Vaccination of Patients With Inflammatory Bowel Disease During the COVID-19 Pandemic

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Abstract: Inflammatory bowel disease and the subsequent immunosuppressive regimens used to treat this condition increase the risk for acquiring viral and bacterial infections. Ensuring that patients are up-to-date with their immunizations may help prevent the development of several of these vaccine-preventable diseases. Therefore, it is imperative that gastroenterology providers offer vaccinations to patients or direct vaccination guidance to primary care providers to minimize the risk for vaccine-preventable diseases. To decrease the risk for co-infection in the setting of the coronavirus disease 2019 pandemic and avoid placing any further burden on the health care system, the call to immunize is more important than ever.

Keywords
Vaccines, preventive care, inflammatory bowel disease, ulcerative colitis, Crohn's disease, COVID-19

Importance of Vaccination in Patients With Inflammatory Bowel Disease

The pathophysiology of inflammatory bowel disease (IBD) in itself increases risk for the development of infections.[1-6] In addition, the corticosteroids, immunomodulators (eg, azathioprine, 6-mercaptopurine, methotrexate), biologics (eg, infliximab, adalimumab, certolizumab pegol [Cimzia, UCB], golimumab [Simponi, Janssen], natalizumab [Tysabri, Biogen], vedolizumab [Entyvio, Takeda], and ustekinumab [Stelara, Janssen]), and small molecules (eg, tofacitinib [Xeljanz, Pfizer]) used to treat IBD may further increase the risk for infections in these patients.[1] The risk for infection is higher when several immunosuppressive agents are used concomitantly.[1] Many of these infections, such as influenza, *Streptococcus* pneumonia, and herpes zoster (HZ), are vaccine-preventable diseases (VPDs).[1-3,7-9]

Historically, immunization rates have been lower in patients with IBD than in the general population.[4,10] Barriers to receiving appropriate

vaccination are related to both providers and patients. Provider barriers include uncertainty as to whether the gastroenterology specialist or the primary care provider (PCP) is responsible for ensuring that patients are up-to-date regarding vaccination history, failure of providers to promote the importance of vaccinations to patients, inadequate education of providers about vaccines, absence of a vaccination reminder system for providers and patients, and the additional expense of storing and administering vaccines in a medical practice.[4,11-13] Patient barriers to receiving vaccinations include a lack of understanding regarding the importance of vaccinations to prevent certain diseases, patient fear that vaccines may exacerbate IBD or cause side effects, lack of reasonable access to obtaining vaccines in a medical office, lack of recommendation from health care providers, inconvenience, fear of pain during administration, and the inability to pay for vaccinations if not covered by insurance.[4,11-13]

The Infectious Diseases Society of America (IDSA) published clinical practice guidelines in 2013, stating that a specialist who cares for an immunocompromised patient shares a responsibility with the patient's PCP to ensure that the patient receives appropriate vaccinations, or the specialist must provide explicit vaccine recommendations to the patient's PCP for appropriate follow-up.[14] The IDSA also recommends that ideally vaccines should be administered before the implementation of immunosuppression, if possible. However, treatment for IBD should not be delayed to administer vaccines.[11] It is recommended that live vaccines be administered at least 4 weeks before the start of immunosuppressive therapy.[14] Live vaccines may be administered to patients with no significant immunologic compromise. This group includes patients on short- or long-term daily prednisone at a dose of less than 20 mg or the equivalent, patients on maintenance corticosteroids at physiologic doses (if 1 month or more has passed since high-dose [HD] corticosteroids were used [≥20 mg of prednisone per day or the equivalent]), and patients on low-dose immunomodulators (azathioprine <3 mg/kg per day, 6-mercaptopurine <1.5 mg/kg per day, methotrexate <0.4 mg/kg per week), but not patients being treated with anti–tumor necrosis factor (TNF) therapy, ustekinumab, or tofacitinib. According to the US Food and Drug Administration (FDA) labeling, live vaccines may be given concurrently with vedolizumab if the benefits outweigh the risks. No data are available regarding secondary transmission by live vaccines in patients on vedolizumab.[15] However, according to the package insert for Vivotif (Emergent BioSolutions), the safety of the live oral typhoid vaccine has not been demonstrated in patients without the ability to mount an immune response, which includes patients on immunosuppressive agents; therefore, according to the manufacturer, this vaccine is not recommended for these persons regardless of the benefits.[16] Live vaccines are not recommended for patients with IBD who are severely immunocompromised. This group includes patients on HD corticosteroids (≥20 mg of prednisone per day or the equivalent), on HD immunomodulators (azathioprine >3 mg/kg per day, 6-mercaptopurine >1.5 mg/kg per day, methotrexate >0.4 mg/kg per week), on a transplant-related immunosuppressive drug (eg, cyclosporine, tacrolimus, mycophenolate), on anti-TNF therapy, on ustekinumab, on tofacitinib, or who have protein calorie malnutrition.[5,14,17,18] In patients with IBD who are severely immunocompromised, immunosuppressive therapy should be withheld for 3 months before they receive live vaccine if the benefits outweigh the risks.[17] Restarting immunosuppression after live vaccination has not been studied, but some experts recommend waiting at least 1 month.[17] If a live vaccine is required, such as before travel, experts from the Centers for Disease Control and Prevention (CDC) recommend a wait of 3 months after the discontinuation of immunosuppressive agents before giving a live vaccine.[17] It is important to consider the risks of withholding immunosuppressive therapy, which may include the development of antidrug antibodies, loss of response, infusion reactions, and/or flares of the underlying IBD.[5] These possibilities support gastroenterology specialists playing an active role in ensuring that patients are up-to-date with their immunization schedule and closing the loop of uncertainty regarding patients' preventive care.

