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Review Article

Vaccinations in patients with inflammatory bowel disease

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ABSTRACT

Treatment of inflammatory bowel disease (IBD) frequently requires administration of immunosuppressive therapies, which increases susceptibility to a number of infectious pathogens. However, many infections can be prevented by correct and appropriate utilization of vaccinations. While several guidelines have been published on vaccination schedules in patients with IBD, vaccination rates remain suboptimal and even lower than those in the general population. This is due to many factors including poor awareness of the importance of vaccines by gastroenterologists and general practitioners as well as potential prejudices of patients regarding the safety and benefits of vaccines. With the aim of increasing awareness about the key role of immunization in the management of patients with IBD, the present review examines the existing literature relating to the main vaccinations and their application in these patients. We also summarize current evidence in order to provide clinicians with an easy source of reference for the principal recommendations for prevention of infectious diseases in patients with IBD. In addition, the recommendations about traveling for IBD patients are briefly explored. Lastly, since it is important for gastroenterologists to be aware of recommendations on vaccination, we recommend implementing educational programs to ensure compliance with current guidelines.

1. Introduction

Inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the small intestinal tract and colon. Being an immunologically mediated disease, treatment of IBD frequently requires administration of immunosuppressive therapies [1]. However, immunosuppression is associated with augmented vulnerability to a range of infectious pathogens, and in reality the main risk of infections in patients with IBD is related to immunosuppressive therapies, and not to the condition itself [1]. In patients with IBD, thiopurines, for example, are associated with a risk of serious systemic viral infections that is increased 3-fold compared to the general population [2], even in the apparent absence of intrinsic systemic immunodeficiency [3]. Moreover, treatment with immunosuppressive drugs, and especially corticosteroids, thiopurines, anti-TNF agents, and combination treatments, has been related with fatal cases of hepatitis B [4], pneumococcal pneumonia [5], TBC reactivation [6,7], varicella, and herpes zoster [5,8]. Many of these infections can be prevented by correct and appropriate use of vaccinations [1].

It is clear that vaccinations can prevent infections in patients with IBD; live vaccines are contraindicated in patients receiving high-level immunosuppression, but can be used in those on low-level immunosuppression. While several guidelines have been published [9–13], vaccination rates in patients with IBD remain suboptimal and lower than those in the general population [10,14–20]. This has been related to several factors, including poor knowledge about the importance and safety of vaccinations in immunocompromised patients, fear of side effects, insufficient clarity on the roles of general practitioners and gastroenterologists in managing patients with IBD, and lack of adequate resources [17,21–23]. Among these, some authors have suggested that poor knowledge among physicians about the key role of prevention is likely to be a predominant factor that accounts for the suboptimal rate of vaccinations in this group of patients [20,24–26]. Among patient-related factors, misunderstandings about possible side effects of vaccines and their impact on the underlying disease have been reported to be associated with low rates of vaccinations in individuals with IBD [16,20]. Finally, lack of sufficient resources and

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personnel, as well as cost concerns and time constraints, may also be important barriers to the application of adequate vaccination plans [16,21].

The present review will explore the existing literature relating to the main vaccinations and their application in patients affected by IBD. Brief notes on recommendations about traveling for IBD patients will also be discussed.

2. Type of immunosuppression and infectious risk

The Infectious Diseases Society of America (IDSA) has categorized immunosuppression as high or low based upon the potency of the immunosuppressive agent [13]. Low-level immunosuppression includes treatment with prednisone <2 mg/kg to a maximum of ≤20 mg/day; methotrexate ≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day [13]. High-level immunosuppressive regimens include treatment with doses higher than those listed for low-dose immunosuppressive agents and tumor necrosis factor (TNF) antagonists [13]. It should be noted, however, that the IDSA guidelines dates to 2013–2014, and thus drugs for IBD that have been introduced after that time, such as vedolizumab, ustekinumab, and tofacitinib, are not categorized in this classification [13].

The combination of more immunosuppressive drugs has been shown to increase infective risk [6,27,28]. In a recent meta-analysis of observational studies, the risk of serious infection was seen to increase considering the combination of an anti-TNF and immunosuppressive agent and with anti-TNF and a corticosteroid compared to therapy with an anti-TNF alone [29]. The same was seen to be the case for combination therapy with an anti-TNF and thiopurine, which raised the risk for both serious and opportunistic infections compared to either agent alone as monotherapy [30].

