

Improving immunization strategies in patients with inflammatory bowel disease

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Abstract

Patients with inflammatory bowel disease (IBD) are susceptible to varieties of opportunistic infections due to immunological changes in the setting of their disease and drug-induced immunosuppression. Even though numerous infections can be prevented by vaccine, vaccination in IBD patients is inadequate. Data showed only 9% were vaccinated against pneumococcal infection and 28% described commonly receiving influenza vaccine. This review article discusses the recent immunizations against influenza virus; pneumococcal infection; human papilloma virus; tetanus, diphtheria and pertussis; measles, mumps and rubella; varicella zoster; and herpes zoster for individuals diagnosed with IBD and those patients with drug-related immunosuppression. In addition, this review discusses concerns about IBD patients planning to travel abroad. Immunization status and screening for opportunistic infection need to be addressed in IBD patients at the time of diagnosis and they should be vaccinated accordingly. Generally, standard vaccination strategies should be pursued in IBD patients, although live vaccines should be avoided while they are not immunocompetent.

Keywords Inflammatory bowel disease, opportunistic infections, immunization

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Introduction

Inflammatory bowel diseases (IBD) are a group of chronic inflammatory conditions of the colon and small intestinal tract [1]. Immunomodulators and biologic agents are approved for treating this group of patients and current data support their introduction early in the disease course [2]. Biologic medications and immunomodulators, or a combination of both, are used as the maintenance therapy in IBD [3]. Immunosuppression increases the risk of infections, some of which are preventable with routine immunization [4]. IBD patients on immunosuppressive treatment have a considerably

weaker reaction to routine vaccinations. The greatest effect is seen in patients on a combination of anti-tumor necrosis factor (TNF) and immunosuppressive therapy [5]. Given the risk of vaccine-related infection, live vaccines are contraindicated in immunodeficient IBD patients (Table 1) [6].

Data have shown poor counselling about vaccinations by gastroenterologists or primary care physicians [7]. Prior studies have proven that physician counseling is a strong predictor of being vaccinated and other preventive care interventions [8]. Therefore, these findings draw attention to the need for a thorough and organized assessment of immunization status at the time of diagnosis of IBD or prior to starting any biologic agents. The aim of this review is to improve gastroenterologists' knowledge of the importance of preventive healthcare within the IBD patient population.

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Materials and methods

MEDLINE records were explored through PubMed with search strategies using search keywords “IBD”, “immunization”, “vaccination recommendation”, “influenza”, “Europe”, “HPV”, “pneumococcal”, “herpes zoster”, “varicella”, “Tdap” and “MMR” to identify studies published between the years 1987 and 2018. Articles were selected from case-control studies, randomized trials, cohort research, and case reports. In addition, abstracts of conferences from important congresses in

the gastroenterology field, United European Gastroenterology Week, and the European Crohn's and Colitis Organisation were searched. Adults with IBD receiving any vaccine type and at any dose were included. Studies related to non-humans or not in the English language were excluded from our review. Abstracts of the articles found by the preliminary search were reviewed by the authors for pertinence to IBD, and all potentially related data were selected and evaluated in detail.

Definition of immunocompromised in IBD

The criteria for impaired immune systems in IBD patients are: 1) patients on glucocorticoid therapy ≥ 20 mg of prednisone for longer than 2 weeks; 2) patients taking immunomodulators, including azathioprine, mercaptopurine and/or methotrexate, calcineurin inhibitors or anti-TNF (infliximab, adalimumab or others); 3) undernourished patients and patients with any condition leading to impaired immune systems, such as asplenia or human immunodeficiency virus infection [4,9]. Another classification specifies high or low levels of immunosuppression according to the strength of the immunosuppressive agents (Table 2) [10].

