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## Vaccines and recommendations for their use in inflammatory bowel disease

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### Abstract

The patient with inflammatory bowel disease will be predisposed to numerous infections due their immune status. It is therefore important to understand the immune and serologic status at diagnosis and to put the patient into an adapted vaccination program. This program would be applied differently according to two patient groups: the immunocompromised and the non-immunocompromised. In general, the first group would avoid the use of live-virus vaccines, and in all cases, inflammatory bowel disease treatment would take precedence over vaccine risk. It is important to individualize vaccination schedules according to the type of patient, the treatment used and the disease pattern. In addition, patient with inflammatory bowel disease should be considered for the following vaccines: varicella vaccine, human papilloma virus, influenza, pneumococcal polysaccharide vaccine and hepatitis B vaccine.

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**Key words:** Vaccines; Inflammatory bowel disease; Crohn's

disease; Ulcerative colitis; Immunocompromised

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### INTRODUCTION

Inflammatory bowel disease (IBD) is associated with a greater predisposition to infections, many of which are preventable with vaccines<sup>[1]</sup>. Many studies show a low rate of seroprotection and adherence to vaccination programs in these patients<sup>[1-4]</sup>. Given that at some point in the progression of the disease, 80% of patients will require treatment with corticosteroids, 40% with thiopurines and around 20% with biological drugs, it is important to consider the number of patients who will be at risk for acquiring infections due solely to the medication they receive<sup>[5]</sup>.

The vaccination plan will be made after thorough study of immunocompetence at the time of diagnosis and prior to any immunomodulating treatment and/or treatment with biological agents<sup>[3]</sup>. After immunocompetence has been assessed, we consider the vaccine schedule, serological studies for certain infections and each patient's personal risk in order to adjust the proper vaccination regimen for each case<sup>[2]</sup>.

### IS OUR PATIENT IMMUNOCOMPETENT?

Evaluation of the patient's immunocompetence is essential prior to starting any immunosuppressant treatment or putting the patient in a vaccination program<sup>[5-7]</sup>. An IBD patient is considered to be immunocompromised when they meet any of the following criteria: first, pa-

tients on corticosteroid treatment at dosages equal to or greater than 20 mg of prednisone for more than two wk, patients on immunomodulators (azathioprine, mercaptopurine and/or methotrexate), calcineurin inhibitors (cyclosporine, tacrolimus) or anti-tumor necrosis factor (TNF) (infliximab, adalimumab or others); malnourished patients and patients with any associated immunocompromise condition [hyposplenism, asplenia, human immunodeficiency virus (HIV), *etc.*]<sup>[5,6]</sup>.

## STUDIES PRIOR TO VACCINATION

Study of the patient with IBD should be individualized based on age, particular risk factors and previously-administered vaccinations prior to inclusion in a vaccination program.

The medical history should be directed towards both their bacterial (especially urinary tract infections), viral [hepatitis A vaccine, hepatitis B vaccine (HBV), herpes zoster vaccine, herpes simplex virus, HIV, varicella], fungal and tuberculosis infectious disease history. Regarding tuberculosis (TB), study should include possible current or previous contacts with tuberculosis patients as well as a history of travel to endemic areas, both in the past and in the foreseeable future<sup>[5,6]</sup>. Careful evaluations for latent TB before the use of anti-TNF therapy is mandatory<sup>[8]</sup>. We suspect a latent TB when there is a history of recent exposure to the disease and positive initial tuberculin skin-test (TST) or positive booster TST and no radiological evidence of active TB. Another chapter delves more on this topic<sup>[5]</sup>.

Laboratory studies will include a hemogram, C-reactive protein, urine analysis (if there is a history of urinary tract infections), the viral serologies mentioned above and a stool culture. The patient's vaccination history will always be useful if the patient has it, as will a study of group risk due to household members or occupational risk (such as teachers or healthcare workers)<sup>[5]</sup>.

## VACCINATION PROGRAM

Ideal vaccination is that which is performed at diagnosis of the disease and/or prior to starting immunosuppressor therapy. In general, all patients should be vaccinated for the following: tetanus, diphtheria and polio, varicella, human papillomavirus, influenza, pneumococcus, HBV, measles, mumps and rubella<sup>[5]</sup>. Confirmation of immunization against infections preventable by live-attenuated viruses is recommended since they are contraindicated in cases of immunosuppression, which may apply to the patient if their immune status changes over the course of the disease (Table 1).

Below we mention each of the vaccines used in these patients and the considerations to be taken into account before, during and after their administration.