3. Types of vaccines and general principles

The two main types of vaccinations currently in use consist of live attenuated microorganisms and inactivated microorganisms or their components [31]. Weakened or attenuated viruses or bacteria capable of only limited replication induce an immune response, which resembles natural infection, can be used at small doses and are frequently effective after administration of a single dose, even if for some vaccines a second dose is given to ensure a long-lasting immunity. Inactivated vaccines contain cultured pathogens that have been inactivated using heat or chemical agents or their antigenic components or toxoids, and may also contain adjuvants to stimulate an immune response. Multiple doses are often required to achieve adequate immune protection.

Patients with IBD who are not receiving immunosuppressive therapies can be vaccinated according to the Advisory Committee on Immunization Practices (ACIP) recommendations for the general population [9,12,32]. For patients receiving immunosuppressive treatment, inactivated vaccines are considered safe, while live vaccines are generally contraindicated and their use can be considered only at least 4 weeks before or 3 months after discontinuing immunosuppressive therapy [9–13]. According to current guidelines, the ideal time to vaccinate patients with IBD is just after the disease is diagnosed [9–13], not only to escape the contraindication of live vaccine administration prior to initiating immunosuppressive therapy, but also to obtain better response rates than those expected in patients on treatment with immunosuppressive agents [33].

An overview of vaccine recommendations is summarized in Table 1.

4. Overview of vaccine recommendations

4.1. Influenza

Patients with IBD are at greater risk of severe complications and hospitalizations related to influenza and seem to be at greater risk of contracting the disease than the general population [34]. Despite this, as is the case for other infectious diseases, vaccination coverage for influenza in IBD patients remains largely suboptimal [17,34]. Inactivated influenza vaccines are considered safe in IBD patients [1,35] and annual influenza vaccination is recommended by a number of guidelines [10–13].

Patients on combined immunosuppressive therapy should not be excluded from vaccination, even if a suboptimal response to influenza vaccine has been reported in some cases [8,36–38]. In a recent randomized trial comparing high dose (HD) vs standard dose (SD) influenza vaccine in patients with IBD receiving monotherapy with an anti-TNF agent, patients in the HD arm developed significantly higher antibody levels than those in the SD arm [39].

4.2. Pneumococcus

IBD patients are at higher risk of pneumonia compared to the general population, particularly those on treatment with corticosteroids, thiopurines, and biologics [5,40]. Moreover, mortality for pneumonia is increased in patients with IBD who are hospitalized [41]. Pneumococcus vaccination with both PCV13 and PPSV23 should be proposed at diagnosis of IBD and in any case preferably administered before starting immunosuppressive therapy [10,12,13,42]. Immunological response to PPSV23 seems to be reduced in IBD patients treated with an anti-TNF combined with immunomodulators [12,13,17,43].

4.3. Meningococcus

Neisseria meningitidis infections can lead to sepsis and meningitis with a high rate of mortality. Anti-meningococcal vaccination is not included in all guidelines, although a survey reported that a substantial proportion of physicians consider it in patients with IBD [26]. ACG guidelines recommend that all adolescents with IBD should receive meningococcal vaccination as in general population [10]. A consensus paper from the British Society of Gastroenterology on the management of IBD patients underlines the importance of exploring immunization status of patients against several pathogens, including meningococcus, before the start of immunosuppressive treatment [11].

The incidence of meningococcal-related disease and the prevalent serogroups vary in different countries, and health authorities have issued guidelines that are pertinent to the specific epidemiological situation [44]. All the available vaccines can be safely administered to patients with IBD regardless of immunosuppressive treatments [10].

4.4. HPV

HPV infection is known to cause cervical and anogenital cancer. Since IBD is often diagnosed at a relatively young age, the risk of HPV infection should be considered, and patients to be treated with immunomodulator therapy should be advised to undergo regular screening at a higher frequency than that recommended in the general population [5,10,45,46]. Although no correlations between IBD and cervical cancer have been found, an increased risk for cervical abnormalities or cervical cancer precursor lesions has been reported in women with IBD, particularly when treated with corticosteroids and immunosuppressants [46,47]. Guidelines rec-

Table 1
Principal recommendations for vaccinations in patients with IBD.