Vaccine Administration During the Coronavirus Disease 2019 Pandemic

IBD is rare before the age of 5 years (approximately 4% of all cases).[19] Therefore, most patients should have received the 2 pediatric live vaccine series—measles, mumps, and rubella (MMR) and varicella—as these are usually administered between 12 months and 4 years of age.[20] Because of the coronavirus disease 2019 (COVID-19) pandemic, rates of childhood immunizations have drastically declined across the United States, increasing the risk for VPD outbreaks.[21] An increase in VPDs can have deleterious effects on immunocompromised patients.[21,22] Postponing or canceling routine vaccinations leaves patients vulnerable to acquiring a VPD, which can be detrimental when the risk is coupled with the potential for acquiring COVID-19. The CDC states that routine vaccination should not be delayed because of the COVID-19 pandemic.[21] All efforts should be made to assess the vaccination history of every patient at each visit to avoid missed opportunities for vaccination and to ensure that vaccinations are updated according to the

recommended CDC immunization schedule, unless a specific contraindication exists.

It is imperative to implement strategies to promote adherence to the appropriate vaccination schedule and ensure catch-up vaccination. Ideally, the recommended time to obtain a patient's vaccination history is during the initial IBD consultation, to be certain that the appropriate vaccinations are recommended or administered.

During the COVID-19 pandemic, telehealth visits have increased and nonurgent, face-to-face medical visits, including those for routine vaccinations, have decreased.[21] The use of telemedicine will likely continue to increase during the remainder of this pandemic and beyond. If gastroenterologists cannot administer vaccines at their clinical practice, it is crucial for them to communicate actively specific vaccine recommendations to each patient's PCP. Alternatively, they can provide prescriptions for vaccines to be administered at a local pharmacy. At the patient's local pharmacy, an immunization-trained pharmacist, student pharmacist, or (in some states) immunization-trained pharmacy technicians operating under the supervision of a pharmacist can safely and efficiently administer vaccinations.[22] Pharmacists can provide current education regarding the benefits of vaccinations and help motivate people to participate in their own health care and adhere to vaccine recommendations.

For ease of access and timely administration, patients can use their local pharmacy to receive vaccinations conveniently on their own time. For additional safety precautions during the pandemic, certain pharmacy chains and outpatient clinics are offering curbside or drive-through vaccination clinics to minimize patient and health care employee exposure.[21,23-25] Pharmacies may also offer appointment-based vaccine clinic days to provide appropriate social distancing and convenient patient wait times. Vaccines administered at a pharmacy are often in ample supply and covered by insurance, or the cost is similar to what it would be at an office visit. For instance, Medicare prescription drug plans (Part D) generally cover all commercially available vaccines (including recombinant zoster vaccine [RZV]), which makes it relatively easy for patients 65 years of age and older to be vaccinated at a pharmacy.[26] Other important benefits of using a pharmacy for vaccine administration include convenience, the lack of a visit fee, shorter wait times, and extended hours.[23-25] In addition, various community efforts are underway in certain cities to collaborate with local medical associations, health systems, pharmacies, health insurance companies, media, and county health departments to increase influenza vaccine awareness, particularly during the COVID-19 pandemic.[27] Through these services, patients of limited means may have access to free or low-cost vaccinations if they qualify.[27]

It is important to ensure that information regarding the administration of vaccines be documented in an appropriate format (eg, state-based immunization information system, patient's electronic medical record, paper proof of immunization provided to the patient, or

Table 1. Effect of Immunosuppressive Agents on Vaccine Immunogenicity in Patients With IBD

Medication Regimen	Effect on Vaccine Response
Aminosalicylates or thiopurine monotherapy	No effect on immune response to vaccines, according to influenza, hepatitis B, and pneumococcal immunogenicity studies[5]
Anti-TNF therapy	May blunt the immune response to certain vaccines
Anti-TNF therapy with immunomodulator (combination therapy)	May blunt the immune response to certain vaccines; associated with poorest immune response
Vedolizumab	Small pilot data suggest no effect on immunogenicity of parenteral vaccines. In healthy controls, vedolizumab did not alter the response to parenterally administered antigens (eg, hepatitis B vaccine); however, decreased response to oral antigens (eg, oral cholera vaccine) supports a gastrointestinal-selective mechanism of action for vedolizumab[37-39]
Ustekinumab or tofacitinib	No generalizable data yet available specifically in patients with IBD; however, in a small pilot study, patients on ustekinumab were effectively vaccinated for seasonal influenza, with no impairment of the immune response to inactivated influenza vaccine[40]

IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

Table 2. Immunization Schedules for Adult Patients With IBD[a]