Table 1 Contraindicated vaccines in patients with inflammatory bowel disease [10,102-107]

Live, attenuated influenza (intranasal vaccine)
Varicella zoster vaccine, Herpes zoster (live zoster vaccine)
Yellow fever vaccine
Measles-mumps-rubella vaccine
Smallpox vaccine
Tuberculosis bacillus Calmette-Guérin vaccine
Polio live oral vaccine
Anthrax vaccine

Table 2 Level of immunosuppression based upon strength of immunosuppressive medication [10]

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

Screening test for infectious disease

The use of biological medications and immunomodulators for IBD is connected to an increased risk of opportunistic infections. Therefore, screening for immunity to serious infection is recommended, but compliance with these recommendations is unknown. It is essential that gastroenterologists involved in IBD care execute a vigilant investigation for infectious disease before starting immunomodulation. Vigilant screening allows the physician to avoid having to stop a biological medication because of the presence of infections with the risk of recurrence of the underlying disease [11] (Table 3).

Rate of infection in IBD patients

The risk of opportunist infections is very high in IBD patients. Kirchgesner *et al* in 2018 showed that, among 190,694 patients with IBD, serious infections occurred in 8561 of them, while 674 patients were dealing with opportunistic infections. The investigators reported that combination therapy was accompanied by higher risks of serious infection (hazard ratio [HR] 1.23, 95% confidence interval [CI] 1.05-1.45) and opportunistic infection (HR 1.96, 95%CI 1.32-2.91), compared with anti-TNF monotherapy [12]. Reactivation of the hepatitis B virus (HBV) has been documented at rates of 16-36% in IBD patients with HBsAg-positive. Longstanding use (defined as more than 3 months) of immunosuppressive therapy and combination therapy without being immunized with antiviral vaccine prophylactically are associated with the risk of HBV reactivation [13]. Huang *et al* showed that the rate of hepatitis C virus (HCV) infection in patients with IBD was not statistically different from that in the general population. Among 714 patients with IBD, the rate of HCV infection was 0.42% compared with 0.36% ($P=0.80$) in non-IBD individuals. This outcome was in line with another study conducted in Italy [14,15]. The latest data indicate that IBD patients have a 1.65% chance of developing a tuberculosis infection, even after latent tuberculosis infection screening, before the initiation of anti TNF- α therapy [16].

Vaccination rate in IBD patients

The vaccination rate among IBD patients is still suboptimal. A survey by Melmed *et al* showed that, among 146 IBD patients, only 41 (28%) had received an influenza vaccine and 13 (9%) reported being vaccinated against pneumococcal infection with a history of application of immunosuppressive agents. A lack of awareness (49%) and fear of side effects (18%) are the most common reasons for non-immunization with the influenza vaccine [17]. Malhi *et al* found that in Canada the rate of self-reported vaccinations among IBD patients is significantly low. The vaccination rates were reported as influenza 61.3%, pneumococcus 10.3%, HBV 61.0%, hepatitis A virus 52.0%, varicella 26.0%, meningococcus 20.7%, herpes

Table 3 Screening test and recommendation for patients with inflammatory bowel disease [99-101]

Infection	Test	Recommendation for screening	Vaccine
TB	QuantiFERON TB-Gold and tuberculin skin test	Yes	Contraindication in immunocompromised
Hepatitis B virus	HBsAg and HBsAb	Yes	Yes
HCV	Anti-HCV serology	Yes	No
HIV	HIV serology	Yes	No
Varicella zoster virus	VZV serology	Yes	Yes
Human papilloma virus	Cervical cytology	Yes	Yes

TB, tuberculosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; VZV, varicella zoster virus

zoster (HZ) 5.3%, and human papillomavirus (HPV) 11.0%. Among IBD patients, insufficient counseling by providers, ambiguity about indications and fears concerning vaccine safety are the most common reasons for non-uptake (22.0%, 20.7% and 5.3%, respectively) [7]. Additionally, physician uncertainties over whether vaccination is indicated in IBD patients and a lack of knowledge about immunizations on the part of providers have been reported [18,19]. Regrettably, data showed only 30% of family medicine specialists felt comfortable managing routine maintenance issues including immunization in the IBD patients, especially when they were immunocompromised [8,20].

Vaccination recommendations

Current practice recommendations proposed by the second European evidence-based consensus for routine vaccinations in IBD patients are presented in (Table 4) [21].

