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VACCINE PREVENTABLE DISEASE IN IBD: RELEVANCE, GUIDELINES AND CONSIDERATIONS FOR IMPLEMENTATION

Introduction

The increasing prevalence of vaccine-preventable diseases (VPDs) in patients with inflammatory bowel disease (IBD) has given rise to increased awareness of the need to educate clinicians and patients about the critical role of immunization in this patient population. In 2023, it was estimated that in the Canadian population, 320,000 individuals (0.83%) were affected by IBD.¹ Patients with IBD are at risk of vaccine-preventable diseases as the result of several factors, including potentially reduced efficacy and safety of vaccinations in the context of systemic immunosuppressive therapies administered for the management of IBD² and a state of malnutrition caused by the disease.³

Barriers to the administration of vaccinations include: Clinicians' reluctance to immunize patients with IBD³; patient lack of awareness regarding the critical importance of a structured vaccination protocol²; gastroenterologists' assumption that immunization falls under the auspices of the primary care provider (PCP); and limited time and resources.²

The objective of this paper is to highlight the need for broader implementation of the 2021 Canadian Association of Gastroenterology (CAG) Guidelines concerning both live and inactivated vaccines in patients with IBD. This overview focuses on commonly encountered VPDs for which administration of live and non-live vaccines may be required and for which an IBD-specific deviation from the NACI recommendations have been made. The vaccines selected for this brief overview are also commonly administered in clinical practice. Clinicians may experience uncertainty in relation to management of these vaccinations in practice.

Role of Vaccination

Many pharmacologic therapeutic options for IBD, including corticosteroids, immunomodulators and biologics, leave patients in an immunosuppressed state.⁴ Additionally, patients with IBD have blunted innate immune responses and experience chronic damage to the gastrointestinal (GI) barrier, potentially increasing susceptibility to infection.^{5,6} Additionally, small-scale clinical studies identify hyposplenism as a complication of IBD infection.^{7,8} Hyposplenism in IBD is associated with decreased production of memory B cells and impaired antibody responses

to intravenous antigen.⁹ This theoretical basis for increased risk of infections in patients with IBD has been reflected in clinical studies examining clinical outcomes. The largest cohort trial to date, involving 190,694 IBD patients in France, reported an increased risk of infection vs untreated patients in those receiving thiopurine monotherapy (hazard ratio [HR] 1.32; 1.23-1.42), anti-TNF monotherapy (HR 2.26; 2.08-2.45), and combination therapy (HR 2.79; 2.40-3.25).¹⁰ A prospective, observational study of 6,273 IBD patients in the United States demonstrated an increase in infection risk associated with prednisone therapy vs untreated patients (HR 1.57; 1.17-2.10) and infliximab (HR 1.43; 1.11-1.84).¹¹

Vaccine Implementation in Clinical Practice

These studies highlight the importance of preventing infection in patients with IBD. Vaccines have been developed to reduce the risk of many infections, including hepatitis B and influenza. Unfortunately, vaccination rates in patients with IBD remain low. In one clinical study of 169 patients with IBD, only 45% were current with their tetanus vaccination; 28% regularly received their flu shots; and only 9% received their pneumococcal vaccine.¹² Several potential explanations exist as to why vaccination uptake among patients with IBD remains low. It may be due to lack of patient awareness of either the increased risks of infection associated with immunosuppressive therapies, or the benefits of vaccination.¹³ Similarly, a knowledge barrier exists amongst physicians who find themselves lacking accurate, up-to-date knowledge regarding the safety and schedule of specific vaccines in the context of immunosuppression.^{13,14} Additionally, controversy exists regarding whether or not vaccination management in clinical practice is the responsibility of the gastroenterologist, PCP or other healthcare practitioner.^{15,16}

Vaccine Selection in Pediatric and Adult Patients

In 2021, the Canadian Association of Gastroenterology (CAG) published guidelines to address potential knowledge gaps that may be acting as barriers to vaccine utilization in patients with IBD. The guidelines are divided into two parts, the first addressing live vaccines² and the second addressing inactivated vaccines.¹⁷ **Table 1** summarizes the Guidelines Consensus Recommendations for immunizations in patients with IBD.