Vaccine	Dosing Schedule
Standard-dose quadrivalent IIV	1 dose seasonally for all patients 18-64 years of age not on anti-TNF monotherapy
High-dose IIV or adjuvanted influenza vaccine	1 dose seasonally for patients ≥65 years of age or 18-64 years of age if on anti-TNF monotherapy[b]
LAIV	Avoid for patients on immunosuppressive agents
Zoster vaccine, RZV	2 doses (2-6 months apart) for all patients ≥50 years of age Consider for patients 40-49 years of age with increased zoster risk factors[b]: • Previous history of zoster • Requiring repeated courses of corticosteroids • On tofacitinib with risk factors (concurrent corticosteroid use, Asian, diabetes mellitus, prior anti-TNF failure, or long-term use of 10 mg of tofacitinib twice daily) • On combination therapy and requiring corticosteroids
9vHPV	All male and female patients with IBD 18-26 years of age should be vaccinated with a 3-dose regimen (at 0, 1-2, and 6 months) 3-dose series for patients 27-45 years of age if likely to have new sexual partners (after shared clinical decision-making)
PCV13 and PPSV23	All persons ≥18 years[b] (see Figure) If no previous vaccination, PCV13 followed by a dose of PPSV23 after ≥8 weeks; if received ≥1 dose of PPSV23, should receive PCV13 ≥1 year after PPSV23; another dose of PPSV23 should be administered 5 years after the initial PPSV23 dose and at age ≥65 years if ≥5 years have elapsed since the previous PPSV23 dose
Hep A	Check hepatitis A immune status at patient's initial visit; if nonimmune to hepatitis A, vaccinate with one of the following: 2-dose series Hep A: Havrix 6-12 months apart or Vaqta 6-18 months apart; minimum interval: 6 months or 3-dose series Hep A-Hep B: Twinrix at 0, 1, 6 months or 4-dose accelerated dosing schedule at 0, 7, 21-30 days, and 12 months (accelerated dosing schedule intended for patients who start vaccination series but are unable to complete standard 3-dose schedule because of anticipated high-risk travel)
Hep B	Check hepatitis B immune status at patient's initial visit; if nonimmune to hepatitis B, vaccinate with one of the following: Engerix-B or Recombivax HB 3-dose series at 0, 1, 6 months or Hep A-Hep B 3-dose series at 0, 1, 6 months or HepB-CpG (Heplisav-B) 2-dose series at 0 and 1 month Check antibody to surface antigen 4-8 weeks after completion of series.
Varicella vaccine, live attenuated	2-dose series 4-8 weeks apart if previously did not receive varicella-containing vaccine (if born during or after 1980 or if born before 1980 and no history of disease or laboratory evidence of immunity) Vaccinate all nonimmune patients as long as they have not been on systemic immunosuppressive therapy within the previous 3 months and there are no plans to start immunosuppressive therapy within the next 6 weeks.
MMR vaccine, live attenuated	2-dose series at least 4 weeks apart if previously did not receive any MMR or 1 dose if previously received 1 dose of MMR Vaccinate all nonimmune patients as long as they have not been on systemic immunosuppressive agents within the previous 3 months and there are no plans to start immunosuppressive agents within the next 6 weeks.

Hep A, hepatitis A vaccine; Hep B, hepatitis B vaccine; IBD, inflammatory bowel disease; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; MMR, measles, mumps, rubella; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; TNF, tumor necrosis factor; VPD, vaccine-preventable disease; 9vHPV, 9-valent human papillomavirus vaccine.

[a]We recommend following the adult immunization schedule outlined by the Advisory Committee on Immunization Practices, except when vaccine use may be recommended because of an increased risk for VPD in patients with IBD as well as in patients who are on certain IBD agents that may decrease vaccine immunogenicity.

[b]Recommendations adapted from Caldera F et al.[5]

state certification of immunization) so that providers will have accurate information regarding a patient's vaccination history and can ensure the continuity of preventive care in the setting of COVID-19. For the timely administration of future or catch-up vaccinations during the COVID-19 pandemic and beyond, gastroenterology clinical practices should consider implementing the following quality improvement strategies in their clinic or health system: vaccination standing orders; electronic health record reminder systems to identify patients who are due for a vaccination; evaluation of state immunization registries; provider assessment and feedback based on performance metrics; administration of vaccines by health care workers during routine home visits; and promotion of vaccine administration in infusion centers, during blood draws, or at a local pharmacy.[23-25,28,29] Patient self-reporting of vaccination status has also been shown to be a reliable and effective method of determining a patient's influenza and pneumococcal immunization status, particularly if medical records and immunization registries are not accessible.[30]

Vaccine Efficacy in Patients With Inflammatory Bowel Disease

The literature evaluating patients with IBD suggests that the use of inactivated vaccinations is safe and not associated with disease flares.[31] The ability or strength of an antigen (eg, delivered via a vaccine) to stimulate an immune response is known as immunogenicity.[32] Multiple studies have evaluated the immunogenicity of inactivated vaccines in immunosuppressed patients with IBD.[33-38] The effects of immunosuppressive agents on the immunogenicity of vaccines in patients with IBD are summarized in Table 1.[5,39]

Review of Vaccines

For the purposes of this article, we address specific vaccinations according to the recently updated Advisory Committee on Immunization Practices (ACIP) recommended adult immunization schedule for 2020[22]; as well, we provide recommendations for specific patients with IBD that are based on vaccine immunogenicity studies in this patient population. When an adult patient with IBD is evaluated, it is important to assess if the patient is in need of the following vaccinations: influenza, pneumococcal pneumonia, HZ, hepatitis A, hepatitis B, human papillomavirus (HPV), varicella, and MMR (Table 2).