Pathogen	Immunization status investigation	Indications for vaccine	Recommendations for travelers [69]
HPV [12]	Regular gynecologic screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators.	Routine prophylactic HPV vaccination is recommended for females and males according to national guidelines.	Routine vaccinations recommended. Update/boost as needed.
HBV [12]	All patients should be tested for HBV (HBsAg, anti-HBAbs, anti-HBcAb) at diagnosis of IBD to determine HBV status. In patients with positive HBsAg, viremia (HBV-DNA) should also be quantified.	HBV vaccination is recommended in all HBV anti-HBcAb seronegative patients.	Routine vaccinations recommended. Update/boost as needed.
Influenza [12]	–	Routine influenza vaccination of patients on immunomodulators is recommended in accordance with national guidelines.	Routine vaccinations recommended. Update/boost as needed.
Pneumococcus [12]	Immunizations status against Pneumococcus should be explored before the start of the therapy.	Pneumococcal vaccination should be given shortly before initiation of immunomodulators.	Routine vaccinations recommended. Update/boost as needed.
VZV [12]	At diagnosis of IBD, patients should be screened by history for susceptibility to primary VZV infection. Those without a clear history of chickenpox, shingles or receipt of two doses of varicella vaccine should be tested for VZV IgG.	Where possible, seronegative patients should complete the two-dose course of varicella vaccine at least 3 weeks prior to commencement of immunomodulator therapy. Subsequent immunization can only be administered after a 3–6-month cessation of all immunosuppressive therapy. Seronegative patients should receive timely post-exposure prophylaxis.	Routine vaccinations recommended. Update/boost as needed.
Meningococcus [10]	–	Adolescents with IBD should receive meningococcal vaccination in accordance with routine vaccination recommendations.	Recommended when traveling to certain countries or areas.
C. difficile [12]	–	Chemoprophylaxis for CDAD is not warranted. Hygiene procedures are recommended in a nosocomial setting. Screening for C. difficile is recommended at every flare in patients with colonic disease.	–
Tuberculosis [12,76]	Before starting biologics or JAK inhibitors and, ideally, before any immunosuppression, IBD patients should be screened for latent TB infection. Consider re-screening patients previously exposed to biologicals and JAK inhibitors before switch or swap. Latent TB infection should be diagnosed by a combination of patient clinical data and epidemiological factors, chest X-ray, and TST or IGRA according to local availability and national recommendations. Patients diagnosed with latent TB infection prior to biological or small-molecule therapy or prolonged high-dose systemic steroids should be treated with a complete therapeutic regimen for TB infection.	In case of latent TB, biological therapy should be delayed for at least 3 weeks after starting chemotherapy. In case of active TB, anti-TB chemotherapy must be started, and biological therapy must be stopped, even if it could be restarted after two months if needed.	Routine vaccinations recommended. Update/boost as needed.
Tetanus, diphtheria, and pertussis	No specific guidelines, but suggested to apply those for the general population [31].	For most patients a booster of Tdap (tetanus, diphtheria, and pertussis) or Td (tetanus and diphtheria) should be administered every 10 years in the absence of a tetanus-prone wound [64].	Routine vaccinations recommended. Update/boost as needed.
Other	–	–	Recommended when traveling to certain countries or areas. • Cholera • Hepatitis • Japanese encephalitis • Rabies • Tick-borne encephalitis • Typhoid fever • Yellow fever

ommend HPV vaccination for both men and women, including patients on immunosuppressive treatment [10–13].

4.5. HBV

Reactivation of HBV in patients treated with immunosuppressive drugs can have serious consequences including hepatic failure, and even death, and the need for preventive care has been stressed [4]. Antibody titers should be checked both before and after administration of immunosuppressive drugs, and an anti-HBs antibodies titer ≥10 mIU/mL is considered protective [48]. Below that titer, all patients should be vaccinated or re-vaccinated. Vaccines against HBV are given in three doses at 1, 1–2, and 4–6 months [10]. The response rates to HBV vaccines in patients with IBD is variable, but frequently lower than in general population [49]. Non-responders can be revaccinated or administered either a double dose HBV vaccination or combined HAV/HBV vaccine [10].

4.6. Varicella/zoster

Patients with IBD, especially if treated with immunosuppressive, biological drugs, or small molecules, are at increased risk of varicella-zoster virus (VZV) infections or reactivations [5,35,50]. VZV is the causative agent of chickenpox and herpes zoster (HZ). HZ is due to the reactivation of the latent VZV within the sensory ganglia. Patients with IBD are at higher risk of severe primary VZV infection and of HZ [51]. The incidence and severity of HZ increase with advancing age, particularly >50 years [52]. In addition, chickenpox often presents more severely and can be life-threatening in immunocompromised patients, who are at risk of pneumonia, hepatitis, and bleeding disorders such as disseminated intravascular coagulation [8,53,54]. Moreover, a combined immunosuppressive treatment regimen has been associated with a greater risk of developing HZ [50].

