among 80 children on various treatments including immunomodulating agents, anti-inflammatory therapy, and a combination of infliximab and immunomodulators, the vaccine was safe for all patients, despite some decreased immune response in the IBD patients on treatment in comparison to healthy individuals (15). In another study by Lu et al, children with IBD were vaccinated with the influenza vaccine and were found to achieve seroprotection regardless of exposure to previous immunosuppressive therapy (16).

Pneumococcus

According to the Advisory Committee on Immunization Practices (ACIP), there are two types of vaccines against pneumococcal infections. The 13-valent pneumococcal conjugate vaccine is recommended for children starting at 2 years of age and the 23-valent pneumococcal polysaccharide vaccine (PPV) is approved for patients ≥ 2 years with certain underlying medical conditions, including those receiving immunosuppression, and routinely for patients ≥ 65 years of age (17). Of note, PPV administration in conjunction with the influenza vaccine is considered safe without a heightened risk of side effects, and co-administration is encouraged to increase compliance with recommendations for both vaccines (18).

A study was done to evaluate response to PPV among adults with IBD on combined immunosuppression with an immunomodulator and TNF blocker ($n = 20$), patients with IBD not on immunosuppression ($n = 25$), and healthy controls ($n = 19$). The patients not on immunosuppressive therapy were found to have similar post-vaccination titers relative to healthy controls, while those receiving combined immunosup-

pression had a significantly reduced response to each of the 5 antigens that were assessed (10). This study highlights the need to ideally vaccinate with PPV prior to initiating immunosuppressive therapy.

Hepatitis A Virus Vaccines

The hepatitis A vaccine is an inactivated vaccine. The targeted patient population has usually been considered to be travelers to endemic areas. Given the transmission mode of fecal-oral and close household contacts, as well as in some cases sexual contact, the ACIP recommends vaccinating the following groups: all children at 1 year of age, travelers to regions with high rates of hepatitis A, men who have sex with men, as well as anyone seeking long-term protection (19). This vaccine is considered to be safe and immunogenic among IBD patients as evidenced by a recent study done by Radzikowski et al among children with IBD wherein 66 children with IBD and 68 controls were exposed to two doses of vaccine. This study reported no statistically significant difference between the two groups in the rate of seroconversion after the second dose of the vaccine with minimal adverse side effects (20).

Hepatitis B Virus Vaccine

Hepatitis B is transmitted via infectious bodily fluids including blood and semen, and can be transmitted via organ transplant, sexual contact, or blood transfusions. Among IBD patients at risk for immunosuppression, reactivation of chronic HBV infection is of concern. Reactivation can occur either with immune reconstitution or from chronic immunosuppression, and has been associated with anti-TNF treatment (21). These patients are at risk for developing life-threatening liver failure. As such, recommendations suggest screening for latent HBV infection prior to initiating immunosuppressive therapy in IBD patients and if detected, initiating antiviral therapy (11).

Meningococcus

The two forms of the meningococcal vaccine include a polysaccharide vaccine as well as a conjugate vaccine, considered more immunogenic (22). According to the

ACIP, this vaccine is recommended for all people from 11–18 years of age, as well as people from 2–55 years of age who are at a particularly increased risk for meningococcal disease such as patients that have had a splenectomy or have functional asplenia, other complement deficiencies or those traveling to prevalent areas (11). No studies have been done to evaluate the safety of this particular vaccine in IBD patients; however, it is generally considered safe in the immunocompromised population (11). This vaccine is particularly relevant to first year college students and military recruits, who live in close quarters, and should be administered regardless of immunosuppression status.

Diphtheria, Tetanus, and Pertussis

The tetanus and diphtheria vaccine is the series of vaccines given to children with booster shots recommended to adults every 10 years (23). It is considered a safe vaccine that can be administered to patients regardless of immune status and therefore appropriate for IBD patients on immunosuppressive therapy (24). Of note, there is currently a pertussis epidemic in California (since 2010), considered the worst in fifty years, and thought to be responsible for the deaths of several infants. To prevent further deaths associated with this infection, all adults are encouraged to receive a booster vaccine regardless of immunosuppressive status (25).

Human Papillomavirus (HPV) Vaccine

HPV predisposes women to cervical dysplasia, and women with IBD have been noted to have a higher association of developing such abnormalities (11). In one study, women with IBD on immunosuppressive therapy were found to have a greater number of Pap smear abnormalities when compared to a similar cohort of healthy controls (26). The current recommendation is to undergo a 3-dose series for all women between the ages of 9–26. It is considered safe even among those who are immunosuppressed (11).