Inactivated vaccines are developed by inactivating or killing viral or bacterial pathogens with chemicals, heat, or radiation. Inactivated vaccines do not contain live microorganisms and therefore may elicit a weaker immune response. Multiple doses are generally required to produce immunity. The immune response to an inactivated vaccine is mostly via the production of antibodies; antibody titers may decrease over time, and therefore patients who have received inactivated vaccines may need supplemental or booster doses to increase the antibody titers. Types of inactivated vaccines include subunit, polysaccharide (pneumococcal, meningococcal vaccines), recombinant (hepatitis B, HPV, RZV vaccines), and toxoid (diphtheria and tetanus vaccines). All inactivated vaccines are considered safe to administer to patients with IBD, even if they are on immunosuppressive agents. Multiple studies evaluating patients with rheumatologic disorders, as well as patients with IBD, have not shown an association between vaccination administration and exacerbation of disease activity.[4] Live vaccines are derived from wild viruses or bacteria that are weakened, or attenuated, in a laboratory with heat, chemicals, and/or repeated culturing. The resultant vaccine organism maintains its ability to replicate and produce immunity, but it usually does not cause illness. Live vaccines are known to produce stronger immune responses than those achieved with inactivated vaccines. Examples of live vaccines include varicella zoster virus (VZV) vaccine and MMR vaccine.[11,39-41]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes

Table 3. ACIP Recommendations for Spacing of Vaccinations[47,64,a,b]

Antigen Combination	Minimum Interval Between Doses
Two or more inactivated[c]	May be administered simultaneously or at any interval between doses
Inactivated and live	May be administered simultaneously or at any interval between doses

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine.

[a]CDC general recommendations advise that recombinant and adjuvanted vaccines, such as RZV, can be administered concomitantly, at different anatomic sites, with other adult vaccines.

[b]The safety and efficacy of administering 2 adjuvanted vaccines, such as RZV and adjuvanted influenza vaccine (Fluad), have not been assessed.

[c]For patients with immunosuppressive high-risk conditions for whom PCV13 and PPSV23 are indicated, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. For persons 65 years or older for whom PCV13 and PPSV23 are indicated, PCV13 should be administered first, and PPSV23 should be administered 6 to 12 months later.

COVID-19. In March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 to be a global pandemic.[42] It is expected that both influenza viruses and SARS-CoV-2 will be circulating during the 2021 winter season.[43] The symptoms of influenza (eg, fever, cough, and shortness of breath) can appear similar to the signs and symptoms of COVID-19.[43] As of September 2020, COVID-19 infections continued to circulate worldwide.[43] It is imperative to promote routine vaccination this winter, especially with the influenza and pneumococcal vaccines, to prevent co-infections and health risks that overlap with those of COVID-19, which has overburdened the health care system.[44] To ensure that vaccinations are not missed, the ACIP supports the simultaneous administration of vaccines for which a patient is eligible, according to current immunization schedules. The ACIP provides guidelines regarding the spacing of live and inactivated vaccines (Table 3).[45] It is recommended that administration of the influenza vaccine be postponed if a person has COVID-19 until he or she is no longer acutely ill and/or has implemented appropriate isolation precautions as recommended by the CDC.[43]

Influenza

In the United States, influenza viruses typically circulate from late fall through early spring. According to the CDC, from the 2010 to 2011 season through the 2015 to 2016 season, influenza vaccination prevented an estimated 1.6 to 6.7 million illnesses, 790,000 to 3.1 million outpatient medical visits, 39,000 to 87,000 hospitalizations, and 3000 to 10,000 respiratory and circulatory deaths each season.[43,46,47] The 2017 to 2018 influenza season was noted for its longer duration of high-level influenza activity in the United States, as well as higher rates of outpatient visits and hospitalizations, compared with previous years.[43,46] During this time, influenza vaccination prevented approximately 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8000 deaths, even though the estimated vaccine effectiveness was 38%.[43,46] Influenza vaccines that are available during the 2020 to 2021 influenza season include standard-dose (SD) quadrivalent inactivated influenza vaccine (IIV4), HD egg-based quadrivalent inactivated influenza vaccine (HD-IIV4), trivalent inactivated influenza vaccine, quadrivalent recombinant influenza vaccine, and live attenuated influenza vaccine.[43] Potential adverse events associated with the inactivated influenza vaccines include localized injection site reactions (soreness, erythema, and induration) that typically last 1 to 2 days. Fever and myalgia have developed in fewer than 1% of persons vaccinated.

The ACIP recommends that all persons older than 6 months of age who are without contraindications should be vaccinated each year.[43] Persons who are immunocompromised for any reason (including but not limited to treatment with immunosuppressive agents) are included in the CDC recommendations.[43] It is recommended that all adult patients with IBD receive an inactivated influenza vaccination every year, regardless of their immunosuppression status. Patients who are immunosuppressed should not receive the live intranasal attenuated influenza vaccine. HD quadrivalent influenza vaccines are now available for the 2020 to 2021 influenza season. The HD influenza vaccine contains 4 times more hemagglutinin than the SD vaccine and has been shown to induce higher antibody concentrations and thus provide better protection against influenza among patients 65 years of age and older.[48] All patients 65 years of age and older (regardless of their immunosuppression status), as well as patients who are on anti-TNF monotherapy, regardless of their age, should receive the HD influenza vaccine because it has been shown to provide a better antibody response to influenza than the SD influenza vaccine in these populations.[39,49,50] Patients with IBD are at greater risk than those without IBD for the development of influenza infection. Patients who are immunosuppressed are at an even greater risk for the development of influenza infection.[39,49,50] Tinsley and colleagues conducted a retrospective cohort study to compare the incidence of influenza and risk for the development of complications in patients who had IBD with the incidence and risk in those who did not have IBD.[9] In their study, the researchers found that patients with IBD had an approximately 30% greater risk for an influenza diagnosis, with attendant health care utilization and comorbidities. Additionally, patients with IBD were at greater risk for pneumonia and hospitalizations within 30 days of an influenza diagnosis than patients without IBD.[9]