At diagnosis of IBD, unvaccinated patients should be screened for history of chickenpox and shingles [35]. Seronegative patients should receive two doses of varicella vaccine 4–8 weeks apart [8,35,55], and HZ vaccine is recommended in patients >60 years of age [8,10,55].

According to the American College of Gastroenterology (ACG), adults with IBD over the age of 50 should consider vaccination against HZ, with one dose given at least one month before starting immunosuppressive therapy; the decision should be made on a case-by-case basis based on the assessment of the benefit-risk profile [10]. Recently, a recombinant vaccine has been approved by FDA and EMA for immunocompetent patients older than 50 years, even if previously vaccinated with live vaccine [56].

4.7. Clostridium difficile

IBD patients have a greater risk of intestinal infections compared with general population [11]. Mylonaki found an incidence of enteric infections of 10.5% in patients with an IBD relapse, with *C. difficile* responsible for half of them [57]. Infections caused by *C. difficile* are associated with an increased risk of complications and mortality in patients with IBD, as well as greater risk for colectomy in the long term [58].

Several toxoid vaccines targeting the A enterotoxin and B cytotoxin are under development. While it has been reported that these vaccines may circumvent manifestations of the disease, they seem to be unable to prevent *C. difficile* colonization in the gastrointestinal tract, or sporulation or shedding of spores in the environment [59,60]. In a recent Phase 3 trial investigating a *C. difficile* toxoid vaccine candidate, the vaccine was not able to prevent infection and the trial was ended for futility [61]. Given the lack on an effective vaccine, current guidelines obviously do not include *C. difficile* vaccination among recommendations. Clinicians should, however, be aware of the possibility of *C. difficile* infections. Of note, all patients with acute flares of IBD should undergo a stool culture, also exploring *C. difficile* [11,12].

4.8. Tuberculosis

In IBD patients, immunosuppressive treatments, especially anti-TNF agents, can induce the reactivation of latent tuberculosis infections, which can have a serious course, with possible extrapulmonary localizations [35]. Latent tuberculosis must be carefully explored at diagnosis and before starting immunomodulating treatment, investigating the patient's history, performing a skin test with tuberculin or an interferon-gamma release assay (QuantiFERON-TB Gold assay or T-SPOT.TB assay), and chest X-ray [44]. BCG is a live and therefore generally contraindicated vaccine in patients with IBD undergoing immunosuppressive treatment [11,17]. In any case, the WHO has recommended that BCG vaccination is given only in countries or settings with a high incidence of tuberculosis or leprosy [62]. Its efficacy varies depends on the age of vaccination and previous exposure to tuberculosis, and ranges from <60% to around 90% [62].

4.9. Tetanus, diphtheria, and pertussis

Compared with the general population, patients with IBD do not appear to be at increased risk for tetanus, diphtheria, or pertussis [31]. Moreover, tetanus and diphtheria infections are now relatively rare in developed countries [63]. There are no specific guidelines for vaccination against tetanus, diphtheria, or pertussis in patients with IBD, but it has been suggested that those for the general population be applied [31]. This means that for most patients a booster of Tdap (tetanus, diphtheria, and pertussis) or Td (tetanus and diphtheria) should be administered every 10 years in the absence of a tetanus-prone wound [64].

4.10. SARS-CoV-2

The ongoing pandemic of COVID-19 caused by infection with SARS-CoV-2 is worthy of a brief comment in the context of vaccinations for patients with IBD. COVID-19 has raised substantial concerns for patients with IBD who are receiving immunosuppressive agents. A recent systematic review on COVID-19 in about 800 IBD patients reported that among the 13 studies included the case fatality rate ranged from 0 to 20% [65]. However, neither immunomodulators nor biologics were associated with a higher risk of COVID-19 or with negative outcomes, even if the administration of systemic corticosteroids was linked to poorer prognosis in some studies. Thus, patients with IBD do not appear to be at greater risk of infection by SARS-CoV-2 compared to the general population, and current treatments are not associated with worse prognosis. However, clinicians should be cautious about the use of systemic steroids for treatment of COVID-19 [66].