Influenza

All patients diagnosed with IBD should be immunized with the influenza vaccine yearly [22]. There are two forms of influenza vaccines: an inactivated form injected intramuscularly and intradermally, and a live form administered intranasally [3]. The inactivated influenza vaccine is safe to be given to patients on immunomodulators or biologic therapy. However, the live intranasal vaccination should be avoided in patients who are immunosuppressed [23].

DeBruyn *et al* showed in a randomized study that, in 137 patients with IBD, serologic protection against the influenza vaccine was reached by around 45-80% on maintenance infliximab therapy, varying by antigen. Essentially, vaccine timing relative to infliximab infusion did not affect the attainment of serologic protection and the influenza vaccine was well tolerated. Consequently, vaccination against influenza is recommended at any point throughout infliximab scheduling [24]. Cullen *et al* reported that, among 108 IBD patients taking the 2009 H1N1 influenza vaccine, the proportion with seroprotection was considerably lower among individuals on combination immunosuppression therapy compared to those not treated with immunosuppressive medications (36%

vs. 64%, $P=0.02$) [25]. Additionally, Hiroko *et al*, in a prospective randomized controlled trial, found that booster doses of the trivalent influenza vaccine were not able to induce a significant immune response in adult IBD patients [26]. Importantly, data showed that the higher dose of influenza vaccine in persons 65 years of age or older triggered significantly higher antibody responses and offered better protection against laboratory-confirmed influenza disease [25].

Pneumococcal infection

Streptococcus pneumoniae is a pathological microorganism that can cause severe infections, such as pneumonia or meningitis [27]. A study in Denmark reported that, even before the diagnosis of IBD, this group of patients was prone to be infected with pneumococcal pneumonia, signifying that the existence of IBD increases the chance of infection [28,29]. In a retrospective cohort study performed among IBD patients who matched non-IBD individuals, the IBD group had a higher risk of developing pneumonia than did patients without IBD (incidence rate ratio [IRR] 1.82, 95%CI 1.75-1.88). It was shown that the use of biologic medications (OR 1.28, 95% CI 1.08-1.52), steroids (OR 3.62, 95%CI 3.30-3.98) or proton pump inhibitors (OR 1.14, 95%CI 1.03-1.25) within 120 days was strongly related to pneumonia [30]. Therefore, the immunization status should be updated even before the initiation of immunosuppressive therapy [28,31].

Presently, there are two forms of pneumococcal vaccines available: 23-valent polysaccharide vaccine (PPSV23) and 13-valent conjugate vaccine (PCV13). According to a recommendation of the Advisory Committee on Immunization Practices (ACIP), all IBD patients should be vaccinated with both PCV13 and PPSV23. A single dose of PCV13 should be given to all IBD patients, followed by a dose of PPSV23 at least 8 weeks later in immunodeficient patients, or after 1 year in immunocompetent patients. A second dose of PPSV23 should be given 5 years after the first dose and needs to be repeated in adults aged 65 years or older. If IBD patients previously received the PPSV23 vaccine, a single dose of the PVC13 vaccine should be administered at least 1 year later, regardless of the patient's immune status [32,33]. The recommendations of the European consensus on opportunistic infection in IBD patients are parallel to those in the USA, where all patients with

Table 4 Summary of current practice recommendations for routine vaccinations in patients with inflammatory bowel disease [21]

Vaccines recommended per routine guidelines
Tetanus (as part of Td, Tdap, or DTaP)
HPV (quadrivalent vaccine against types 6, 11, 16, and 18) ^a
Hepatitis A (single-antigen vaccine or as part of hepatitis A and B combination vaccine)
Hepatitis B vaccine
Poliomyelitis
Pertussis (as part of Tdap or DTaP)
Inactivated influenza (trivalent inactivated vaccine, annually)
Vaccines recommended prior to initiation of immune-modulator therapy
Varicella vaccine ^b
Pneumococcus vaccine (PCV13, PPSV23) ^c

^aBoth males and females, according to national guidelines. The current Canadian guidelines recommend the HPV vaccine to both males and females between 9 and 26 years of age

^bIn those without a clear history of chickenpox, shingles, or receipt of two doses of varicella vaccine and seronegative for varicella zoster virus antibody [VZV] IgG