Influenza seasons vary each year in regard to timing, duration, and location. In the United States, to ensure optimal immunity throughout the flu season, influenza vaccines should be administered preferably in September and October, although patients can receive the vaccine any time during the influenza season.[43,51] Vaccination before September may result in decreased immunity before the influenza season ends, particularly in older patients. As long as influenza vaccine is available, it is recommended that annual vaccinations be continued during every season.[43,51]

Pneumococcal Pneumonia

Streptococcus pneumoniae is a gram-positive, encapsulated bacterium that has contributed significantly to morbidity and mortality worldwide by causing invasive pneumococcal infections such as pneumonia, meningitis, and bacteremia.[52] An estimated 4000 deaths occur in the United States each year because of *Streptococcus pneumoniae*

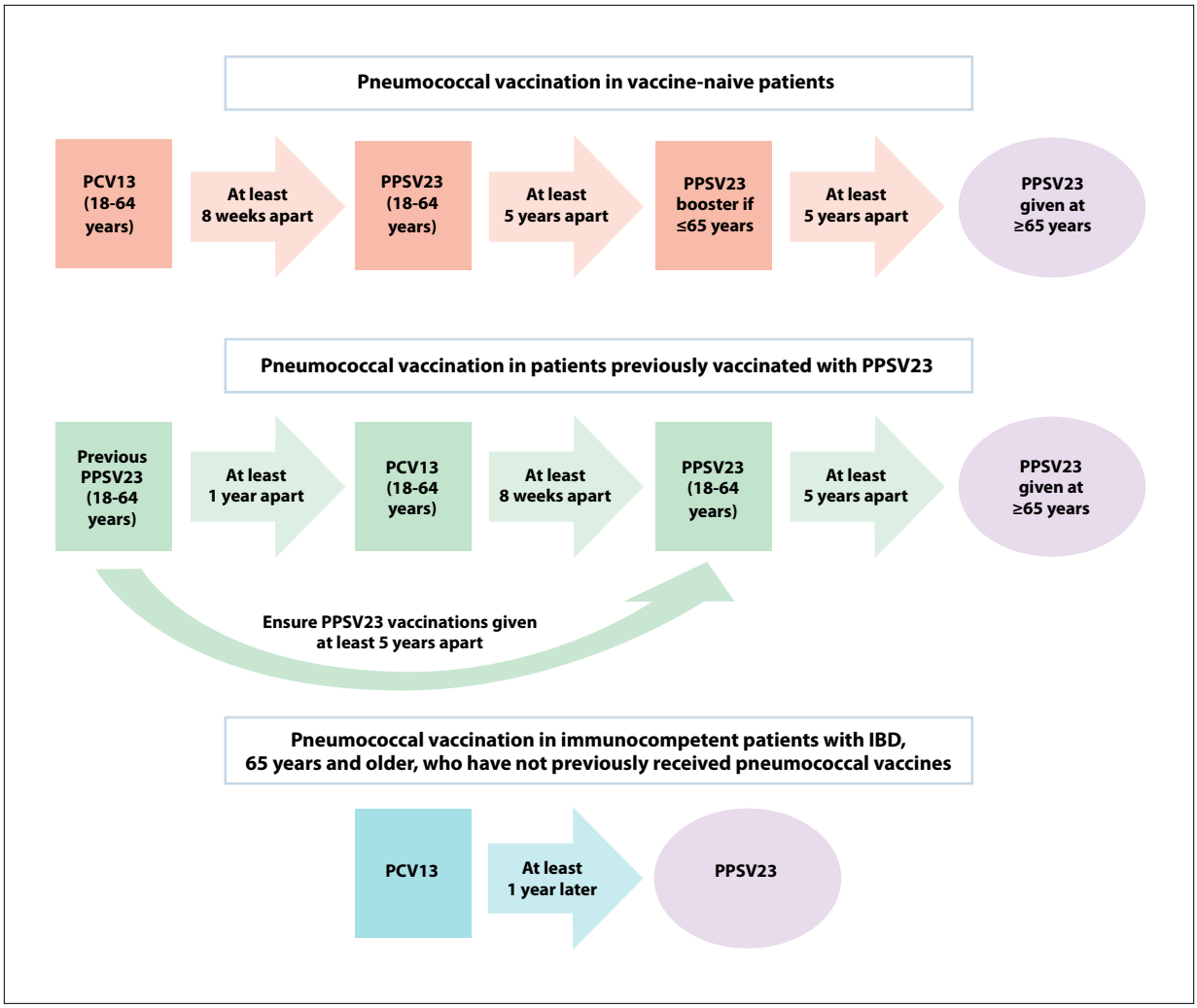

Figure. Recommended pneumococcal vaccination regimens for patients with IBD. Adapted from Caldera F et al.[5]

IBD, inflammatory bowel disease; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

infection, primarily in the adult population.[52,53] Patients with IBD are at greater risk for pneumococcal infection than patients without IBD.[11] Even without drug-induced immunosuppression, patients who have IBD are at high risk for infection both before and after diagnosis, possibly as a consequence of malnutrition, genetic alteration of immune responses, and/or damage of the gastrointestinal mucosa predisposing patients to bacterial infections.[6,52] Many studies have observed that patients on anti-TNF monotherapy or combination therapy may have a blunted response to pneumococcal vaccines, similar to what is observed with influenza vaccine.[6,52] In a recent, large US cohort study, Gregory and colleagues found that patients with IBD who received corticosteroids followed by TNF-alpha inhibitors were at greater risk for pneumonia.[54] Therefore, gastroenterologists should follow the ACIP recommendation and provide pneumococcal vaccines to patients planning or initiating immunosuppression. The pneumococcal vaccines should be administered at the time of diagnosis and before immunosuppressive agents are started, if possible, to provide higher levels of seroprotection from multiple pneumococcal strains and an optimal immune response.[5]