Principles of immunization of patients with IBD • Recommendation 1: In all patients with IBD, a complete review of the patient's history of immunization and VPDs should be performed at diagnosis and updated at regular intervals by IBD care providers. Ungraded good practice statement. • Recommendation 2: In patients with IBD, all appropriate vaccinations should be given as soon as possible, and ideally prior to initiation of immunosuppressive therapy. Ungraded good practice statement. • Recommendation 3: In patients with IBD who require urgent immunosuppressive therapy, treatment should not be delayed in order to provide vaccinations. Ungraded good practice statement.
Live vaccines • MMR » Recommendation 4A: In MMR-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend MMR vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 4B: In MMR-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving MMR vaccine. GRADE: Conditional recommendation, very low CoE » Recommendation 5A: In MMR-susceptible adult patients with IBD not on immunosuppressive therapy, we recommend MMR vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 5B: In MMR-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving MMR vaccine. GRADE: Conditional recommendation, very low CoE • Varicella » Recommendation 6A: In varicella-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend varicella vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 6B: In varicella-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving varicella vaccine. GRADE: Conditional recommendation, very low CoE » Recommendation 7A: In varicella-susceptible adult patients with IBD not on immunosuppressive therapy, we suggest varicella vaccine be given. GRADE: Conditional recommendation, very low CoE Recommendation 7B: In varicella-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving varicella vaccine. GRADE: Conditional recommendation, very low CoE
Statements with no recommendations • No Recommendation A: In infants born of mothers using biologic therapies, the consensus group could not make a recommendation for or against giving live vaccines in the first 6 months of life. • CoE, certainty of evidence; MMR, measles-mumps-rubella; VPDs, vaccine preventable diseases.
Inactivated Vaccines • Hib » Recommendation 8A: In pediatric patients with IBD, 5 years of age and younger, we recommend Hib vaccine be given. GRADE: Strong recommendation, moderate CoE Recommendation 8B: In unimmunized pediatric patients with IBD, older than 5 years of age, we suggest Hib vaccine be given. GRADE: Conditional recommendation, low CoE » Recommendation 9: In unimmunized adult patients with IBD, we suggest Hib vaccine be given. GRADE: Conditional recommendation, very low CoE • HZ » Recommendation 10A: In adult patients with IBD 50 years of age and older, we recommend recombinant zoster vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 10B: In adult patients with IBD younger than 50 years of age, we suggest recombinant zoster vaccine be given. GRADE: Conditional recommendation, low CoE • Hepatitis B » Recommendation 11: In pediatric patients with IBD, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 12A: In unimmunized adult patients with IBD with a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 12B: In unimmunized adult patients with IBD without a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given. GRADE: Strong recommendation, low CoE • Influenza » Recommendation 13: In pediatric patients with IBD, we recommend influenza vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 14: In adult patients with IBD, we recommend influenza vaccine be given. GRADE: Strong recommendation, moderate CoE • Pneumococcal vaccine » Recommendation 15: In pediatric patients with IBD, we recommend age-appropriate pneumococcal vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 16A: In adult patients with IBD not on immunosuppressive therapy, with a risk factor for pneumococcal disease, we recommend pneumococcal vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 16B: In adult patients with IBD on immunosuppressive therapy, we suggest pneumococcal vaccines be given. GRADE: Strong recommendation, low CoE • Meningococcal vaccine » Recommendation 17: In pediatric patients with IBD, we recommend age-appropriate meningococcal vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 18: In adult patients with IBD with a risk factor for invasive meningococcal disease, we recommend meningococcal vaccines be given. GRADE: Strong recommendation, moderate CoE • Diphtheria, tetanus, and pertussis » Recommendation 19: In pediatric patients with IBD, we recommend age-appropriate tetanus, diphtheria, and pertussis-containing vaccines be given. GRADE: Strong recommendation, moderate CoE » Recommendation 20: In adult patients with IBD, we recommend tetanus, reduced diphtheria, and acellular pertussis/tetanus and diphtheria vaccine be given. GRADE: Strong recommendation, moderate CoE • HPV » Recommendation 21: In female patients with IBD aged 9-26 years we recommend HPV vaccine be given. GRADE: Strong recommendation, moderate CoE » Recommendation 22: In male patients with IBD aged 9-26 years, we suggest HPV vaccine be given. GRADE: Conditional recommendation, very low CoE
Statements with no recommendations • No Recommendation B: In unimmunized adult patients with IBD on immunosuppressive therapy, the consensus group could not make a recommendation for or against giving double-dose hepatitis B vaccine. • No Recommendation C: In patients with IBD on maintenance biologic therapy, the consensus group could not make a recommendation for or against timing seasonal influenza immunization in relation to the biologic dose. • No Recommendation D: In adult patients with IBD not on immunosuppressive therapy and without a risk factor for pneumococcal disease, the consensus group could not make a recommendation for or against giving pneumococcal vaccines. • No Recommendation E: In adult patients with IBD without a risk factor for IMD, the consensus group could not make a recommendation for or against giving meningococcal vaccines. • No Recommendation F: In female and male patients with IBD aged 27-45 years, the consensus group could not make a recommendation for or against giving HPV vaccine.