^cThe specific sequence of administration for these two vaccines varies with patient characteristics and history of prior vaccination, as outlined in the CDC-ACIP vaccination schedule [<http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf>]

Td, tetanus, diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis; DTaP, pediatric combination vaccine against tetanus, diphtheria, and acellular pertussis; HPV, human papillomavirus; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; CDC-ACIP, Centers for Disease Control and Prevention – Advisory Committee on Immunization Practices

IBD treated with immunosuppressive medications, and who have not previously been vaccinated with PCV13 or PPV23, should be given a single dose of PCV13, followed by a dose of PPV23 at least 8 weeks later. A second dose of PPV23 vaccine is suggested 5 years later. Patients who have previously received PPV23 should be vaccinated with a PCV13 dose 12 months after their last PPV23 [21].

HZ

Varicella zoster virus (VZV) is a worldwide pathogen that only infects humans. Primary infection by VZV leads to varicella (chickenpox) disorder and subsequently the virus remains dormant in the nervous system. Treatment with immunosuppressive agents can debilitate cell-mediated immunity to VZV, leading to its reactivation [34]. VZV infection risk is high for IBD patients [35,36]. A retrospective cohort study by Long *et al* showed that the IBD cohort had a higher risk of HZ infection compared with the general population (IRR 1.68, 95%CI 1.60-1.76) [37]. Moreover, in another study by Gupta *et al*, patients with ulcerative colitis and Crohn's disease had a higher incidence of zoster infection compared with their matched controls. The investigators reported that the use of azathioprine/6-mercaptopurine medications (adjusted OR 3.1, 95%CI 1.7-5.6) in corticosteroid recipients (adjusted OR 1.5, 95%CI 1.1-2.2) was associated with a higher chance of developing shingles [38]. In line with previous studies, Cullen *et al* showed that VZV can be associated with a significant risk of morbidity and mortality in immunosuppressed patients, especially those under treatment with corticosteroids and combination immunosuppression, including methotrexate and azathioprine [39].

Immunosuppression increases the risk, but not all immunosuppression might carry the same risk, as vedolizumab has been reported to have a low incidence of serious infections [40]. Moreover, another study by Papp *et al* demonstrated that the rates of serious infection for infliximab and other biologics were significantly greater than that for ustekinumab [41].

The HZ vaccine is recommended in IBD patients aged 60 years and older, regardless of whether they have had a previous zoster episode. The vaccination is effective for reducing the incidence of HZ by 51% and post-herpetic neuralgia by 67% [42]. However, the zoster vaccine is contraindicated while IBD patients are on biological agents, given the fact that the zoster vaccine is a live, attenuated vaccine. Given the risk of developing HZ infections, this vaccine should be considered even in those managed with low-dose immunosuppression, such as low-dose prednisone (<20 mg/daily), 6-mercaptopurine (<1.5 mg/kg/day) or azathioprine (<2.5 mg/kg/day) [43]. Therefore, the vaccine needs to be given ≥ 3 weeks prior to the initiation of any immunosuppressant medication [44]. However, Khan *et al* showed that, in 59 patients treated with anti-TNF medication, of whom 12 (20%) were also using thiopurine, once they received the vaccine no case of HZ infection was seen within 0-42 days after its administration [45].

Varicella

It was suggested by the Centers for Disease Control and Prevention (CDC) that all individuals who lack evidence of VZV immunity by serology testing should receive two doses of varicella vaccine, given at least 4-8 weeks apart [46]. All IBD patients need to be screened for immunity to VZV at

the time of diagnosis. Unimmunized and immunocompetent IBD patients should be offered vaccination with a 2-dose series of live varicella vaccine at least 3 weeks prior to the start of immunosuppressive therapy. Because varicella vaccine is a live virus vaccine, it should be administered in immunocompromised patients at least 3 months after the immunosuppressive treatment is discontinued [4,47]. In line with this, the European Crohn's and Colitis Organisation suggests administering the live vaccine either 3 weeks prior to starting treatment or 3-6 months after discontinuation of immunosuppressive agents [21,48]. Lindsey *et al* showed that the HZ vaccination (Zostavax) was safe in patients with rheumatoid, psoriatic arthritis and spondyloarthropathies who were on infused biologics [49].