Currently, 2 types of pneumococcal vaccine are available: 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23). The ACIP recommends that adults 18 years of age and older with immunocompromising conditions who have not previously received PCV13 or PPSV23 should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose is recommended at least 5 years after the first PPSV23 dose for immunocompromised persons 18 to 64 years of age. Persons who received PPSV23 before

65 years of age for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have elapsed since their previous PPSV23 dose. In addition, the ACIP recommends that adults 18 years of age or older with immunocompromising conditions who previously received 1 or more doses of PPSV23 should receive a PCV13 dose 1 year or more after the last PPSV23 dose was received. For patients who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23 (Figure).[5,8,39,53] Adverse events in the general population associated with the pneumococcal vaccine include localized injection site reactions (erythema, pain, swelling), most of which were usually mild and resolved in less than 48 hours. Fever and myalgias are rare. Adverse effects experienced are similar to those associated with other vaccines.[51]

Herpes Zoster

HZ, commonly known as shingles, is caused by reactivation of VZV, the virus that causes varicella (chickenpox), within the dorsal root or cranial nerve ganglia. Reactivation of VZV can cause a painful, maculopapular rash that follows a dermatomal pattern and is usually described as painful, itchy, or tingly.[55] The rash may develop into clusters of infectious vesicles that progressively crust over. These vesicles usually heal in 2 to 4 weeks.[55] A complication of HZ is the development of postherpetic neuralgia (PHN), which is persistent pain in the area where the rash was located.[55] PHN may develop in approximately 18% of all adults with shingles and in 33% of those 79 years of age or older.[51] PHN is the most frequent chronic complication of HZ, occurring in approximately 20% of patients, and can lead to chronic neuropathic pain. HZ can also cause neurologic (eg, Bell palsy, Ramsay Hunt syndrome, transient ischemic attacks) or ophthalmic (eg, scleritis, uveitis) complications. A severe, long-lasting rash and disseminated HZ may be more likely to develop in immunocompromised patients. Approximately 1 million cases of HZ occur each year in the United States. The annual incidence of HZ is approximately 4 cases per 1000 US population, and this increases with age to 1 case per 100 US population among people 60 years of age or older.[55]

Patients who have IBD have a 2-fold increased risk for the development of HZ compared with the general population, regardless of whether they are on immunosuppressive agents.[3] The incidence and severity of HZ tend to increase over a patient's lifetime, in association with the decline in cellular immunity that accompanies advancing age.[56] In their study, Gupta and colleagues found that both Crohn's disease and ulcerative colitis were associated with an increased relative risk for HZ.[56] Within the population of patients with IBD evaluated in this study, the risk for HZ was greater in those with Crohn's disease and those treated with immunomodulators and corticosteroids.[56] Because of their mechanisms of action, corticosteroids, azathioprine, and 6-mercaptopurine contribute to a decrease in cell-mediated immunity, potentially increasing the risk for acquiring opportunistic infections such as HZ.[56]

In October 2017, the ACIP recommended the 2-dose adjuvant RZV for immunocompromised patients 50 years of age and older. RZV is also recommended for immunocompetent adults who have previously received zoster vaccine live (ZVL). Furthermore, the ACIP prefers RZV over ZVL for the prevention of HZ and related complications.[22] In clinical trials, overall RZV series efficacy against HZ was 97.2% (95% CI, 93.7%-99%) compared with placebo, and overall efficacy was maintained in patients older than 70 years of age. ZVL was not recommended for most immunosuppressed patients and was associated with lower efficacy rates in preventing HZ.[57] Among adults 50 years of age and older, the most common adverse events were injection site pain (78%), redness (38.1%), and swelling (25.9%). General adverse reactions in patients 50 years of age and older included myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).[57] The literature reviewing the incidence of HZ in patients with IBD who are younger than 50 years of age indicates that they are at increased risk for HZ, and 40-year-old patients with IBD may have a greater risk for HZ than healthy 50-year-olds.[3] Long and colleagues performed a retrospective cohort and nested case-control study and found that the treatment of IBD with thiopurines, anti-TNF agents, combination therapy, and corticosteroids increased HZ risk.[3] Khan and colleagues analyzed data from a large nationwide cohort of patients with IBD and found that the following were independent risk factors for the development of HZ: the IBD process itself, older age, use of thiopurines, combination therapy (thiopurines and anti-TNF agents), IBD flare, higher cumulative use of prednisone, and use of prednisone within the last 30 days.[58] In addition, tofacitinib, a nonselective Janus kinase inhibitor, has been associated with higher rates of HZ compared with other immunosuppressive agents.[59]

The ACIP recommends that all immunocompetent patients 50 years of age and older receive the RZV series.[22] In addition, Caldera and colleagues support the use of RZV in certain patients with IBD who are younger than 50 years, who may benefit from immunization because they are at an increased risk for acquiring HZ as depicted in various studies.[3,5,60,61] These patients include those who are 40 to 49 years of age and have a history of HZ, are receiving repeated courses of corticosteroids, are on

combination therapy requiring corticosteroids, or are on tofacitinib (with 1 of the following risk factors: baseline oral corticosteroid use, Asian, diabetes mellitus, previous anti-TNF failure, or long-term use of 10 mg of tofacitinib twice daily).[5,59]