At the time of the manuscript was drafted, no specific guidelines for vaccination against SARS-Cov-2 in patients with IBD and no published studies in patients with immunodeficiencies by disease or by medication are available. Recently, a consensus on behalf of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) provided several statements supporting SARS-CoV-2 vaccination in patients with IBD regardless the immune-modifying therapies [67]. Similar message was published in a position statement endorsed by the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section and IBD Clinical Research Group [68]. Both organizations agreed on the lack

of available data related to this topic and that further studies are needed [68].

4.11. Traveling with IBD

IBD in itself is not a contraindication to travelling, although patients should undergo a pre-travel consultation, particularly when being treated with immunomodulators, to assess the risk of infection in different countries and how to prevent them [12,19,69]. IBD patients are subject to the same infections as the general population. Beside this, they are at risk for opportunistic infections related to treatment with immunomodulators. Moreover, they can experience possible relapses, exacerbations, or complications of their disease due to gastrointestinal infections, change in diet or IBD treatment. Specific preventive measures, including vaccination programs, should be implemented to minimize these risks [12,70].

A vaccination program for IBD travelers should take into consideration include travel destination and its infectious disease profile, season of travel, type of accommodation, length of stay, and the patient's age and overall health status [12,70].

Vaccine recommendations for immunocompromised travelers are similar to those for non-immunocompromised travelers, but some vaccines, like those against yellow fever, are live and should not be administered, or administered at >3 months after stopping immunosuppressive treatment, which can only be restarted no earlier than 3 weeks after the last dose of vaccine [11,12,69,70]. Considering the mechanism of action of specific treatments like $\alpha 4\beta 7$ integrin monoclonal antibody, selective for the gastrointestinal system, it is important to pay attention when oral vaccines should be concurrently administered as response to oral antigens could be reduced [71]. There are no known cases of infectious complications related to the administration of inactivated vaccines, however, and the rate of adverse events is comparable to that seen in the general population [12]. Travel recommendations for specific vaccines in patients with IBD are summarized in Table 1.

5. Conclusions

Many studies have shown that vaccination rates in IBD patients are suboptimal [10,14–20]. There is often poor awareness of the importance of vaccines for these patients by gastroenterologists and general practitioners as well as by patients themselves [20,26]. In addition, patients often have prejudices regarding the safety of vaccines and on the benefits that they can receive from them [16,20]. Gastroenterologists are the primary healthcare providers treating patients with IBD, and therefore play a key role in ensuring adequate management of disease. Unfortunately, as has emerged from specific surveys, gastroenterologists' knowledge on the correct use of vaccines is often insufficient [23,25,26,72]; moreover, they do not always provide adequate patient counselling [16], and coordination with general practitioners should be improved [20,23,73].

In a recent survey that explored the awareness of physicians regarding the importance of the vaccination plan in IBD patients, the 82.9% of responders recognized the importance of vaccinations recommended by guidelines [26]. However, only the 55.6% of responding physicians prescribed the appropriate vaccinations to patients at IBD diagnosis, with the lowest percentage of prescribers among physicians practicing for >15 years; while recommendations for some vaccinations (influenza and, unexpectedly, meningococcus) are provided in a substantial percentage of cases, the prescription of vaccinations such as pneumococcus or human papilloma virus were largely suboptimal [26].

Surveys have underlined that there is poor communication among general practitioners, gastroenterologists, and patients themselves, who sometimes receive inadequate counselling [20,23]. Many gastroenterologists have the belief that general practitioners should be responsible for planning and administering vaccinations [23], even if no more than 30% of general practitioners actually do so in patients with IBD [74].

Physicians, and in particular gastroenterologists, should be encouraged to conduct a structured interview of all IBD patients at diagnosis, with a systematic review of immunization status and definition of a vaccination plan before the start of immunosuppressive treatment [11–13,42]. Specific checklists have been established to assist the physician in this task [75]; the checklist by ECCO, to be used during the first visit, includes data on the patient's history, physical examination, laboratory tests, and vaccinations; in addition, the final section is dedicated to patient education and referral to other specialists, especially for gynecological screening and for travel [75]. Finally, the necessary vaccinations should be administered on the basis of findings in the individual patient [1,11,13,16,20,72].

Given the increased infection-related risk in IBD, there is substantial interest in mitigating clinical risk. Correct immunization has a key role in the management of patients with IBD, and it is important for gastroenterologists to be aware of recommendations on vaccination. To achieve this goal, educational programs should be implemented to ensure compliance with current guidelines, and specialists should also have an educational role with both patients and other healthcare providers. In this regard, it is highly desirable that scientific societies implement initiatives to increase awareness about this important topic.

Declaration of Competing Interest

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