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Winter Is Coming! Clinical, Immunologic, and Practical Considerations for Vaccinating Patients With Inflammatory Bowel Disease During the Coronavirus Disease-2019 Pandemic

As summer turns to fall, clinicians' minds usually turn to the upcoming winter season and preparing for winter infections, particularly influenza. In 2020, though, we face a new and formidable foe: the severe acute respiratory syndrome novel coronavirus-2 (SARS-CoV-2). Although we hope that an effective vaccine against SARS-CoV-2 will soon be available, the distribution of an effective vaccine is not likely to occur soon, so it is especially appropriate to use the other tools already at our disposal to keep our patients with inflammatory bowel disease (IBD) well. This includes making sure that our patients are in stable steroid-free remission, but also guaranteeing that they are updated regarding other vaccinations. We need to ensure that our patients are educated and encouraged to receive the influenza vaccination as well as vaccinations against pneumococcal infection. Discriminating coronavirus disease-2019 (COVID-19) from influenza or other respiratory infections based on symptoms alone will be difficult and concomitant infection with SARS-CoV-2 and other respiratory pathogens will likely increase morbidity and mortality. In this commentary, we outline the usefulness and rationale for existing practices related to vaccine-preventable illnesses in IBD, and discuss the emerging science and ethical challenges related to the highly anticipated vaccines against SARS-CoV-2.

Preparing Patients with IBD for Influenza Season

Many studies have evaluated the efficacy of vaccines among patients with IBD, including those on different immunomodulatory regimens (Table 1).[1,2] There are several important messages to be learned from these studies. First, vaccine efficacy may be blunted by immunomodulators, some biologics, and corticosteroids. However, a blunted response does not necessarily translate to vaccine inefficacy, and partial protection is better than none. Therefore, vaccines should not be withheld just because a patient is receiving immunosuppressive treatment for their IBD.[3] Second, vaccination while on immunosuppressive treatments may be associated with an accelerated waning of protective antibody titers.[4,5] The implications of this phenomenon are not entirely clear, although for some infections like hepatitis B, it may be appropriate to assess postvaccination titers and consider additional booster dosing for low or absent titers.[4] Third, predictors of efficacy relevant to the general population are also applicable to those with IBD. These may include age, gender, body mass index, prior infection, immune compromise or senescence, and genetic polymorphisms.[6] Older patients are generally more vulnerable to infections, and the ability to mount a robust vaccine response tends to decrease with advancing age. Genetic polymorphisms may be associated with blunted vaccine responses, although it is unclear how these translate into differences in efficacy. Finally, the risk of an IBD relapse from vaccination is reassuringly negligible; published evidence to date does not suggest an association between any specific vaccine and exacerbation of IBD.

This year, because of clinical similarities between COVID-19 and influenza, vaccination against influenza is a critically important public health recommendation and highly relevant for patients with IBD who are both at increased risk for acquiring influenza and at increased risk from the complications thereof.[7] Vaccination against influenza is recommended annually owing to antigenic drift, or mutations in the surface hemagglutinin or neuraminidase proteins involved in host recognition of the viral particle, which render each season's influenza viruses sufficiently different from past viruses to evade previous host immunity. Despite the variable effectiveness of the vaccine, influenza vaccination has been shown to decrease the signs and symptoms of the flu, decrease hospitalizations, decrease mortality in children and adults, prevent disease in those with chronic health conditions, protect women during and after pregnancy, decrease the severity of the flu among those with partial immunity, and provide herd immunity for those susceptible to infection.[8–11] For the 2020–2021 season, both trivalent and quadrivalent vaccines have been developed based on recommendations from the World Health Organization (Table 2).[12] These vaccines are available as high-dose vaccines (for those age $\geq$65), egg-free formulations (for those with egg allergies), and as a live-attenuated nasal vaccine. All individuals older than 6 months are advised to receive an influenza vaccination with any of these approved formulations. For patients with IBD on immunosuppressive therapies, any inactivated vaccine would be appropriate, but the live-attenuated intranasal formulation is not. High-dose and quadrivalent influenza vaccines have been evaluated in patients with IBD, and should be considered, especially among those older than 65.[13]