Because the inactivated zoster vaccine (ZV_{IN}) is not a live vaccine, no issues should be expected when it is administered to immunocompromised patients. Parrino *et al* showed that, in patients with hematologic malignancies receiving anti-CD20 monoclonal antibodies, ZV_{IN} was tolerated well and caused statistically significant VZV-specific T-cell immune responses [50]. Additionally, another study reported that, in patients with autoimmune diseases, ZV_{IN} produced statistically significant immune responses [51].

The presence of VZV antibodies shows a prior infection with varicella and protection against this virus. VZV-specific antibody testing to measure immunity in those previously immunized with the varicella vaccine is not endorsed by the Advisory Committee on Immunization Practices [52]. As data showed, the reason for this is that the varicella vaccine produces lower VZV antigen-antibody concentration compared to natural immunity after varicella infection.

The recent commercial antibody, enzyme-linked immunosorbent assay (ELISA), is not sensitive enough to assess vaccine-induced VZV antibody levels in all patients, particularly those with a distant history of vaccination. Investigators from the CDC discovered that their ELISA, comparable with or more sensitive than commercial assays, had a 34% false-negative rate when compared with the glycoprotein ELISA developed by Merck [52,53].

Gastroenterologists need to be aware of the limitations of VZV serology using the commercially available immunoassays when they measure varicella immunity in those immunized. We need to rely more upon the patient's history of immunization, rather than current commercial ELISA, to evaluate the immunity to varicella [54].

Tetanus, diphtheria, acellular pertussis

Diphtheria and tetanus have become uncommon infections in developed countries but outbreaks have occurred in former Soviet Republics [55]. As per ACIP recommendations, adults who did not receive primary vaccination, or who did not complete the primary series, should begin or complete the primary vaccination series with three doses of tetanus- and diphtheria-containing vaccines, one of which should be a Tdap dose. All IBD patients should be given the combined tetanus

and diphtheria toxoids (Td) booster every 10 years, regardless of their immunosuppression status [56]. In 2014, 40,727 cases of pertussis were reported to The European Surveillance System (TESSy) by 29 countries of the European Union (EU) or European Economic Area (EEA) [57]. Additionally, in 2015, state health departments reported 20,762 cases of pertussis to the CDC [58,56]. Regardless of previous Tdap vaccination records, Tdap was recommended by ACIP for all pregnant women in the third trimester of their pregnancies [59]. The Tdap vaccine was recommended for all pregnant women in the United Kingdom and Ireland (Table 5) [60,61]. Dezfoli *et al*, in a controlled trial, evaluated the immunogenicity of the Tdap vaccine and found that, regardless of immunosuppressive regimen, patients have a normal booster response. They suggested patients with IBD should be vaccinated with Tdap prior to starting immunomodulators, especially once combination therapy with anti-TNF is started [62]. Additionally, in a cross-sectional study, Caldera *et al* showed that IBD patients on combination therapy or biological monotherapy had lower sustained pertussis antibody concentration [63]. Brogan *et al* suggested that patients with IBD had significantly impaired *in vitro* production of anti-tetanus toxoid antibody during an 8-day pokeweed mitogen-stimulated culture period. They reported that their results indicated many IBD patients have an impaired humoral immune response to tetanus toxoid booster immunization. This impaired immune response may be due to an inability to generate B cell precursors of anti-tetanus toxoid IgG-producing B cells, rather than to abnormal circulating helper or suppressor T-cell activity or natural killer cell regulatory activity [64].

Measles, mumps, rubella (MMR)

According to The Regional Verification Commission for Measles and Rubella Elimination at the WHO Regional Office for Europe, measles elimination was not reached in 14 of the 53 member states (26%) of the WHO European Region at the end of 2015 [65]. In January-February 2017, 10 EU/EEA countries reported more than double the number of cases compared to the same period in 2016 [66].