Table 1. Clinical Practice Guidelines for Immunizations in Patients with IBD; adapted from Benchimol, E. et al, 2021

General population

The CAG guidelines recommend that in all patients with IBD, a complete review of immunizations be performed at diagnosis and at regular intervals. Observational studies have demonstrated significantly lower serological responses to routine vaccinations in IBD patients already being administered immunosuppressive therapies. Therefore, the ideal time to review a patient's immunization status is at diagnosis, prior to the administration of immunosuppressive therapies.¹⁷ The authors acknowledge that it may not be practical to take a detailed vaccination history at every patient visit but do provide important time points that may prompt immunization review, including changes to immunosuppressive regimens and changes in occupation/travel. When a healthcare provider determines that a patient requires certain immunizations, the guidelines recommend that they be administered as soon as possible, ideally prior to the initiation of immunosuppressive therapy. However, in patients who require urgent immunosuppressive therapy, treatment should not be delayed to administer vaccinations.²

Live vaccines

MMR vaccine

The guidelines recommend that patients with IBD not receiving immunosuppressive therapy receive the live measles, mumps and rubella (MMR) vaccine if they are susceptible. However, they recommend against giving live vaccines to those already being administered immunosuppressive therapy, due to efficacy and safety concerns.² In MMR-susceptible pediatric patients with IBD not on immunosuppressive therapy, the guidelines recommend that live vaccines be administered. In MMR-susceptible pediatric patients with IBD on immunosuppressive therapy, they recommend against administering the MMR vaccine.²

Varicella

Similarly, in varicella-susceptible pediatric patients with IBD not on immunosuppressive therapy, the recommendation is that the varicella vaccine be administered. In varicella-susceptible pediatric patients with IBD on immunosuppressive therapy, the guidelines suggest against its use.²

Timing of Live Vaccines

The American College of Gastroenterology (ACG) Guidelines stipulate that if an IBD patient's vaccination history is unknown or in cases where

there is no documentation of immunization in an IBD patient about to initiate immunosuppression, there is a conditional recommendation that the patients receive 2 doses of the MMR vaccine 28 days apart at least 6 weeks prior to the initiation of the immunosuppressive therapy. In the West, where the overall prevalence of measles is low, clinicians are advised to weigh the benefits of measles vaccination against the risks of delaying the initiation of immunosuppressive therapy for 10 weeks.¹⁸

Non-live vaccines

Influenza vaccine

The guidelines recommend that patients with IBD should receive the influenza vaccine yearly.

In clinical practice, clinicians often make recommendations about when to administer the influenza vaccine to patients on biologic therapies. The theory that giving the vaccine at a time during the biologic interval when the drug exposure is likely to be lowest will lead to improved effectiveness underpins this advice. One randomized controlled trial demonstrated no significant difference in immunogenicity when influenza vaccine was administered at the same time as biologic infusion compared to midway between infusions.¹⁹ However, the guidelines concluded there was insufficient data to make a recommendation regarding the timing of influenza vaccination in relation to the biologic. More importantly, risk factors for severe influenza (chronic medical comorbidities, women who are or will be pregnant, children on long term salicylate medications, residents of nursing homes or other facilities, indigenous people, and extreme obesity) should be considered and vaccination not delayed due to concerns about timing throughout biologic interval.