### Flu vaccine and pneumococcal vaccine

Flu is one of the most common vaccine-preventable

**Table 1 General vaccination and contraindicated live vaccines in inflammatory bowel disease patients**

IBD patients
General vaccination
VZV varicella vaccine
Human papilloma virus
Influenza (trivalent inactivated vaccine)
Pneumococcal polysaccharide vaccine
Hepatitis B vaccine in all HBV seronegative patients
Contraindicated live vaccines
Anthrax vaccine
Intranasal influenza
Measles-Mumps-rubella
Polio live oral vaccine
Smallpox vaccine
Tuberculosis BCG vaccine
Typhoid live oral vaccine
Varicella yellow fever

IBD: Inflammatory bowel disease; HBV: Hepatitis B virus; BCG: Bacille Calmette Guérin.; VZV: Varicella zoster virus

diseases in adults<sup>[9]</sup>. The European Crohn's and Colitis Organisation (ECCO) guidelines recommend the inactivated trivalent vaccine on an annual basis in all patients with IBD with or without immunocompromise<sup>[5]</sup>. However, it has been confirmed that the two most common reasons for not receiving the flu vaccine were the patient's lack of awareness (49%) and fear of side effects (18%). Several studies have shown that the inactive trivalent vaccine does not affect IBD activity and caution is only recommended in those patients who have previously had adverse reactions to the vaccine<sup>[9,10]</sup>. The Mamula study observed that among patients who received infliximab and immunomodulator treatment, response to two of the vaccine's antigens may be reduced, with significantly lower antibody titers<sup>[11]</sup>. Later it was shown that seroconversion after the flu vaccine is not reduced by corticosteroids, methotrexate or anti-TNF treatment<sup>[5,9,12]</sup>. However, seroconversion was not guaranteed with combined use of these agents. Thiopurines and cyclosporine did reduce the rate of seroconversion<sup>[13-15]</sup>.

The polyvalent pneumococcal vaccine is recommended in immune-compromised patients, as is revaccination at 5 years from the first vaccination if immunosuppression persists<sup>[16]</sup>. Treatment with methotrexate is associated with a lower seroconversion rate<sup>[5,6]</sup>.

### Hepatitis B vaccine

The prevalence of HBV infection in IBD is similar to the general population. The HBV vaccine is recommended in all seronegative patients<sup>[17]</sup>. Patients with IBD may have an increased risk of developing hepatitis B<sup>[18]</sup>. Invasive procedures such as endoscopies and surgery might be some of the reasons for this. Moreover, the use of immunosuppressors may reactivate a latent infection<sup>[19-21]</sup>. Effective vaccination is only present in 12% of IBD patients although it is indicated in all with or without immunosuppression. It was observed that the only factor associated with higher efficacy of the vaccine was younger age

and the number of immunomodulators that the patient takes. The use of high antigen doses or administration of a fourth dose is sometimes needed in order to improve response to the vaccine. The response rate in the general population is related to reaching surface antibody levels (HBsAb) that are equal to or greater than 10 mU/mL. The immunological memory conferred by the vaccine produces an anamnestic immune response upon contact with the wild virus that quashes the infection or at least leads to an unapparent infection<sup>[17,18]</sup>. Only patients who do not respond to this vaccine should be subjected to intense vaccination schedules such as administration of a fourth dose, complete revaccination and/or the use of high dosages (40 µg) of HBV surface antigen. The conventional HBV vaccination regimen requires three doses at 0, 1 and 6 mo. If faster vaccination is required, the first two doses can be administered at a three or four-week interval (0, 1 and 2 mo)<sup>[18-20]</sup>. In another chapter will be explained in more detail the performance against HBV.

Confirmation of HBsAb seroconversion is recommended one or two months after the last dose of the vaccine<sup>[22]</sup>. The efficacy of the vaccine is affected by the type and number of immunomodulators, with anti-TNF being the slowest. Several authors suggest that the HBsAb concentration in these patients should be greater, with titers greater than 100 mU/mL considered protective. Annual measurement of HBsAb titers is recommended and administration of a booster is recommended when these patients are older than 10, especially in patients with IBD and immunosuppressor treatment<sup>[5]</sup>.

### **Measles, mumps and rubella vaccine**

Because this is a live attenuated virus, it is important for the patient to receive it prior to converting to an immunocompromised state<sup>[6,23]</sup>. Previous review of the documented medical record or serology at diagnosis and protection of the seronegative group are recommended. In patients with stable IBD who are high risk of contagion, vaccination will be evaluated after discontinuing immunosuppressor therapy for at least 3 mo prior to vaccination<sup>[23,24]</sup>.