The effectiveness of the measles-component of the MMR vaccine was reported as 95-98% after a single dose and more than 99% following the second dose of the vaccine [67]. Similarly to measles protection, the MMR vaccine achieves more than 95% seroprotection against rubella after 1 dose and more than 99% following 2 doses [67,68]. However, the potency of the MMR vaccine against mumps is not as effective as against measles and rubella: seroconversion for mumps is 64-95% with 1 dose of vaccine and 88-95% following 2 doses [67,68].

Cleveland *et al*, in a prospective study, showed that a significant number of IBD patients lack immunity to measles [69]. The MMR vaccine is only available as a live, attenuated vaccine. Therefore, immunocompromised IBD patients should not be vaccinated with MMR [70]. Consequently, this vaccine should be administered at least

Table 5 Vaccination guidelines against tetanus, diphtheria, and pertussis [60,61]

Country	Adult (18-65 years)	Elderly>65 years
Austria ^a	Every 10 years	Every 5 years
Belgium ^b	Every 10 years	Every 10 years
Cyprus	Every 10 years	Every 10 years
Denmark	-	-
Sweden	Every 20 years	Every 20 years
France	^c Td-IPV at age 25 and 45 years	Every 10 years
Germany	Every 10 years	Every 10 years
Ireland	Tdap for each pregnant women	-
Norway	-	-
United Kingdom	Tdap for each pregnant women	-
Spain	-	Td at age around 65 years
Italy	Every 10 years	-

^aDiphtheria, tetanus, acellular pertussis (DTaP) and inactivated poliomyelitis vaccine (DTaP-IPV) should be given every 10 years between 18 and 60 years of age

^bOne of the booster doses should contain the pertussis antigen (Tdap) for those who have not previously received a single dose of Tdap

^cFor those who did not receive a dose of pertussis-containing vaccine during the past 5 years, a booster with a quadrivalent vaccine (DTaP-IPV) is recommended when Td-IPV booster is administered at age 25

1 month before the start of immunosuppressive agents [71]. The MMR vaccine can be given safely to the household or close contacts of an immunocompromised IBD patient [67].

HPV

The International Agency for Research on Cancer (IARC) has shown proof of a strong association between HPV and cancer sites such as anus and cervix [72]. HPV might be accountable for other malignancies, including cancer of the esophagus, oral cavity and lip. However, a causal role for HPV has not been recognized [73]. The incidence of HPV-related cancers is typically higher in immunosuppressed patients [74]. Shah *et al* demonstrated that there was a trend toward abnormal anal Papanicolaou in IBD subjects compared with a healthy control. There was no difference based on immunosuppression [75].

The quadrivalent HPV (qHPV) vaccine has been proven to prevent vaccine-related persistent anal HPV infections in addition to anal intraepithelial neoplasia [76]. A handful of studies have examined the prevalence of cervical dysplasia in IBD patients. Jacobson *et al* reported that IBD patients aged 9-26 on immunosuppressive therapy showed a proper immune response with 100% seroconversion to the HPV4 quadrivalent vaccine (against HPV types 16, 18, 6, and 11). They did not find any serious side-effects or worsening of disease activity due to the HPV4 vaccine [77]. Allegretti *et al* showed that IBD patients on immunosuppressive medication have a higher risk of high-grade cervical dysplasia and cervical cancer (OR 1.34, 95%CI 1.23-1.46) compared with the general population [78]. Likewise, Singh *et al* documented that combination therapy with steroids and immunosuppressive agents can increase the risk of

cervical abnormalities (OR 1.46, 95%CI 1.09-1.81) compared with IBD patients who are not on these medications [79]. The recommendation for the HPV vaccination schedules was updated by the CDC in October 2016. It was advised 2 doses of HPV vaccine for individuals younger than 15 years and 3 doses of HPV vaccine series for those aged 15 or older and have certain immunodeficiency conditions. The CDC continues to recommend routine HPV vaccination series for girls and boys aged 11 or 12 years. For immunocompromised patients aged 9 to 26 years, 3 doses of HPV vaccine (0, 1-2, 6 months) are recommended. The HPV vaccination series can be started at age 9 years and is also suggested for women through age 26 years and men through age 21 years. Individuals whose immune responses might be insufficient or lower (because of HIV infection, malignancy, autoimmune disorder, or use of immunosuppressant medications) should receive 3 doses to ensure they receive the most benefit [80]. In Europe there are two vaccines (Cervarix® and Gardasil®) against HPV authorized centrally by the European Medicines Agency. Cervarix is itemized to be administered with the reduced schedule in girls aged 9-14 years and Gardasil received positive feedback for use in 9-13-year-old adolescent girls and boys [81].