Herpes Zoster vaccine

The guidelines recommend that patients with IBD should receive the 2-dose series recombinant (non-live) zoster vaccine given the observed increased incidence of zoster in adults with IBD on immunosuppressive therapy.²⁰⁻²⁵ This is preferred over the live attenuated zoster vaccine because of superior efficacy and safety. This differs from recommendations for the general (non-IBD) population in which the zoster vaccine is recommended for patients aged 50 years and older.

Pneumococcal and meningococcal vaccine

The pneumococcal vaccine should be administered to patients with IBD on immunosuppressive therapy, as well as to non-immunosuppressed patients with a

risk factor for pneumococcal disease. This includes patients >65 years of age; who suffer from asplenia; are active smokers; have alcohol use disorder; and those with comorbidities such as diabetes, or chronic heart, liver or kidney disease.¹⁷ The meningococcal vaccine should be administered to patients with IBD with a risk factor for meningococcal disease, including asplenia or human immunodeficiency virus (HIV); who have had exposure to a confirmed case; or who engage in certain occupations such as the military. Finally, patients aged 9 to 26 years should receive the HPV vaccine.¹⁷

Hepatitis B vaccination

The Canadian guidelines support vaccinating both pediatric and adult patients with IBD, particularly if there is a risk factor for hepatitis B. In the United States, guidelines recommend the vaccination of patients with IBD against hepatitis B as hepatitis B infection and reactivation are a concern due to these patients' immunocompromised status. This is particularly true if tumour necrosis factor- α (TNF- α) therapy is needed, as fulminant and fatal cases have been reported in the literature. It is important for gastroenterologists and other clinicians to note that IBD patients, particularly those being administered TNF- α agents, do not achieve hepatitis B surface antibody (HBsAb) levels considered adequate for immunity at the same rate achieved in the general population.²⁶

In consideration of this, the guidelines recommend rechecking titers one month following the final dose of a 3-dose regimen (0, 1 and 6 months). If patients do not respond to this initial course of therapy, the recommendation is to revaccinate with the regular vaccine, revaccinate with a double dose vaccine, or revaccinate with a combined HAV/HBV vaccine. Currently, there is no consensus regarding the most appropriate method of revaccinating IBD patients unresponsive to the initial course of vaccination. The key consideration is to assess hepatitis B exposure and vaccination status prior to the initiation of any immunosuppressive agent in patients with IBD.¹⁸

SARS-CoV-2 vaccination

The international response to the COVID-19 pandemic ushered in a series of highly effective vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). However, patients with IBD were excluded from the clinical trials that led to the approval of these vaccines. While regulatory bodies were initially hesitant to endorse the use of COVID-19 vaccines in patients with IBD for this reason, real-world data has demonstrated that these vaccines are effective and safe in patients

with IBD. This has led to multiple expert panels, including the CAG, recommending vaccination against the SARS-CoV-2 virus.²⁷ Given that the SARS-CoV-2 vaccines are not live vaccines, there is no theoretical reason to believe that individuals with IBD on immunosuppressives would be at risk of virus reactivation, and multiple observational studies have not suggested any cause for concern. The rate of adverse events in a clinical study of 246 patients with IBD who received a SARS-CoV-2 vaccine was similar to that of the general population.²⁸

Another theoretical concern is whether or not SARS-CoV-2 vaccines would be effective in patients with IBD on immunosuppressive therapy. Observational studies have demonstrated reduced effectiveness of the SARS-CoV-2 vaccine in patients who receive the complete series. The CLARITY-IBD study reported less robust immune responses to the *first* dose of the Pfizer and AstraZeneca vaccine in patients with IBD on infliximab vs vedolizumab. However, in the same study, seroconversion was robust following the second dose of vaccine and in individuals who received a dose of vaccine following recovery from COVID-19 infection.²⁹ A separate clinical study of approximately 15,000 patients with IBD receiving a number of immunosuppressives reported 80.4% vaccine effectiveness rates for those who received their second dose of mRNA vaccine.³⁰ In fact, Canadian,²⁷ European³¹ and international³² gastroenterology organizations recommend that patients with IBD receive the primary series of the SARS-CoV-2 vaccine at the earliest opportunity. The IBD Task Force of Crohn's and Colitis Canada recommends the primary series of 3 doses of mRNA-based, bivalent or polyvalent COVID-19 vaccinations. After the primary series, they recommend boosters using bivalent or polyvalent vaccines every 4-6 months.