Pneumococcal vaccination is recommended for patients with IBD, especially if on immunosuppression or age 60 of years or older.[14] Pneumococcal vaccination is available as a 23-valent polysaccharide vaccine, and a 13-valent conjugate vaccine. Immunosuppressed patients should receive the conjugate vaccine, followed by the polysaccharide vaccine at least 8 weeks later, and a polysaccharide vaccine booster every 5 years.[15]

Table 1. Factors Impacting Vaccine Failure

Factors Impacting Vaccine Response	Specific Relevance to Patients with Inflammatory Bowel Disease
Pathogen factors	
Antigenic drift/distance between vaccine and circulating strains	Theoretically increased risk for co-infection with other viruses (eg, influenza)
Co-infections—interference	
Viral decoy mechanisms	
Viral immune evasion mechanisms	
Host factors	
Immunocompromised	Immunocompromised status from malnutrition and/or medications
Comorbidities	Comorbidities as relevant (age, obesity, underlying cardiopulmonary morbidity)
Age/immunosenescence	
Obesity	
Genetic restriction	
Medications	Medications (corticosteroids, immunomodulators, anti-TNF therapies)
Negative interference	
Role of humoral vs cellular immunity	
Waning immunity	Waning immunity seen with other vaccines
Preexisting infection	
Immunologic interference	
Vaccine factors	
Improper administration	Potential need for alternate dosage/number of doses/timing of vaccinations based on c oncurrent medications
Differences in immunogenicity (adjuvanted vs nonadjuvanted)	
Dosage and number of doses	
Time between vaccination and development of immunity	
Egg-passage-induced antigenic changes in vaccine	
Handling	
Temperature inactivation	
Vaccine-vaccine interference	
Study and study design factors	
Geography	Efficacy determined in trials unlikely to include patients with IBD/immunocompromised
Confounding biases	
Efficacy vs effectiveness	Effectiveness for those with IBD will need to be studied in registries and postmarketing studies
Prevalence of infection	
Study design	
Specificity of study outcomes	
Year of study	
Laboratory assays used	
Incubation period vs timing of immunization	

IBD, inflammatory bowel disease; TNF, tumor necrosis factor.
Adapted from the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Definition and Application of Terms for Vaccine Pharmacovigilance.[26]

Progress in the Development of SARS-CoV-2 Vaccines

The international effort to deploy safe and effective vaccines against SARS-CoV-2 is unprecedented, compressing vaccine development time from decades to 1–2 years. At the time of this writing, there are more than 90 animal studies of preclinical vaccines, and approximately 40 human vaccine studies in progress. This effort is remarkable, given that the sequence of the virus genome only became available in January 2020. A number of different approaches for developing vaccines that stimulate production of neutralizing antibodies against the viral receptor binding domain and other spike 'S' protein epitopes have been deployed, including:

1. "Genetic" vaccines based on inoculation with viral RNA or DNA (Moderna/NIH – lipid-nanoparticle encapsulated mRNA: Pfizer/BioNTech/Fosua Pharma – 3 lipid-nanoparticle mRNAs).
2. Nonreplicating (simian or human) viral vector vaccines in which viruses are engineered to carry coronavirus genes (CanSino Biologics – adenovirus type 5 vector: Gamaleya Research Institute – Adenovirus-based vector: Astra-Zeneca/University of Oxford – Simian ChAdOx1-S vector).
3. Vaccines that contain whole or fragments of coronavirus proteins such as the Spike protein and often administered together with an adjuvant to enhance immune responses (none in phase III trials currently and a number in phase II trials).
4. Inactivated virus-based vaccines (Sinovac: Wuhan Institute of Biological Products/Sinopharm; Beijing Institute of Biological Products/Sinopharm).

In addition to these novel approaches, a number of groups are looking to repurpose existing vaccines, the most high profile of which is the antituberculosis Bacillus Calmette-Guerin (BCG) vaccine, currently in phase III studies (BRACE trial, Murdoch Children's Research Institute, Australia). The rationale for BCG includes intriguing epidemiologic data suggesting decreased mortality from COVID-19 in populations previously exposed to BCG.[16] Additional updated information about active phase III vaccine trials are available at www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

Table 2. Considerations for SARS-CoV-2 Vaccine Distribution as it Relates to Patients with IBD

Individual risk factors	Age >65 Hypertension Diabetes Obesity
IBD-related risk factors	Steroid use (probably >20 mg/d prednisone equivalent)/steroid dependence Moderately to severely active disease (possibly)
Geographic risk factors	Local/regional prevalence of COVID-19 based on test positive rate (often >8% triggers mitigation plans) or by Re (reproductive rate of the virus in the population after social distancing and other plans are activated)
Likelihood of occupational exposure to SARS-CoV-2	Patients with IBD who are health care workers, teachers, daycare workers, other essential workers

COVID-19, coronavirus disease-2019; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome novel coronavirus-2.