Varicella and Zoster Vaccines

The varicella-zoster virus (VZV) is a virus that in normal individuals with a competent immune system is

usually not fatal, but can be disseminated in adults. Adults and children with IBD who may be immunosuppressed, however, can develop widespread dissemination of VZV, which can be fatal. Given that the VZV vaccine is a live attenuated vaccine, it is contraindicated in immunocompromised patients. According to the ACIP, patients should have immunity to varicella evaluated and if naïve to this infection, should be immunized prior to initiating immunosuppressive therapy (11). A case series, by Lu et al, reported on the administration of varicella vaccine to 6 children with IBD receiving immunosuppressive therapy who tolerated the vaccine well without adverse reactions and who had an appropriate immune response (27). According to the ACIP, patients on low-dose steroid therapy (<20 mg/day of prednisone or its equivalent) can receive the varicella vaccine safely (11,28). Withholding steroids for 2–3 weeks after vaccination has also been suggested by experts and has been considered safe (29). Careful risk to benefit assessment for vaccination with varicella should be made with infectious disease consultation in cases where immunosuppressed individuals are naïve to the infection, but may be occupationally at risk for exposure to natural infection.

Reactivation of latent varicella infection develops into herpes zoster, and the associated post-herpetic neuralgia. In immunocompromised individuals, disseminated zoster can develop which can be fatal (30). According to current recommendations, the zoster vaccine should be administered to patients >60 years of age as it can reduce the incidence of zoster by 51% and post-herpetic neuralgia by 67% (31). The zoster vaccine is also a live, attenuated virus vaccine that is a potent form of the varicella antigen. Given the heightened risk of developing such infections, consideration for this vaccine should be undertaken even in those treated with “low dose” immunosuppression that includes low dose prednisone (<20 mg/daily), 6-mercaptopurine (<1.5 mg/kg/day), and azathioprine (<2.5 mg/kg/day) (32). The zoster vaccine is contraindicated in patients receiving anti-TNF therapy.

Measles, Mumps, Rubella Vaccine

The MMR vaccine is a live attenuated vaccine and as such, is contraindicated in patients on immunosup-

Case 1.

An 18-year-old female with Crohn's disease controlled on adalimumab, is going to college. What vaccinations should be considered?

This individual is a young woman on biologic therapy who will be living in the close quarters of a campus dormitory. She should undergo (if she has not already) vaccination against meningococcus, pneumococcus, influenza (using the injected, inactivated vaccine), and Hepatitis A and B. She should undergo assessment of varicella status if it is in doubt, but not vaccinated against varicella while on adalimumab. In addition, she is eligible for HPV vaccination given her age.

Case 2.

A 60-year-old physician with ulcerative colitis maintained on 5-ASA products works in a community hospital. What vaccinations should be considered?

This patient is not immunocompromised, but has an unpredictable probability of requiring immunosuppression in his future. Furthermore, as a healthcare worker in a hospital he does come in contact with patients who may be immunocompromised. He should be up-to-date with and receive all the age-appropriate vaccinations, including the annual influenza vaccine, pneumococcal vaccine, hepatitis A and B vaccine (if not immune), zoster (shingles) vaccination, and tetanus booster (Tdap) if not obtained in the last 10 years.

pression. It should be administered one month prior to initiation of immunosuppressive therapy. Current recommendations for this vaccine are to initiate the 2 dose vaccination series in children >1 year of age and in adults born after 1957 who were previously not vaccinated with a second vaccine at age >50 years with risk factors (33). The MMR vaccine is considered safe for household contacts of immunosuppressed persons with IBD (34).

TRAVEL, HOUSEHOLD CONTACTS AND THE HEALTHCARE PROVIDER

When traveling, patients should obtain expert advice from a travel medicine specialist to guide appropriate prophylaxis as well as to provide additional precautions that may be needed when traveling to an endemic area

(11). Based on local requirements, patients may require vaccination against Hepatitis A, B, yellow fever (a live attenuated vaccine), typhoid and others (9). If possible, the immunocompromised patient should defer travel to highly endemic regions until their immune system is robust (24). In particular, yellow fever is contraindicated among those who are immunosuppressed, yet may be an absolute requirement to visit an endemic area. In these cases, consultation with a travel medicine specialist is critical, as patients may require a formal medical waiver of vaccination and will need counseling against mosquito vector transmission.

Household members and healthcare workers in contact with immunosuppressed individuals with IBD must also be cognizant of the potential of exposing the immunosuppressed patient to transmissible infections. As such, these individuals should undergo appropriate and routine vaccines including influenza, MMR, and VZV (11). The live attenuated intranasal influenza vaccine may shed live virus for several days following vaccination, and is therefore discouraged among these individuals (35). The role of the healthcare provider is critical in educating both the immunocompromised patient as well as their household members for the need to adhere to appropriate vaccinations and hygiene precautions in order to minimize the risk of infection transmission.

CONCLUSION

Patients with IBD on immunosuppressive therapy are at a risk of infection with vaccine-preventable diseases. As such, these patients should routinely receive prophylactic immunizations. Ideally, upon initial presentation and prior to initiation of immunosuppressive therapy, patients should have their vaccine history evaluated and be appropriately educated and vaccinated. Both gastroenterologists and primary care physicians should be educated regarding the importance of optimizing vaccination history among patients, as there appears to be a gap in knowledge among healthcare providers in general, and it is clear that patients are not being appropriately immunized against preventable infections. ■

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