### **Varicella vaccine**

ECCO recommends ensuring immunization against this virus in patients with IBD before their immune status changes<sup>[5,24]</sup>. Immunization is performed at diagnosis, at least three weeks before starting immunomodulator therapy or at least 3 mo after discontinuing the immunosuppressor, if the IBD situation permits. Because this is a live attenuated virus vaccine, vaccination is not recommended in patients on immunosuppressor therapy except for seronegative patients who are at a very high risk of contagion (healthcare personnel or teachers) who are on monotherapy with thiopurine drugs. In patients in whom it is decided not to vaccinate, group protection is recommended by adequate household vaccination<sup>[25]</sup>. The seroconversion rate in adults and adolescents is less than in children (78% *vs* 97%), so a second dose of the

vaccine is recommended 6-8 mo after the first dose. The Advisory Committee of Immunization Practices of the Centers for Disease Control and Prevention recommends discontinuing 5-aminosalicylic acid (5-ASA) until 6 mo after administering the varicella vaccine. The effects of 5-ASA may theoretically increase the risk of Reye syndrome associated with the use of live virus vaccines such as varicella<sup>[6,23,26]</sup>.

For patients with increased risk of occupational exposure to varicella (for example, an early childhood teacher or healthcare worker) without prior immunity, careful consideration of the risks of acquiring the infection need to be weighed against the potential risks and benefits of vaccination<sup>[23,24,27]</sup>. In cases of active varicella exposure in these patients, postexposure prophylaxis with varicella zoster immunoglobulin is recommended.

### **Human papillomavirus vaccine**

The human papilloma virus (HPV) vaccine is a quadrivalent vaccine that targets the 4 HPV serotypes associated with highest risk of progression to cervical dysplasia and cancer<sup>[28,29]</sup>. This vaccine is indicated in all women between 11 and 14 years of age, in addition to strict cytological monitoring, according to the guidelines of each country<sup>[30-32]</sup>. There are no studies that defend the use of this vaccine on a routine basis in women over 26 years of age. Because this is not a live virus vaccine, it can be administered to immunocompromised patients with IBD. Interruption of immunomodulator treatment should be considered in patients with extensive cutaneous warts and/or condyloma. However, past HPV infection is not a contraindication for immunomodulator therapy<sup>[10,23]</sup>.

### **Other vaccines**

Universal administration of the tetanus and diphtheria vaccine and the inactivated polio vaccine is recommended in patients with IBD, including immunocompromised patients<sup>[33,34]</sup>.

The hepatitis A vaccine is indicated in travelers to medium or highly-endemic areas, groups at high occupational or behavioral risk and immunocompromised individuals<sup>[35,36]</sup>.

Patients with IBD who wish to travel abroad should consult their physician 4 to 6 mo prior to traveling. There are three types of vaccines in travel guidelines: systematic, recommended and required<sup>[4]</sup>. The option of administering live virus vaccines should be considered in all IBD patients based on their immunocompromise status. Infections caused by enteropathogens can cause reactivation of quiescent IBD. The oral cholera vaccine will be indicated in all travelers to highly endemic areas. The oral typhoid vaccine should not be prescribed to patients who have undergone colectomy due to the loss of colonic bacterial colonization, though the parenteral vaccine can be administered<sup>[5,37-40]</sup>. Patients who take immunomodulators should be discouraged from traveling to South America or Sub-Saharan Africa where yellow fever is endemic and vaccination with live virus vaccines is

required. Other vaccine-preventable diseases in travelers that should be considered are the following: Japanese encephalitis (inactivated virus), meningococcal meningitis, tick-borne encephalitis, malaria, travelers' diarrhea, tuberculosis and insect-borne diseases<sup>[35,40]</sup>.

The majority of childhood vaccinations occur in the first two years of life<sup>[34]</sup>. The use of live virus vaccines is contraindicated in pediatric patients who receive biological treatment. In addition, children who have been exposed to biological treatment *in utero* should not receive live virus vaccines while the biological agents are still detectable in their blood, generally for the first 6 mo of life<sup>[10,37,41]</sup>. Booster immunizations are recommended in the second decade of life at the onset of IBD. Booster recommendations include hepatitis B, diphtheria, polio, tetanus, measles, mumps, rubella and varicella<sup>[6]</sup>. The ability to mount an effective immune response will depend on the presence of immunosuppression in the 2 wk after immunization. Adequate immune response is recovered between 3 mo and one year after discontinuing the immunosuppressor<sup>[4,5]</sup>.

In conclusion, all patients who are recently diagnosed with IBD should have their vaccine serology and immunocompromise status studied thoroughly. If the patient is immunocompromised, they will receive the following vaccines: diphtheria, tetanus, inactivated polio, pertussis, hepatitis B, pneumococcus, human papillomavirus, hepatitis A and flu, among others. If the patient is not immunocompromised, live virus vaccines will be added based on the vaccination schedule in each country and based on the patients behavioral and professional risk. This measure will prevent infectious problems over the course of their disease and reduce morbidity. The patient's disease and its treatment may vary over the course of the disease, which is why we must take prophylactic measures in order to avoid problems in the future when immunocompromise may hinder treatment. The use of immunosuppressants such as immunomodulators and/or biological agents in IBD is becoming more intense and frequent, making it necessary to take prophylactic measures such as the use of vaccines.

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