Current vaccination regimens being studied in phase III include both single-dose approaches as well as 2-dose strategies that vary anywhere from 28 days to 56 days between doses. Human and animal data on both humoral and cellular immune responses to the vaccines have been promising and to date, safety signals have been reassuring.[17] Even if the vaccine studies show efficacy, many outstanding questions remain and some are particularly pertinent to the IBD community. Can we extrapolate efficacy and safety results from a generally healthy, mostly White, European ancestry population to groups who may be particularly vulnerable to COVID-19, including immunocompromised, the elderly, and Black/Latinx populations? Furthermore, what are the effects of the vaccines in individuals who are elderly and who also have comorbidities such as IBD? Although safety signals have been reassuring to date, there have been media reports that the Astra Zeneca/Oxford study temporarily stopped recruitment owing to a case of transverse myelitis (although it is unclear whether this event was vaccine related or not[18]). It is unclear whether rare immune-mediated reactions such as immune complex–related phenomena or antibody-dependent enhancement (where vaccines induce binding antibodies that facilitate viral entry into cells instead of inducing neutralizing antibodies) are more common (or less common?) in patients with ongoing systemic inflammation, or in those receiving immunosuppressants. The complex lipid delivery systems necessary for delivering the mRNA ('naked' mRNA is rapidly degraded) in the Moderna and Pfizer studies can induce inflammatory responses often manifested by fever, and it is unclear whether these can also trigger further inflammatory responses. Non-replicating viral vector vaccines require extremely large numbers (hundreds of millions) of viruses to be delivered and these types of inoculations have, in the past, resulted in cytokine storms.[19] Will individuals treated with anticytokine therapies/immunocompromised be at increased (or decreased!) risk of these types of adverse events? It also remains unclear whether prior infection with SARS-CoV-2 will increase the likelihood of vaccine-related adverse events. Although these phenomena are relevant to the general population there are theoretic reasons, at least, suggesting that the IBD population may be at increased risk of some. IBD health care providers will therefore need vigilance for these types of reactions to inform vaccine-specific counseling to patients with IBD receiving a vaccine.

Beyond safety it will, of course, be important to evaluate vaccine efficacy in patients with IBD given experience with other vaccines. How efficacious are the vaccines in the setting of systemic inflammation or immunotherapy? Will higher doses or additional boosters be needed, and how long will immunity last? Do distinct vaccine modalities induce differences in the degree and/or duration of immunity in patients with immune-mediated diseases? It is also still unknown which measure of humoral and cellular immune responses will best determine immunity and whether this will be different in patients with IBD. To answer these and questions about safety, it is vital that patients with IBD be closely monitored and studied in prospective cohorts with serial assessments after receiving any vaccine.

Ethical and Logistical Considerations for Dissemination of SARS-CoV-2 Vaccines

There are a number of ethical considerations to the development and distribution of vaccinations for SARS-CoV-2 that must be considered and are similar to considerations for any new medical intervention and for any limited resource. First, as mentioned elsewhere in this article and specifically related to beneficence and non-maleficence, because patients with immune conditions, including those with IBD, are excluded from the clinical trials of vaccine effectiveness and safety, extrapolation of the results from such trials will be necessary. Additional postmarketing studies will be necessary in such populations. Although our understanding of existing vaccines in patients with IBD will likely translate to these new vaccines, there

will remain important studies that must occur.