Khan and colleagues conducted a retrospective cohort study of patients with IBD who were followed by the Veterans Health Administration. They found that among 18,825 patients with IBD eligible for vaccination, the rate of vaccination for HZ was very low (20.96%). This finding draws attention to the need for improvement and a consideration of evaluating HZ vaccination rates as part of quality assessment.[58,61] Further research is needed to assess the efficacy and safety of inactivated RZV in immunosuppressed patients with IBD, and to assess the risk for HZ flare after vaccination.[60,62] Satyam and colleagues recently conducted a prospective observational study of 67 patients with IBD who received RZV from February 2018 to July 2019 and observed a low rate of IBD flare (1.5%) after RZV administration.[63] Although RZV has been shown to be safe and immunogenic in patients with other autoimmune conditions,[64] the ACIP has not made specific recommendations regarding RZV use in immunocompromised patients because they were excluded from the original studies evaluating efficacy. This topic is under review and slated for discussion at upcoming ACIP meetings as additional data become available.[22,65] According to the CDC, ZVL was not to be sold in the United States after July 1, 2020.[55]

Hepatitis B

In 2015, according to the WHO, 257 million people had chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positivity). In the same year, HBV resulted in more than 800,000 deaths worldwide, mainly from cirrhosis and hepatocellular carcinoma.[66,67] Patients with IBD are at increased risk for HBV infection, particularly those who are on immunosuppressive agents. Risk factors for HBV infection include use of immunosuppressive agents, prior blood transfusion, undergoing surgery and endoscopy, travel to regions of endemicity, intravenous drug use, high-risk sexual behavior, end-stage renal disease, and being a health care provider.[68,69] HBV may be reactivated in chronic carriers who are on immunosuppressive agents.[69] Chronic infection is defined as the persistence of HBsAg for at least 6 months (with or without concurrent hepatitis B e antigen). HBsAg persistence is considered the main marker of risk for development of chronic liver disease and liver cancer later in life.[66] Millonig and colleagues described a patient with Crohn's disease in whom subfulminant HBV developed after an infliximab infusion because of an unrecognized HBsAg carrier state.[70] Esteve and colleagues reported HBV reactivation in 2 of 3 patients with Crohn's disease and concomitant chronic HBV (among a cohort of 80 patients) who were treated with infliximab; one of those cases resulted in death.[71] According to Jiang and colleagues, the rate of response to HBV vaccination in patients with IBD is low and can vary.[72] A systematic review and meta-analysis revealed a rate of response to HBV vaccination of 61% among the patients with IBD in their study. An antibody to HBsAg (anti-HBs) level above 10 mIU/mL was determined to be an effective immune response.[72] Risk factors for a poor immunologic response to hepatitis B vaccine include immunomodulator or anti-TNF therapy, active IBD, malnutrition due to low serum albumin levels, smoking, obesity, older age, chronic medical conditions, drug use, male sex, diabetes, and genetic factors.[67,72]

Hepatitis B immunization remains the most effective measure to prevent HBV infection and subsequent complications (eg, cirrhosis, liver cancer, liver failure, and death).[67] The ACIP lists both the 2- and 3-dose series hepatitis B vaccines as options for vaccination, but does not state a particular vaccine preference.[22] The FDA approved the 2-dose recombinant hepatitis B vaccine HepB-CpG (Heplisav-B, Dynavax Technologies) in November 2017. HepB-CpG vaccine can be conveniently given in 2 doses, 1 month apart, whereas the 3-dose hepatitis B vaccine series is given over 6 months. HepB-CpG vaccine was approved for the prevention of HBV infection in adults 18 years of age and older. Seroprotective anti-HBs levels were achieved in 90.0% to 100.0% of patients who received HepB-CpG vaccine, compared with 70.5% to 90.2% of patients who received Engerix-B (GSK).[67] Adverse effects may include injection site pain, redness, swelling, fatigue, headache, malaise, or fever.[73]

It is recommended that the hepatitis B immune status of all patients with IBD be checked, particularly at the initial visit, during remission, or before immunosuppressive therapy is started.[4] Adult patients with IBD should receive the hepatitis B vaccine series if they have never been immunized because serious sequelae can occur if HBV develops in anyone with IBD.[4] Anti-HBs levels in an immunized patient may fall to below 10 mIU/mL, but such low levels are not necessarily associated with loss of immunity because memory B lymphocytes remain. These lymphocytes are capable of mounting an anti-HBs response, and long-term memory is demonstrated by rapid increases in the antibody level following a booster vaccination.[74] A study in health care workers showed that the majority of individuals immunized as infants or children sustain immunity to HBV.[75]

To determine hepatitis B immunity in a patient who has been immunized and whose anti-HBs level is below 10 mIU/mL, a challenge dose of hepatitis B vaccine should be given, followed by another anti-HBs assay in 1 month. If

the anti-HBs level remains below 10 mIU/mL thereafter, then the patient needs to complete a hepatitis B vaccine series. If the anti-HBs level is 10 mIU/mL or higher after a single challenge dose of hepatitis B vaccine, then the patient is considered to have had an anamnestic response and to be immune, and no additional vaccines are necessary. This level indicates persistent immunity.[11,39,67,71,72] Future research will be beneficial to evaluate the immunogenic response to hepatitis B vaccine in patients with IBD, as well as to determine safety and immunogenicity when HepB-CpG vaccine is interchanged with hepatitis B vaccines from other manufacturers.[67]