Effectiveness of Vaccinations

Clinical studies on the vaccination regimens in the IBD patient population have reported varied efficacy results. In a systematic review of observational studies, including 2,852 IBD patients receiving immunosuppressive therapies, in a comparison of immunosuppressive-exposed and non-exposed patients, some studies demonstrated a reduced serological response, while other showed no significant differences.²

Although results of observational studies are varied, one study of the serologic antibody status of adults administered the MMR vaccine suggested no difference in antibody concentrations between IBD patients who received MMR vaccines as children prior to their IBD diagnosis vs healthy controls. However,

the relevance of MMR serology is unknown as antibody titers may be low or undetectable despite previous remote vaccination. In this case patients may have an anamnestic response. In a pediatric study, reported serologic protection rates were: 67.6% for measles, 63.3% for mumps, and 81.4% for rubella.²

Vaccination for Infants When the Mother is on Biologic Therapy

The CAG guidelines could not make a recommendation for or against giving live vaccines in the first 6 months of life to infants born of mothers using biologic therapies. There is a theoretical risk of infection after administration of live vaccines in infants who have been exposed to biologic therapies from their mother via the placenta. Studies have demonstrated detectable levels of biologic therapies at birth, with some being detectable up to 12 months of age.³³ This is relevant because the live attenuated rotavirus vaccine is routinely given at 2 months of age. Some small cohort studies and case series have shown no serious adverse events among infants exposed to biologic therapies in utero who then received rotavirus vaccine.³⁴⁻³⁶ However from a health system perspective, routine rotavirus vaccination programs are not cost-effective in high-income settings, thus the guidelines could not recommend for or against their routine use in infants born to mothers on biologic therapies.^{37,38}

Future considerations for implementation of vaccines in patients with IBD

While the CAG guidelines provide clear recommendations on which vaccinations should be administered to patients with IBD, they do not provide guidance on how these recommendations can be implemented effectively in clinical practice. Many potential barriers to implementation of evidence based IBD vaccine preventable disease guidelines in clinical practice exist. These include patient education, knowledge gaps among healthcare providers, and uncertainty regarding whether gastroenterologists or PCPs are responsible for the management of vaccine preventable disease. Unfortunately, vaccination utilization among patients with IBD remains low.³⁹ A limited number of clinical studies have evaluated interventions designed to improve vaccination uptake in gastroenterology practices. One prospective interventional study at two outpatient clinics involving 50 patients with IBD demonstrated that an electronic medical record order set and a patient educational handout led to an increase in influenza and pneumococcal vaccination rates from 19% and 2%, respectively, pre-intervention, to 85% and 38%, respectively, post-intervention.³²

Likewise, few clinical studies have assessed patient, gastroenterologist and other important stakeholder perspectives concerning barriers to, and facilitators of, the implementation of evidence-based guidelines for VPD. A qualitative clinical study by Zhou et al (2022) assessing perceived barriers to implementation of IBD VPI guidelines among community and academic gastroenterologists and IBD nurses is underway.⁴⁰ The study participants agreed that assessment of immunization status and making appropriate recommendations for indicated vaccines is within the scope of practice of the gastroenterologist. However, preliminary themes indicate that additional support is needed to administer vaccines in clinical practice. Reported barriers to implementation of IBD VPI guidelines include incomplete understanding of coverage of, and access to vaccines; limited time in scheduled appointments to provide comprehensive patient care; and lack of access to primary care providers. Interventions that could potentially help overcome these barriers include clinical decision support tools, support from allied healthcare providers, and third-party support.

To date, no clinical studies have used rigorous implementation science approaches to design their intervention or to perform an analysis of the target behaviour or population. Implementation science is a growing field that attempts to close the gap between what healthcare providers know and the actions they take. Implementation frameworks allow for the characterization of behaviours that could facilitate or impede implementation.⁴¹ The application of these frameworks to understand the barriers, facilitators and potential intervention functions for the implementation of evidence-based guidelines is necessary to ensure that the design of the interventions and implementation strategy are appropriate and sensitive to the local context. At the same time, implementation strategies must be adaptable to facilitate their scale and dissemination. The study by Zhou et al seeks to understand the barriers from the academic and community-based gastroenterologist's perspective and is an important first step in developing an effective implementation strategy for the Canadian healthcare system.

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