Second, is the ethical issue of justice and allocation of a scarce resource. We will need to grapple with decisions about who should receive the vaccines, which will likely have distribution and availability limitations initially. The US Centers for Disease Control and Prevention has proffered a tiered approach (tier 1 high priority to tier 5 low priority) for vaccine distribution based on population categories and severity of the pandemic (low to very high severity).[20] In their table, most health care workers are considered tier 1 and would receive the vaccine early for any degree of severity of the pandemic. Among patient types, pregnant women, infants, and toddlers are also considered tier 1 for all degrees of severity of the pandemic. Adults age 19–64 years old with high-risk conditions are tier 2 for low severity pandemic, but tier 3 or 4 for a moderate or a high or very high severity pandemic. It is likely that patients with IBD, despite the available data that suggest that they are not at high risk for adverse COVID-19 outcomes, will be stratified into the high-risk population. It is essential that we continue to educate our patients with IBD about their actual risks based on available and reassuring data.[21]

It is expected that there will be a great demand for the vaccines. As health care providers and physician leaders, it is our responsibility to manage the needs of our most at-risk patients and to distribute a limited resource equitably.[22] This mandate translates into an approach such that older patients with IBD, patients who are steroid dependent, and those with other established COVID-relevant comorbidities (obesity, hypertension, diabetes, etc) should receive vaccines before other patients. Additional factors of consideration will be based on regional prevalence of COVID-19 and then, separately, ethnicity and race, recognizing the data of increased risk of infection and adverse outcomes in Black and Latinx populations. The risk of infection and adverse outcomes should be evaluated in conjunction with practical considerations of access to health care access. Nationally, organized updates and a national surveillance plan for SARS-CoV-2 prevalence will be needed, and in the absence of such organization, local and regional public health officials should guide distribution and provide regular updates.

Finally, it is essential that we actively address misinformation and conspiracy theories about vaccinations in general, and about the new SARS-CoV-2 vaccines. It is unfortunate that the scientific method and regulatory pathways for medical therapies and vaccines have become politicized and even discarded. We must promote reliable, scientifically rigorous information and consider the public health implications of an effectively vaccinated population. This process will include highlighting limitations to the datasets and advocating on behalf of our patients if there is insufficient information from which to draw conclusions. Specifically, we should proactively remind our patients that IBD is not caused or exacerbated by vaccinations, and that the SARS-CoV-2 vaccines will not have risk of causing COVID-19.

Pressing Research Questions for the IBD Population

The information about SARS-CoV-2 and IBD is evolving rapidly, but there remain many uncertainties and a pressing need for ongoing research. What is the true prevalence of anti–SARS-CoV-2 in the IBD population and how does that compare with non-IBD populations? A recent study from Germany demonstrated low SARS-CoV-2 seroconversion in anticytokine-exposed patients with immune-mediated conditions, but the reasons for this finding are not known.[23] Is this a result of medication-related protection from infection, a decrease in sustained immunity, a result of disease-associated biology, or due to increased sheltering? Will vaccine responses be different in patients with IBD, and what will be the effect of immune-modifying medications on seroconversion and durability of immunity after vaccination? Will the specific mechanism and dosing regimen of a SARS-CoV-2 vaccine be important considerations for those on immune modifying therapies? After recovery from COVID-19, when can IBD patients restart medications and which medications would be the safest?

Conclusions

Patients with IBD look to their gastroenterologists as the most reliable sources of accurate information regarding preventive vaccinations,[24] so we must ourselves be informed and educated to provide clear, unambiguous messages to our patients and the medical communities in which we practice. First, we should advise all patients with IBD, regardless of immunosuppression, to receive the inactivated influenza vaccination and pneumococcal immunization. We must also be ready to respond to anti-vaccination tropes and nonscientifically valid arguments against preventive immunizations. Second, we should stay apprised of the progress of SARS-CoV-2 vaccines and anticipate that our patients will look to us for guidance. Thus far, we can reassure our patients that the major candidate vaccine mechanisms seem safe for most, if not all, patient populations, but that further clarity may be needed among those who are immunosuppressed. Although it is unlikely that any vaccine will be 100% effective against SARS-CoV-2 transmission, the most effective prevention strategy will include both vaccination and continued hygiene practices, including handwashing and judicious masking and physical distancing. Third, we must acknowledge that the initial demand for vaccines will exceed supply, and that a tiered approach to vaccine prioritization is ethically valid. This process will involve prioritizing health care workers as well as vulnerable populations with increased risk for COVID-19 complications. Finally, we should seek opportunities within the IBD community to enroll patients in postmarketing registries to better

understand the effects of SARS-CoV-2 vaccines on various IBD population profiles and establish evidence to further guide optimal vaccination strategies for our patients with IBD. Winter may be coming, but can spring be far behind?[25]

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Conflicts of interest

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