IBD vaccination and travel

All IBD patients who plan to travel overseas need to check what specific vaccinations they need according to where they are planning to travel [82]. It is important that they discuss their travel plans with a traveler's clinic beforehand and to go over the required vaccinations. They should familiarize themselves with the endemic infections of the specific areas

they plan to visit by reviewing the traveler's health information from the World Health Organization [83]. Yellow fever is one of the biggest challenges for IBD patients who plan to visit South America and sub-Saharan Africa. Unfortunately, the yellow fever vaccine is a live vaccine and should be avoided in drug-induced immunocompromised IBD patients [82]. The yellow fever vaccine can be given to this group of patients if immunosuppressive medications are discontinued for at least 4 months before vaccination [23,84]. Otherwise, if their immunosuppressive medications cannot be terminated because of medical necessity, they need to be instructed against visiting areas where yellow fever is endemic [23]. Enteric fever is another serious disease that IBD patients should be concerned about if they plan to travel to the Indian subcontinent. Accordingly, all patients with IBD need to be vaccinated with the parenteral inactive typhoid vaccine (Vi vaccine) before they travel [85]. Rabies is a fatal disease that is broadly distributed throughout the world and cell-culture-derived vaccines are available for use by IBD patients traveling to high risk areas such as Africa, Asia and Latin America [86,87]. Regarding HBV, the immune status needs to be screened if there is intention to visit areas where HBV is endemic, such as Africa, China and Southeast Asia. HBV booster should be offered to those who are immunocompromised and whose immune titers are less than 10 mIU/mL [88].

Viral meningoencephalitis is mostly caused by Japanese encephalitis (JE) in large parts of Asia [89]. Patients on anti-TNF therapy or dealing with a chronic medical condition may qualify for the JE vaccine [18]. An inactivated Japanese encephalitis vaccine (IXIARO®) has been approved in Europe and the United States and can be safely offered to IBD patients [82,90,91].

Concluding remarks

Proper immunizations are an essential part of medical management in IBD patients [20]. Because immunomodulators are used to treat IBD patients, these patients are susceptible to infection, with a high rate of morbidity and mortality [92,93]. Therefore, this group of patients should be immunized prophylactically against these infections [94], preferably upon initial presentation and once the start of immunosuppressive agents is planned [95]. Given the increased risk of vaccine-related infections, live vaccines should be avoided in immunocompromised patients. Importantly, the majority of immunocompromised patients exhibit a proper and sufficient seroconversion once they are vaccinated [3].

However, vaccination rates for these preventable diseases continue to be suboptimal in the face of a decade of research proving that IBD patients are at an increased risk of vaccine-preventable infections [96]. Prior data have shown that recommendations from physicians are the most important factor for receiving preventative health services such as vaccination and screening for cancer [97]. As per previous data, in the majority of IBD patients the screening test for HBV serology was missed by their gastroenterologists. This

suggests that providers may not be effectively instructed and do not regularly recommend screening for HBV and vaccination for their IBD patients, whether they are on or off immunosuppressive medications [98]. Vaccination assessments yearly, and prior to initiation of treatment with immunosuppressive agents, were important predictors of vaccination completion [7].

In conclusion, taking care of patients with IBD often includes making complex medical decisions. Gastroenterologists are usually the primary providers for patients with IBD; consequently, it is critical to have a broad knowledge of the issues surrounding the administration of vaccines to patients with IBD. The vaccination recommendation should be tailored to each patient, taking into account his/her age, comorbidities, nutritional status, IBD disease severity, immunosuppressive therapy, risk of exposure to pathogens and geographic clustering. Moreover, vaccination should not delay urgent medical therapy and gastroenterologists should involve infectious specialists when they face a challenging situation not addressed by guidelines.

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