Hepatitis A

Hepatitis A is caused by the hepatitis A virus, a picornavirus, which is transmitted mainly via the fecal-oral route. Transmission is either through person-to-person contact or the ingestion of contaminated food or water. Populations at risk for hepatitis A include people who have chronic liver disease, come into direct contact with someone who has hepatitis A, engage in high-risk sexual behavior or intravenous drug use, have a clotting factor disorder, travel to an area of endemicity, come into close contact with an international adoptee during the first 60 days after the adoptee's arrival from an area of endemicity, are homeless, or work with hepatitis A virus in a laboratory or with infected nonhuman primates.[22,51] For patients with IBD, we suggest that the hepatitis A immune status be checked at the initial office visit. If a patient is not immune to hepatitis A, he or she should be vaccinated with a 2-dose hepatitis A vaccine at 0 and 6 months (unless a hepatitis A–hepatitis B vaccine is available, which requires 3 doses).[5,11]

Human Papillomavirus

HPV is a small DNA virus that is transmitted through sexual contact with an infected person. Most HPV infections do not cause symptoms; however, depending on the HPV type, they may lead to serious complications. More than 120 types of HPV exist, of which 40 may infect the mucosal epithelium. Types 6 and 11 are linked to relatively benign, low-grade cervical cell abnormalities, genital warts, and laryngeal papillomas. Types 16 and 18 are more oncogenic and may cause low- or high-grade cervical cell abnormalities that can be cancer precursors. HPV can cause cervical, vulvar, vaginal, penile, anal, and some oropharyngeal cancers.[51] Patients with IBD may benefit from the HPV vaccine because they are at an increased risk for cervical cell abnormalities and oral cancers; patients with perianal disease are at increased risk for HPV-related cancer of the anal canal.[39,76-78]

The 9-valent HPV vaccine is currently the only HPV vaccine available in the United States. If the HPV series is initiated after a patient reaches 15 years of age, then a 3-dose series is recommended, which can be given at 0, 1 to 2, and 6 months. The ACIP recommends HPV vaccination for all adults (males and females) ages up to and including 26 years. For persons 27 to 45 years of age, shared clinical decision-making is recommended, with vaccination considered for those who have new sexual partners.[22]

Varicella

Patients with IBD are at long-term risk for the development of VZV infection.[79] The risk for VZV infection increases with the use of immunosuppressant agents in patients with IBD, particularly corticosteroids and combination immunosuppression. Disseminated VZV infection has been found to cause cell lysis and organ failure, in some cases resulting in death.[7] Primary infection with VZV causes chickenpox, which is a highly contagious vesicular skin rash. It is commonly transmitted through direct contact with infected skin lesions, as well as through airborne droplets.[51]

Patients with IBD should be evaluated for prior exposure to varicella and vaccinated when possible if no evidence of immunity is found before immunosuppressive therapy is initiated.[4] If a patient is not immune, the ACIP recommends that the 2-dose series be administered 4 to 8 weeks apart.[22] Serology is not recommended to determine vaccine-induced immunity in patients who have appropriate evidence of immunity.[5,22] Evidence of immunity is covered by birth in the United States before 1980 (except for pregnant women and health care personnel), documentation of the administration of 2 doses of varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of a history of varicella or HZ by a health care provider, and laboratory evidence of immunity or disease.[22] Varicella vaccine is a live attenuated vaccine; therefore, it is recommended that all nonimmune patients be vaccinated with varicella zoster vaccine as long as they have not been on immunosuppressive agents within the previous 3 months and there are no plans to start immunosuppressive therapy for at least 4 weeks.[11,14,80] The IDSA guidelines state that vaccination for VZV is safe in patients without evidence of varicella immunity who are on long-term, low-level immunosuppressive agents.[4,11,14] If a rash develops in a household member after vaccination, then the immunocompromised patient should avoid direct contact with that person until the rash has resolved.[4]

Measles, Mumps, and Rubella

The MMR vaccine is an attenuated live virus vaccine that is usually given as a 2-dose series, with the first dose at 12 to 15 months of age and the second at 4 to 6 years of age. Children can receive the second dose earlier if it is given

at least 28 days after the first dose.[81] MMR vaccination is recommended for patients with IBD whose evidence of immunity to MMR is unknown.[11] Serology is not recommended to determine vaccine-induced immunity in patients who have appropriate evidence of immunity because of the possibility of a false-negative result.[5] Evidence of immunity consists of birth before 1957, documentation of MMR vaccination, or laboratory evidence of immunity or disease.[51] A cross-sectional study evaluating MMR antibody concentrations in immunosuppressed patients with IBD demonstrated that antibody responses to the measles and rubella components of the MMR vaccine were sustained in patients with IBD who received the MMR vaccine series before starting immunosuppressive agents when these patients were compared with healthy controls. This finding supports the importance of following the ACIP recommendations and using the immunization record when available to determine immunity to measles and rubella in patients with IBD.[82] Because the MMR vaccine is a live vaccine, it is recommended that the vaccine be given to all patients with IBD who are not immune as long as they have not been on immunosuppressive agents within the previous 3 months and there are no plans to start immunosuppressive therapy for at least 4 weeks.[11,14,83]

Conclusion

The COVID-19 pandemic has affected the vaccination of patients with IBD in multiple ways. It reminds us of the importance of vaccination, not just for the general public but, more importantly, for patients with IBD. The current pandemic has also, because of the requirement for social distancing, contributed to geographic lockdowns and the fear of exposure to COVID-19 at physician offices. These barriers can affect the ability of patients, including those with IBD, to keep up-to-date with their vaccinations. Health maintenance via vaccination remains important for all patients during the current pandemic. However, because of the nature of IBD and the treatments that may further immunocompromise patients with this disease, current preventive vaccination is critical.

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